Dermatology Practical & Conceptual

# Delphi Consensus Among International Experts on the Diagnosis, Management, and Surveillance for Lentigo Maligna

Caterina Longo,[1,2*] Cristian Navarrete-Dechent,[3,4*] Philipp Tschandl[5], Zoe Apalla[6], Giuseppe Argenziano[7], Ralph P. Braun[8], Veronique Bataille[9], Horacio Cabo[10], Rainer Hoffmann-Wellhenhof[11], Ana Maria Forsea[12], Claus Garbe[13], Pascale Guitera[14], Karls Raimond[15], Ashfaq A. Marghoob[16], Josep Malvehy[17], Veronique del Marmol[18], David Moreno[19], Kishwer S. Nehal[16], Eduardo Nagore[20], John Paoli[21], Giovanni Pellacani[22], Ketty Peris[23], Susana Puig[17], H. Peter Soyer[24], Susan Swetter[25], Alexander Stratigos[26], Wilhelm Stolz[27], Luc Thomas[28], Danica Tiodorovic[29], Iris Zalaudek[30], Harald Kittler[5], Aimilios Lallas[31]

**1** Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy
**2** Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Skin Cancer Center, Reggio Emilia, Italy
**3** Department of Dermatology, Escuela de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Chile
**4** Melanoma and Skin Cancer Unit, Escuela de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Chile
**5** Department of Dermatology, Medical University of Vienna, Vienna, Austria
**6** Second Dermatology Department, Aristotle University of Thessaloniki, Greece
**7** Dermatology Unit, University of Campania, Naples
**8** Department of Dermatology, University Hospital of Zürich, University of Zürich, Zürich, Switzerland
**9** Dermatology, Mount Vernon Cancer Centre, Northwood, Middlesex, UK
**10** Dermatology Department "Instituto de Investigaciones Médicas A. Lanari", University of Buenos Aires, Argentina
**11** Nonmelanoma Skin Cancer Unit, Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria
**12** Dermatology Department, Elias University Hospital, Carol Davila University of Medicine and Pharmacy Bucharest, Romania
**13** Center for Dermatooncology, Department of Dermatology, Eberhard Karls University, Tübingen, Germany
**14** Melanoma Institute Australia, The University of Sydney, Sydney, Australia; Faculty of Medicine and Health, University of New South Wales, Sydney, Australia; Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Sydney, Australia
**15** Derma Clinic Riga, Riga, Latvia
**16** Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
**17** Dermatology Department, Hospital Clinic of Barcelona, University of Barcelona, Spain
**18** Department of Dermatology, CUB Hôpital Erasme - Brussels University Clinics, Université Libre de Bruxelles, Brussels, Belgium
**19** Dermatology Unit, Hospital Universitario Virgen Macarena, Seville, Spain
**20** Dermatology Department, Instituto Valenciano de Oncología, Valencia, Spain
**21** Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
**22** Dermatology Clinic, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy
**23** Institute of Dermatology, Università Cattolica-Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
**24** Dermatology Research Centre, The University of Queensland Diamantina Institute, The University of Queensland, Brisbane, QLD 4102, Australia
**25** Department of Dermatology, Pigmented Lesion and Melanoma Program, Stanford University Medical Center and Cancer Institute, Stanford, California
**26** Department of Dermatology-Venereology, Faculty of Medicine, National and Kapodistrian University of Athens, 'A. Sygros' Hospital for Skin and Venereal Diseases, Athens, Greece

27 Department of Dermatology, Allergology, and Environmental Medicine Clinic Thalkirchen, Hospital Munich, Munich, Germany
28 Department of Dermatology, Lyon-1 University, and Cancer research center Lyon, Lyon, France
29 Clinic of Dermatovenereology, Clinical Center of Nis, Serbia
30 Department of Dermatology and Venereology, Dermatology Clinic, Maggiore Hospital, University of Trieste, Trieste, Italy
31 First Department of Dermatology, School of Medicine, Aristotle University, Thessaloniki, Greece
*Co-first authors

**Key words:** melanoma, lentigo maligna, Delphi, diagnosis, management

**Citation:** Longo C, Navarrete-Dechent C, Tschandl P, et al. Delphi Consensus Among International Experts on the Diagnosis, Management, and Surveillance for Lentigo Maligna. *Dermatol Pract Concept.* 2023;13(3):e2023244. DOI: https://doi.org/10.5826/dpc.1303a244

**Accepted:** April 24, 2023; **Published:** July 2023



**Funding:** None.

**Competing interests:** None.

**Authorship:** All authors have contributed significantly to this publication.

**Corresponding author:** Caterina Longo, MD, PhD, Department of Dermatology, University of Modena and Reggio Emilia, Italy. Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Skin Cancer Center, Reggio Emilia, Italy Phone: +390522295612 ORCID Caterina Longo: http://orcid.org/0000-0002-8218-3896 E-mail: longo.caterina@gmail.com

## ABSTRACT

**Introduction:** Melanoma of the lentigo maligna (LM) type is challenging. There is lack of consensus on the optimal diagnosis, treatment, and follow-up.

**Objectives:** To obtain general consensus on the diagnosis, treatment, and follow-up for LM.

**Methods:** A modified Delphi method was used. The invited participants were either members of the International Dermoscopy Society, academic experts, or authors of published articles relating to skin cancer and melanoma. Participants were required to respond across three rounds using a 4-point Likert scale). Consensus was defined as >75% of participants agreeing/strongly agreeing or disagreeing/strongly disagreeing.

**Results:** Of the 31 experts invited to participate in this Delphi study, 29 participants completed Round 1 (89.9% response rate), 25/31 completed Round 2 (77.5% response rate), and 25/31 completed Round 3 (77.5% response rate). Experts agreed that LM diagnosis should be based on a clinical and dermatoscopic approach (92%) followed by a biopsy. The most appropriate primary treatment of LM was deemed to be margin-controlled surgery (83.3%), although non-surgical modalities, especially imiquimod, were commonly used either as alternative off-label primary treatment in selected patients or as adjuvant therapy following surgery; 62% participants responded life-long clinical follow-up was needed for LM.

**Conclusions:** Clinical and histological diagnosis of LM is challenging and should be based on macroscopic, dermatoscopic, and RCM examination followed by a biopsy. Different treatment modalities and follow-up should be carefully discussed with the patient.

## Introduction

Lentigo maligna (LM) is a subtype of melanoma in situ arising on chronically sun-damaged skin and it comprises 4–15% of all melanomas [1-7]. Clinically, LM is often difficult to differentiate from its mimickers, necessitating a biopsy to confirm or exclude the diagnosis. Dermoscopy and reflectance confocal microscopy (RCM) have been shown to increase the sensitivity and specificity of LM diagnosis compared to the visual inspection alone [8,9].

Histopathologically, LM is characterized by an increased density of atypical melanocytes at the dermo-epidermal junction with frequent adnexal involvement [10-12]. Differentiation between LM and melanocytic hyperplasia of sun-damaged skin can be challenging, especially if a small partial biopsy is available (eg punch biopsy) [13]. It is worth mentioning that after partial biopsy of LM, an invasive component (ie upstaging) might be found in 9% of the cases [14-17].

Regarding treatment, wide surgical excision is considered the standard therapy for melanoma on the trunk and extremities and most randomized controlled trials of surgical margins for invasive melanoma excluded LM. In the recent years, the use of lateral and deep margin-controlled techniques such as staged excision with permanent sections or Mohs micrographic surgery (MMS) have been developed for LM [13,18-20]. Additionally, nonsurgical treatments such as radiotherapy and imiquimod have been used for LM therapy [13,21-26].

Despite LM progressing slowly, once invasive, LM melanoma (LMM) has the same prognosis when adjusted for Breslow thickness compared to other melanoma subtypes [27]. However, the risk of LM to progress to invasive melanoma is believed to be very low, around 2% – 5% [28,29]. This is particularly relevant in the light of evidence suggesting that overdiagnosis of melanomas that do not have the potential to harm patients might result in unneeded treatments and unnecessary physical, psychological, and social costs [30,31]. Considering the above issues, the management of LM remains challenging in many aspects [25,32].

## Objectives

The objective of this study was to build consensus among international experts in the field of LM using Delphi methodology on: (i) the definition of the best diagnostic strategy of LM; (ii) the most appropriate surgical treatment; (iii) the use of non-surgical therapeutic options as primary treatments or in an adjuvant setting.

## Methods

This study was conducted between January 1st 2020 and December 31st 2021 under the framework of the International Dermoscopy Society (IDS).

### Study Design

The study used the Delphi consensus methodology. The technique has been described elsewhere [33-35]. Three rounds of the modified Delphi method were required to finalize consensus (Figure 1). Consensus was defined as >75% of participants agreeing/strongly agreeing or disagreeing/strongly disagreeing with a statement was based on prior Delphi studies [33,34]. A dropout rate of 20% was expected over the rounds, in accordance with previous Delphi studies.

### Expert Panel Recruitment

The invited participants were either members of the IDS Executive Board, academics or authors of articles related to skin cancer and melanoma. To complete the Delphi process, participants were required to respond across all three rounds. Therefore, those who did not respond to Round 1 were not invited to participate in Round 2 and similarly for Round 3. There was space for free-text responses from Round 1 to be incorporated as new statements in Round 2 and re-evaluated considering the group consensus in Round 3 (Figure 1). All surveys were administered using SurveyMonkey (Momentive Inc.) through a web link or QR code.

Initial statements presented on the first round were developed by 3 core authors (C.L., P.T., A.L.), following a review of the literature. The survey statements were constructed to highlight key challenges and opportunities, and to obtain actionable statements for effective approaches in clinical practice. Three authors (C.L., P.T., A.L.) jointly analyzed the responses, counting the votes and selected new statements for the next round. An iterative process of feedback was undertaken to improve the structure and readability of statements, and to determine whether any additional statements were needed.

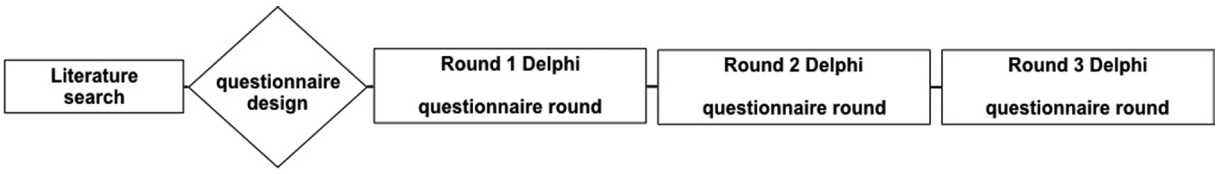


**Figure 1.** The Delphi process in the Lentigo maligna Consensus of Experts.

### Round 1

Participants were asked to independently rank a total of 51 statements, across seven domains, using a 4-point Likert scale ('strongly agree', 'agree', 'disagree', 'strongly disagree'). In Round 1, data on participant demographics were also collected including: biologic sex, year of birth, country of residence, current job position, highest educational qualification obtained and time (in years) working in the field of skin cancer research. Statements derived from the free-text responses in round 1 led to eight new statements in round 2. Further, the free-text responses from Round 1 helped to clarify one statement which was then added as a new statement in Round 2.

### Rounds 2 and 3

In round 2, each participant received a survey comprising 23 statements which were presented alongside participants own responses from Round 1, as well as the group collective response (percentage agreement/disagreement) to each statement. Participants were asked to reconsider their responses in the light of the group responses via email. In round 3, each participant received a survey with 3 final statements (Figure 2).

## Results

Of the 31 experts invited to participate in this Delphi study, 29 participants completed Round 1 (89.9% response rate), 25 completed Round 2 (77.5% response rate) and 25 completed Round 3 (77.5% response rate). Table 1 presents the demographic characteristics of the participants in each round. Participants' mean age ranged from 51 to 55 years across the three rounds, and the majority resided in Europe (75.8%). Most respondents were senior academics, had doctoral degrees, and had been working in the field of skin cancer research for more than 10 years.

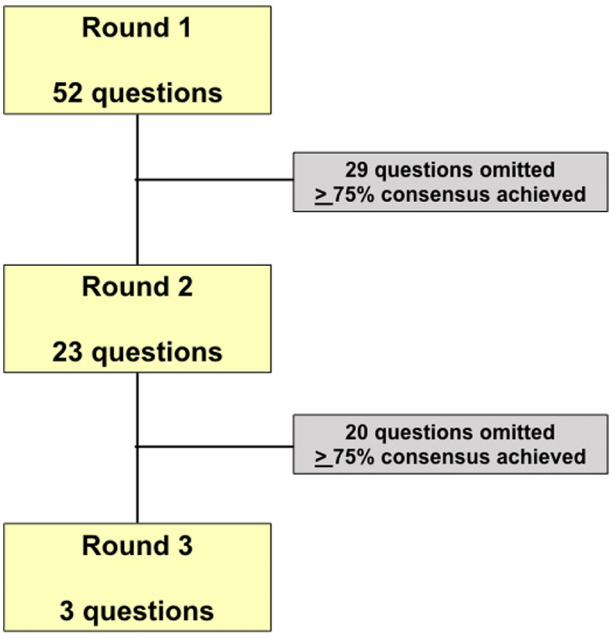


**Figure 2.** Flow diagram illustrating the three survey rounds of the Delphi study.

### LM Diagnosis

Consensus was achieved in 4 out of 4 questions addressing LM clinical diagnosis (Table 2). More specifically, participants agreed on that LM diagnosis should be based on a clinical and dermoscopic integrated approach (92%) and, when available, RCM could be used as an adjunct for diagnosis and pre-surgical margin evaluation. Punch biopsies, possibly from multiple sites, were considered the best choice for histopathologic diagnosis (agreement of 73.3%) followed by broad shave biopsy (66.6%) (Table 3).

### LM Treatment

Consensus was achieved on margin-controlled surgery (83.3%) being the most appropriate primary treatment (after biopsy) of LM. When margin-controlled surgery is not feasible, participants agreed that conventional wide excision with 5-10 mm of clinical margins to the unaffected skin is optimal (73.3%). Furthermore, in cases of a pathology report showing an invasive component, wide surgical margin-appropriate re-excision was considered the most appropriate choice by participants (73.3%). Regarding the possibility of non-surgical treatments, consensus was achieved that there is no specific age threshold to consider alternative treatment to standard surgical excision, but that these options should be based on patient performance status (80%). Imiquimod was regarded as the alternative treatment of choice when surgery was not feasible (93.3%), followed by radiotherapy (agree 66,7%, strongly agree 26%).

### LM Adjuvant Therapy

There was no agreement on the use of imiquimod 5% cream as an adjuvant in cases of LM with clear histologic margins (Table 3). In Round 3, for LM excised with clear margins, 48% never used imiquimod as adjuvant treatment, 40% of respondents used imiquimod 'sometimes', whereas 12% used imiquimod 'always'. Finally, 70% of responders used imiquimod as adjuvant treatment in cases of narrow or histologically involved margins without clinical evidence of residual LM. Of these, 69.23% prescribed imiquimod 5-7 times per week for 6 weeks, 15.3% use imiquimod 5-7 times per week for 12 weeks, and 15.3% use imiquimod 5-7 weeks until onset of inflammatory response (Table 4).

### LM Follow-up

Regarding LM follow-up, 62% responded that clinical follow-up of LM should be life-long, 50% for 10 years, and 37% for only 5 years following treatment.

**Table 1.** Demographic characteristics of Delphi participants.

| | Round 1 N = 29 | Round 2 N = 25 | Round 3 N = 25 |
|---|---|---|---|
| Biologic Sex | | | |
| Male | 13 (44.83%) | 9 (36%) | 9 (36%) |
| Female | 16 (55.17%) | 16 (64%) | 16 (64%) |
| Mean age in years | 55 | 51 | 51 |
| Area of residence | | | |
| Australia | 2 | 2 | 2 |
| Europe | 22 | 20 | 20 |
| USA | 4 | 3 | 3 |
| U.K. | 1 | 0 | 0 |
| Practice model | | | |
| Academic practice | 25 (86.21%) | 24 (96%) | 24 (96%) |
| Hospital based | 2 (6.9%) | 0 | 0 |
| Private practice | 2 (6.9%) | 1 (4%) | 1 (4%) |
| Highest education | | | |
| MD | 15 (50%) | 12 (48%) | 12 (48%) |
| PhD | 14 (46.47%) | 12 (48%) | 12 (48%) |
| Master | 1 (3.33%) | 1 (4%) | 1 (4%) |
| Years working in the field | | | |
| Less than 5y | 0 | 0 | 0 |
| 5 to 10y | 2 (6.67%) | 1 (4%) | 1 (4%) |
| More than 10y | 28 (93.33%) | 24 (96%) | 24 (96%) |

Y = years.

**Table 2.** Responses to statements included in Round 1.

| | Round 1 | |
|---|---|---|
| | Agree % | Disagree % |
| Dermatoscopy improves the clinical diagnosis of LM and should always be applied | 100% | 0% |
| Diagnosis of LM is based on a combined clinical and dermatoscopic examination | 100% | 0% |
| The final diagnosis of LM is based on histopathologic findings | 90.00% | 10.00% |
| The final diagnosis of LM is based on integration of clinical and dermatoscopic and histopathologic findings | 96.67% | 3.33% |
| Reflectance confocal microscopy is useful for the diagnosis of LM | 96.67% | 3.33% |
| The most appropriate diagnostic biopsy technique is excisional biopsy | 46.67% | 53.33% |
| The most appropriate diagnostic biopsy technique is punch biopsy | 31.04% | 68.96% |
| The most appropriate diagnostic biopsy technique is punch biopsy, possibly in multiple sites | 73.34% | 26.67% |
| The most appropriate diagnostic biopsy technique is broad shave biopsy | 66.66% | 33.33% |
| The most appropriate treatment of LM is surgical excision with clear margins (even narrow) | 73.34% | 26.66% |
| The most appropriate treatment of LM is surgical excision with 5 mm margin | 73.34% | 26.66% |
| The most appropriate treatment of LM is surgical excision with 10 mm margin | 13.33% | 86.66% |
| The most appropriate treatment of LM is staged surgical excision with margin control (slow Mohs, spaghetti technique or similar) | 83.34% | 16.67% |
| The most appropriate treatment of LM is Mohs micrographic surgery | 43.34% | 56.67% |

*Table2 continues*

**Table 2.** Responses to statements included in Round 1. *(continued)*

| | Round 1 | |
|---|---|---|
| | Agree % | Disagree % |
| Alternative treatments should only be considered when the choice treatment is absolutely impossible | 70.00% | 30.00% |
| Alternative treatments can also be considered for elderly individuals even in good health status | 83.33% | 16.67% |
| Radiotherapy is my alternative treatment of choice | 40.00% | 60.00% |
| Imiquimod 5% cream is my alternative treatment of choice | 93.33% | 6.66% |
| Cryotherapy is my alternative treatment of choice | 10.00% | 90.00% |
| Laser CO2/electrodissection is my alternative treatment of choice strongly agree | 0% | 100% |
| Wait and see might also be an option for elderly patients | 53.33% | 46.67% |
| If, after the excision, one or more margins are involved, re-excision is always mandatory | 46.67% | 53.33% |
| If, after the excision, one or more margins are involved, the decision to re-excise depends on the age | 66.66% | 33.33% |
| If, after the excision, one or more margins are narrower than 5mm, re-excision is mandatory | 10.00% | 90.00% |
| If, after the excision, one or more margins are narrower than 5mm, the decision to re-excise depends on the age | 46.67% | 53.33% |
| If, after the excision, one or more margins are narrower than 10mm, re-excision is mandatory | 0% | 100% |
| If, after the excision, one or more margins are narrower than 10mm, the decision to re-excise depends on the age | 10.00% | 90.00% |
| If pathology reports an invasive component, a wide re-excision (according to Breslow thickness) is always mandatory | 73.33% | 26.67% |
| If pathology reports an invasive component, the decision for wide re-excision (according to Breslow thickness) depends on the age | 43.33% | 56.66% |
| I never use adjuvant treatments for LM | 23.33% | 76.66% |
| An adjuvant treatment is indicated after excision of LM in clear margins (even narrow) | 30.00% | 70.00% |
| An adjuvant treatment is indicated after excision of LM in 5mm margins | 23.33% | 76.66% |
| An adjuvant treatment is indicated after excision of LM in 10mm margins | 10.00% | 90.00% |
| Radiotherapy is the best option as an adjuvant modality | 20.00% | 80.00% |
| Imiquimod is the best option as an adjuvant modality | 83.33% | 16.67% |
| When I use imiquimod 5% cream as an adjuvant modality, I apply it 3 days per week for 4 weeks | 10.00% | 90.00% |
| When I use imiquimod as an adjuvant modality, I apply it 5 days per week for 6 weeks | 50.00% | 50.00% |
| When I use imiquimod as an adjuvant modality, I apply it 7 days per week for 6 weeks | 50.00% | 50.00% |
| In case of large difficult to treat LM, a multidisciplinary approach with tumor board involvement is the best choice | 93.10% | 6.90% |
| Tumor board should consider patient's age, comorbidities, patient's compliance and available facilities of the Unit (i.e. Mohs unit) | 100% | 0% |
| Age threshold to start thinking alternative treatment options than the choice treatment: 80 years old | 33.33% | 66.67% |
| Age threshold to start thinking alternative treatment options than the choice treatment: over 90 years old | 43.33% | 56.66% |
| Age threshold to start thinking alternative treatment options than the choice treatment: over 75 years old if comorbidities | 60.00% | 40.00% |
| Clinical follow up schedule for LM should be 10 years as per any other in situ melanoma | 50.00% | 50.00% |
| Clinical follow up schedule for LM should be 5 years | 37.93% | 62.07% |
| Clinical follow up schedule for LM should be for ever | 62.07% | 37.93% |

## Conclusions

This Delphi study aimed to determine consensus among international experts on controversial issues related to the diagnosis, treatment, and surveillance of patients with LM/LMM. A recent survey with responses from 415 of the European Academy of Dermatology and Venereology (EADV) members showed the wide variations in the diagnostic and the therapeutic approaches for LM [36]. To the best of our knowledge, the present Delphi consensus is the

**Table 3.** Responses to statements included in Round 2.

| | Round 2 | |
|---|---|---|
| | Agree % | Disagree % |
| The final diagnosis of LM is based only on histopathologic findings | 25.93% | 74.07% |
| The final diagnosis of LM is based on integration of clinical and dermatoscopic and histopathologic findings | 92.59% | 7.40% |
| The most appropriate diagnostic biopsy techniques are multiple punch biopsies and/or broad shave biopsy | 85.18% | 14.81% |
| The most appropriate primary treatment (after biopsy) of LM is margin-controlled surgery. If this is not feasible, surgical excision to clinically unaffected narrow margins are optimal. | 85.18% | 14.82% |
| If, after the excision, histologic margins are clear, there is no need for further excision even if the clear margins are very narrow (< 1mm) | 59.25% | 40.74% |
| If pathology reports an invasive component, a wide re-excision (according to Breslow thickness) is always mandatory | 77.78% | 22.22% |
| Alternative treatments should only be considered if the treatment of choice is absolutely impossible | 59.26% | 40.74% |
| There is no specific age threshold to start thinking alternative treatment options but it's based on patient performance status | 81.48% | 18.51% |
| Radiotherapy is a possible alternative treatment | 92.60% | 7.40% |
| Wait and see might also be an option for elderly patients | 77.78% | 22.22% |
| Alternative treatments should be considered in elderly or when comorbidities | 85.18% | 14.81% |
| An adjuvant topical treatment of LM is beneficial after excision with clear histological margins | 51.85% | 48.14% |
| When Imiquimod 5% cream is used as an adjuvant treatment, it can be applied 5 or 7 days/week for 6 weeks | 70.37% | 29.63% |
| When Imiquimod 5% cream is used as an adjuvant treatment, it can be applied 5 or 7 days/week for 12 weeks | 51.85% | 48.14% |
| When Imiquimod 5% cream is used as an adjuvant treatment and there is no inflammatory response after 6 weeks, there is no reason to continue the treatment | 62.96% | 37.04% |
| When Imiquimod 5% cream is used as an adjuvant treatment and it has to be discontinued because of adverse reactions earlier than 6 weeks, then it should be re-initiated in order to complete the 6-weeks cycle | 66.67% | 33.33% |
| Patients with LM should go under annual clinical surveillance | 96.29% | 3.70% |

**Table 4.** Responses to statements included in Round 3.

| | Round 3 |
|---|---|
| How often do you use Imiquimod 5% cream as an adjuvant treatment after the excision of a LM with histopathologically clear margins? | |
| always or almost always | 12.00% |
| sometimes | 40.00% |
| never or almost never | 48.00% |
| Only if you answered "sometimes" on Q1, which of the following factors influencing your decision to use Imiquimod in adjuvant modality (multiple answers are possible) (PLEASE SKIP the Q2 if you answered always/never in Q1) | |
| age | 20.00% |
| sex | 0% |
| location | 0% |
| narrow margins | 70.00% |
| Only for doctors using IMI as adjuvant: Which is your treatment schedule for imiquimod 5% cream as adjuvant therapy (PLASE SKIP this question if you answered never in Q1) | |
| 5-7 times per week for 6 weeks | 69.23% |
| 5-7 times per week for 12 weeks | 15.38% |
| 5-7 times per week until the onset of inflammatory response | 15.38% |
| Other (please specify) | 0% |

first initiative with the goal of characterizing, describing, and homogenizing the different approaches to LM globally.

Regarding the diagnosis of LM, strong consensus was achieved on the use of a combined approach that should include clinical and dermoscopic examination, in line with current guidelines that reflect routine practice in many countries [13,37,38]. Dermoscopy has been used in clinical setting over decades to diagnose LM and to identify early LM recurrences [9]. More recently, RCM has served as a useful adjunct for LM diagnosis and margin mapping, although RCM use is limited by a relatively scarce availability in most centers and the need for extensive training [39-48].

A large consensus agreed to obtain multiple punch biopsies or a broad shave biopsy to minimize the risk of underestimation of LM. A study by Ng et al showed that single punch biopsies were associated with risk of histopathologic misdiagnosis (OR 16.6), adverse outcomes (OR 20), and incorrect microstaging (OR 5.1) when compared with excisional biopsies [49]. Shave biopsies were not associated with adverse outcomes but with misdiagnosis (OR 2.6) and incorrect microstaging (OR 2.3) when compared with excisional biopsies, albeit at a lower magnitude than single punch biopsy. Multiple punch biopsies were not evaluated in that study. Ideally, the area to be biopsied should be chosen based on dermoscopy or RCM, although this aspect was not included in the questionnaires [40,50].

Regarding the best treatment modality, surgical excision was considered the best option for LM treatment and, more specifically, surgery with controlled margins was the treatment of choice, if available. Multiple retrospective studies have demonstrated a lower local recurrence rates when using margin-controlled modalities, though no prospective randomized trials have compared conventional excision with MMS or staged excision for local recurrence [20,51]. In addition, some studies have shown that clinical margins wider than 5-mm may be necessary for histopathological clearance of LM [52,53]. This translates into standard 5-mm wide local excision clinical margins being associated with recurrence rates of up to 20% [20,54-58]; although data being of poor quality and robust studies are needed [59]. The main limitation to margin-controlled techniques is the need for extensive training in surgery involving comprehensive margin assessment, a dedicated histotechnology laboratory for MMS, and the need for expert dermatopathologists with quick turn-around time for staged excision with permanent sections, which limits access to these techniques [20,59].

When surgery is not feasible or is declined by the patient due to cosmetic, functional or comorbid factors, imiquimod 5% cream as monotherapy was regarded as the treatment of choice. There was no agreement on the best therapeutic regimen, but 5-7 times per week for 6-12 weeks (30-60 applications) was the preferred schema. A systematic review by Tio et al including 471 patients using imiquimod for LM showed an overall complete clinical clearance of 78% and a histopathological clearance of 77% [23]. Also, the use of imiquimod for more than 60 applications during a treatment period of 12 weeks had 7.8 times greater odds of complete clearance compared to less than 60 total applications. Based on published data and our study findings, imiquimod should be used for at least 60 applications if possible, when used as primary (monotherapy) treatment.

Another use of imiquimod is in the adjuvant setting when narrow or histologically positive LM margins are found. In the current study, there was no consensus on whether imiquimod should be used after excision of LM in the setting of clear histopathologic margins, with an equal number of positive and negative answers. The precise treatment schedule was not evaluated in the present Delphi consensus, and further studies are warranted for clarification. A multicenter study in seven European centers including 149 patients with LM found that surgical excision with narrow histopathological margins followed by imiquimod 7 times per week for 6 weeks achieved a clearance rate of 94.4% at a mean follow up of 32.5 months [26]. Another study including 45 LM cases used adjuvant imiquimod 3-5 times/week for 12 weeks (30 – 60 applications) [60]. They found a 94% clearance rate in patients with narrow-margins surgical resection or complete clinical but not histopathologic clearance of LM.

Regarding additional management of LM after surgical excision according to the clinical and histopathologic margins, consensus was only reached for a few statements. Specifically, the group agreed that re-excision is not mandatory at any age when histopathologic margins are free and clinical surgical margins were between 5 and 10 mm. The group also agreed that re-excision is not always mandatory when histopathologic margins are free and clinical surgical margins were histologic narrower than 5mm. The survey did not evaluate for the specific histological margin of clearance needed (ie 2 mm versus 3 mm). There was no agreement on the need for re-excision in case of histopathologically positive surgical margins. Although the lack of agreement on the latter points does not allow direct recommendations, it reflects a more conservative approach for LM as compared to other melanoma in situ subtypes. Strong agreement was achieved on the management in case of presence of an invasive component, which should follow surgical guidelines according to Breslow thickness [27].

Finally, as LM can recur more than 10 years after initial treatment and due to the high-risk of developing another neoplasm (either melanoma or keratinocyte cancers), there was agreement on life-long follow-up that should be performed using clinical examination, dermoscopy and, if available, RCM [40].

This study was based on a Delphi consensus of experts, which was restricted to a highly selected group of participants and might be subject of selection bias. Only dermatologists participated and no surgical oncologists, medical oncologists, plastic surgeons, radiation oncologists, or surgical pathologists were included. Some specific scenarios might have not been addressed (eg presence of desmoplastic melanoma). Dermoscopic and RCM criteria were not included in the survey.

LM is a complex melanoma subtype typically affecting cosmetic and functionally sensitive sites. It has specific challenges compared to other melanoma subtypes. This survey represents a framework on which to base further LM studies and evidence to help develop future clinical practice guidelines which are based on high level evidence. There is a need for prospective studies on LM.

## Acknowledgement

We thank Dr Marica Mirra and Margherita Raucci for their technical assistance.

## References

1. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med.* 2005;353(20): 2135-2147. DOI: 10.1056/NEJMoa050092. PMID: 16291983.
2. FFreedman JA, Tyler DS, Nevins JR, Augustine CK. Use of gene expression and pathway signatures to characterize the complexity of human melanoma. *Am J Pathol.* 2011;178(6):2513-2252. DOI: 10.1016/j.ajpath.2011.02.037. PMID: 21641377. PMCID: PMC3124358.
3. DDeWane ME, Kelsey A, Oliviero M, Rabinovitz H, Grant-Kels JM. Melanoma on chronically sun-damaged skin: Lentigo maligna and desmoplastic melanoma. *J Am Acad Dermatol.* 2019;81(3):823-833. DOI: 10.1016/j.jaad.2019.03.066. PMID: 30930085.
4. C Cox NH, Aitchison TC, Sirel JM, MacKie RM. Comparison between lentigo maligna melanoma and other histogenetic types of malignant melanoma of the head and neck. Scottish Melanoma Group. *Br J Cancer.* 1996;73(7):940-944. DOI: 10.1038/bjc.1996.168. PMID: 8611411. PMCID: PMC2074252.
5. Swetter SM, Boldrick JC, Jung SY, Egbert BM, Harvell JD. Increasing incidence of lentigo maligna melanoma subtypes: northern California and national trends 1990-2000. *J Invest Dermatol.* 2005;125(4):685-691. DOI: 10.1111/j.0022-202X.2005.23852.x. PMID: 16185266.
6. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol.* 2019;80(1):208-250. DOI: 10.1016/j.jaad.2018.08.055. PMID: 30392755.
7. Koh HK, Michalik E, Sober AJ, et al. Lentigo maligna melanoma has no better prognosis than other types of melanoma. *J Clin Oncol.* 1984;2(9):994-1001. DOI: 10.1200/JCO.1984.2.9.994. PMID: 6470757.
8. GGuitera P, Pellacani G, Crotty KA, et al. The impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. *J Invest Dermatol.* 2010;130(8):2080-2091. DOI: 10.1038/jid.2010.84. PMID: 20393481.
9. SSchiffner R, Schiffner-Rohe J, Vogt T, et al. Improvement of early recognition of lentigo maligna using dermatoscopy. *J Am Acad Dermatol.* 2000;42(1 Pt 1):25-32. DOI: 10.1016/s0190-9622(00)90005-7. PMID: 10607316.
10. Farrahi F, Egbert BM, Swetter SM. Histologic similarities between lentigo maligna and dysplastic nevus: importance of clinicopathologic distinction. *J Cutan Pathol.* 2005;32(6):405-412. DOI: 10.1111/j.0303-6987.2005.00355.x. PMID: 15953373.
11. Connolly KL, Giordano C, Dusza S, Busam KJ, Nehal K. Follicular involvement is frequent in lentigo maligna: Implications for treatment. *J Am Acad Dermatol.* 2019;80(2):532-537. DOI: 10.1016/j.jaad.2018.07.071. PMID: 30266559. PMCID: PMC6333487.
12. Navarrete-Dechent C, Aleissa S, Connolly K, et al. Clinical size is a poor predictor of invasion in melanoma of the lentigo maligna type. *J Am Acad Dermatol.* 2021;84(5):1295-1301. DOI: 10.1016/j.jaad.2020.10.023. PMID: 33096134. PMCID: PMC8046713.
13. Fosko SW, Navarrete-Dechent CP, Nehal KS. Lentigo Maligna-Challenges, Observations, Imiquimod, Confocal Microscopy, and Personalized Treatment. *JAMA Dermatol.* 2018;154(8):879-881. DOI: 10.1001/jamadermatol.2018.0531. PMID: 29847677.
14. ZZoutendijk J, Tio D, Koljenovic S, van den Bos RR. Nine per cent of biopsy-proven lentigo maligna lesions are reclassified as lentigo maligna melanoma after surgery. *Br J Dermatol.* 2019;181(2):383-384. DOI: 10.1111/bjd.17714. PMID: 30716164. PMCID: PMC6850063.
15. Moreno A, Manrique-Silva E, Virós A, et al. Histologic Features Associated With an Invasive Component in Lentigo Maligna Lesions. *JAMA Dermatol.* 2019;155(7):782-788. DOI: 10.1001/jamadermatol.2019.0467. PMID: 31066867. PMCID: PMC6506897.
16. Aouidad I, Fargeas C, Romero P, et al. Histologic predictors of invasion in partially biopsied lentigo maligna melanoma. *J Am Acad Dermatol.* 2019;80(4):1150-1152. DOI: 10.1016/j.jaad.2018.10.036. PMID: 30879481.
17. Peruilh-Bagolini L, Apalla Z, González-Cuevas R, et al. Dermoscopic predictors to discriminate between in situ and early invasive lentigo maligna melanoma: A retrospective observational study. *J Am Acad Dermatol.* 2020;83(1):269-271. DOI: 10.1016/j.jaad.2020.03.030. PMID: 32199898.
18. Rzepecki AK, Hwang CD, Etzkorn JR, et al. The rule of 10s versus the rule of 2s: High complication rates after conventional excision with postoperative margin assessment of specialty site versus trunk and proximal extremity melanomas. *J Am Acad Dermatol.* 2021;85(2):442-452. DOI: 10.1016/j.jaad.2018.11.008. PMID: 30447316.
19. Robinson M, Primiero C, Guitera P, et al. Evidence-Based Clinical Practice Guidelines for the Management of Patients with Lentigo Maligna. *Dermatology.* 2020;236(2):111-116. DOI: 10.1159/000502470. PMID: 31639788.
20. Hazan C, Dusza SW, Delgado R, Busam KJ, Halpern AC, Nehal KS. Staged excision for lentigo maligna and lentigo maligna melanoma: A retrospective analysis of 117 cases. *J Am Acad Dermatol.*

2008;58(1):142-148. DOI: 10.1016/j.jaad.2007.09.023. PMID: 18029055.

21. Fogarty GB, Hong A, Economides A, Guitera P. Experience with Treating Lentigo Maligna with Definitive Radiotherapy. *Dermatol Res Pract*. 2018;2018:7439807. DOI: 10.1155/2018/7439807. PMID: 30105052. PMCID: PMC6076978.
22. Drakensjö IRT, Rosen E, Frohm Nilsson M, Girnita A. Ten-year Follow-up Study of Grenz Ray Treatment for Lentigo Maligna and Early Lentigo Maligna Melanoma. *Acta Derm Venereol*. 2020;100(17):adv00282. DOI: 10.2340/00015555-3631. PMID: 32926174. PMCID: PMC9274915.
23. Tio D, van der Woude J, Prinsen CAC, Jansma EP, Hoekzema R, van Montfrans C. A systematic review on the role of imiquimod in lentigo maligna and lentigo maligna melanoma: need for standardization of treatment schedule and outcome measures. *J Eur Acad Dermatol Venereol*. 2017;31(4):616-624. DOI: 10.1111 /jdv.14085. PMID: 27987308.
24. Donigan JM, Hyde MA, Goldgar DE, Hadley ML, Bowling M, Bowen GM. Rate of Recurrence of Lentigo Maligna Treated With Off-Label Neoadjuvant Topical Imiquimod, 5%, Cream Prior to Conservatively Staged Excision. *JAMA Dermatol*. 2018;154(8):885-889. DOI: 10.1001/jamadermatol.2018.0530. PMID: 29847610. PMCID: PMC6143025.
25. Wildemore JK 4th, Schuchter L, Mick R, et al. Locally recurrent malignant melanoma characteristics and outcomes: a single-institution study. *Ann Plast Surg*. 2001;46(5):488-494. DOI: 10.1097/00000637-200105000-00006. PMID: 11352421.
26. Lallas A, Moscarella E, Kittler H, et al. Real-world experience of off-label use of imiquimod 5% as an adjuvant therapy after surgery or as a monotherapy for lentigo maligna. *Br J Dermatol*. 2021;185(3):675-677. DOI: 10.1111/bjd.20407. PMID: 33894006.
27. Florell SR, Boucher KM, Leachman SA, et al. Histopathologic recognition of involved margins of lentigo maligna excised by staged excision: an interobserver comparison study. *Arch Dermatol*. 2003;139(5):595-604. DOI: 10.1001/archderm.139.5.595. PMID: 12756096.
28. W Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. *Br J Dermatol*. 1987;116(3):303-310. DOI: 10.1111/j.1365-2133.1987. tb05843.x. PMID: 3567069.
29. GGreveling K, Wakkee M, Nijsten T, van den Bos RR, Hollestein LM. Epidemiology of Lentigo Maligna and Lentigo Maligna Melanoma in the Netherlands, 1989-2013. *J Invest Dermatol*. 2016;136(10):1955-1960. DOI: 10.1016/j.jid.2016.06.014. PMID: 27349862.
30. Kurtansky NR, Dusza SW, Halpern AC, et al. An Epidemiologic Analysis of Melanoma Overdiagnosis in the United States, 1975-2017. *J Invest Dermatol*. 2022;142(7):1804-1811.e6. DOI: 10.1016/j.jid.2021.12.003. PMID: 34902365. PMCID: PMC9187775.
31. Welch HG, Mazer BL, Adamson AS. The Rapid Rise in Cutaneous Melanoma Diagnoses. *N Engl J Med*. 2021;384(1):72-79. DOI: 10.1056/NEJMsb2019760. PMID: 33406334.
32. McLeod M, Choudhary S, Giannakakis G, Nouri K. Surgical treatments for lentigo maligna: a review. *Dermatol Surg*. 2011;37(9):1210-1228. DOI: 10.1111/j.1524-4725.2011.02042.x. PMID: 21631635.
33. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol*. 2014;67(4): 401-409. DOI: 10.1016/j.jclinepi.2013.12.002. PMID: 24581294.
34. NNavarrete-Dechent C, Liopyris K, Molenda MA, et al. Human surface anatomy terminology for dermatology: a Delphi consensus from the International Skin Imaging Collaboration. *J Eur Acad Dermatol Venereol*. 2020;34(11):2659-2663. DOI: 10.1111/jdv.16855. PMID: 32770737. PMCID: PMC8236240.
35. K Katragadda C, Finnane A, Soyer HP, et al. Technique Standards for Skin Lesion Imaging: A Delphi Consensus Statement. *JAMA Dermatol*. 2017;153(2):207-213. DOI: 10.1001/jamadermatol.2016.3949. PMID: 27892996.
36. Tio D, Prinsen CAC, Dréno B, Hoekzema R, Augustin M, van Montfrans C. Variation in the diagnosis and clinical management of lentigo maligna across Europe: a survey study among European Association of Dermatologists and Venereologists members. *J Eur Acad Dermatol Venereol*. 2018;32(9):1476-1484. DOI: 10.1111/jdv.14850. PMID: 29419913.
37. Barlow JO, Maize J Sr, Lang PG. The density and distribution of melanocytes adjacent to melanoma and nonmelanoma skin cancers. *Dermatol Surg*. 2007;33(2):199-207. DOI: 10.1111/j.1524-4725.2006.33039.x. PMID: 17300606.
38. Weyers W, Bonczkowitz M, Weyers I, Bittinger A, Schill WB. Melanoma in situ versus melanocytic hyperplasia in sun-damaged skin. Assessment of the significance of histopathologic criteria for differential diagnosis. *Am J Dermatopathol*. 1996;18(6): 560-566. DOI: 10.1097/00000372-199612000-00002. PMID: 8989926.
39. Navarrete-Dechent C, Cordova M, Aleissa S, et al. Lentigo maligna melanoma mapping using reflectance confocal microscopy correlates with staged excision: A prospective study. *J Am Acad Dermatol*. 2023;88(2):371-379. DOI: 10.1016/j .jaad.2019.11.058. PMID: 31812621. PMCID: PMC10210015.
40. Navarrete-Dechent C, Cordova M, Liopyris K, Ret al. Reflectance confocal microscopy and dermoscopy aid in evaluating repigmentation within or adjacent to lentigo maligna melanoma surgical scars. *J Eur Acad Dermatol Venereol*. 2020;34(1): 74-81. DOI: 10.1111/jdv.15819. PMID: 31325402. PMCID: PMC7592341.
41. N Navarrete-Dechent C, Aleissa S, Cordova M, et al. Incompletely excised lentigo maligna melanoma is associated with unpredictable residual disease: clinical features and the emerging role of reflectance confocal microscopy. *J Eur Acad Dermatol Venereol*. 2020;34(10):2280-2287. DOI: 10.1111/jdv.16272. PMID: 32030827. PMCID: PMC8409509.
42. Navarrete-Dechent C, Hibler BP, Cordova F, Cordova M, Rossi AM. Lentigo Maligna Margin Template for Surgical Excision Using Reflectance Confocal Microscopy and a Transparent Adhesive Dressing. *Dermatol Surg*. 2020;46(7):967-969. DOI: 10.1097/DSS.0000000000001988. PMID: 31356439. PMCID: PMC8422434.
43. Guitera P, Moloney FJ, Menzies SW, et al. Improving management and patient care in lentigo maligna by mapping with in vivo confocal microscopy. *JAMA Dermatol*. 2013 Jun;149(6):692-698. DOI: 10.1001/jamadermatol.2013.2301. PMID: 23553208.
44. Chen CS, Elias M, Busam K, Rajadhyaksha M, Marghoob AA. Multimodal in vivo optical imaging, including confocal microscopy, facilitates presurgical margin mapping for clinically complex lentigo maligna melanoma. *Br J Dermatol*. 2005;153(5): 1031-1036. DOI: 10.1111/j.1365-2133.2005.06831.x. PMID: 16225620.

45. Pellacani G, De Carvalho N, Ciardo S, et al. The smart approach: feasibility of lentigo maligna superficial margin assessment with hand-held reflectance confocal microscopy technology. *J Eur Acad Dermatol Venereol.* 2018;32(10):1687-1694. DOI: 10.1111/jdv.15033. PMID: 29704275.
46. Yélamos O, Cordova M, Blank N, et al. Correlation of Handheld Reflectance Confocal Microscopy With Radial Video Mosaicing for Margin Mapping of Lentigo Maligna and Lentigo Maligna Melanoma. *JAMA Dermatol.* 2017;153(12):1278-1284. DOI: 10.1001/jamadermatol.2017.3114. PMID: 29049429. PMCID: PMC5730495.
47. Menge TD, Hibler BP, Cordova MA, Nehal KS, Rossi AM. Concordance of handheld reflectance confocal microscopy (RCM) with histopathology in the diagnosis of lentigo maligna (LM): A prospective study. *J Am Acad Dermatol.* 2016;74(6):1114-1120. DOI: 10.1016/j.jaad.2015.12.045. PMID: 26826051.
48. Mehta PP, Oh Y, Cordova M, et al. Patterns of the use of reflectance confocal microscopy at a tertiary referral dermatology clinic. *J Am Acad Dermatol.* 2022;87(4):882-884. DOI: 10.1016/j.jaad.2021.11.054. PMID: 34875302. PMCID: PMC9166163.
49. Ng JC, Swain S, Dowling JP, Wolfe R, Simpson P, Kelly JW. The impact of partial biopsy on histopathologic diagnosis of cutaneous melanoma: experience of an Australian tertiary referral service. *Arch Dermatol.* 2010;146(3):234-239. DOI: 10.1001/archdermatol.2010.14. PMID: 20231492.
50. Navarrete-Dechent C, Cordova M, Sahu A, et al. Optical imaging guided- 'precision' biopsy of skin tumors: a novel approach for targeted sampling and histopathologic correlation. *Arch Dermatol Res.* 2021;313(7):517-529. DOI: 10.1007/s00403-020-02126-6. PMID: 32844312. PMCID: PMC10185006.
51. Kelley LC, Starkus L. Immunohistochemical staining of lentigo maligna during Mohs micrographic surgery using MART-1. *J Am Acad Dermatol.* 2002;46(1):78-84. DOI: 10.1067/mjd.2002.119197. PMID: 11756950.
52. Navarrete-Dechent C, Aleissa S, Ariyan C, Busam KJ, Nehal KS. Comment on "Comparison of surgical margins for lentigo maligna versus melanoma in situ". *J Am Acad Dermatol.* 2019;81(4):e115-e116. DOI: 10.1016/j.jaad.2019.05.104. PMID: 31233855.
53. Kunishige JH, Doan L, Brodland DG, Zitelli JA. Comparison of surgical margins for lentigo maligna versus melanoma in situ. *J Am Acad Dermatol.* 2019;81(1):204-212. DOI: 10.1016/j.jaad.2019.01.051. PMID: 31014825.
54. National Comprehensive Cancer Network. Melanoma (Version 2.2018).
55. Agarwal-Antal N, Bowen GM, Gerwels JW. Histologic evaluation of lentigo maligna with permanent sections: implications regarding current guidelines. *J Am Acad Dermatol.* 2002;47(5):743-748. DOI: 10.1067/mjd.2002.124085. PMID: 12399768.
56. Kunishige JH, Doan L, Brodland DG, Zitelli JA. Comparison of surgical margins for lentigo maligna versus melanoma in situ. *J Am Acad Dermatol.* 2019;81(1):204-212. DOI: 10.1016/j.jaad.2019.01.051. PMID: 31014825.
57. Karanetz I, Stanley S, Knobel D, et al. Melanoma Extirpation with Immediate Reconstruction: The Oncologic Safety and Cost Savings of Single-Stage Treatment. *Plast Reconstr Surg.* 2016;138(1):256-261. DOI: 10.1097/PRS.0000000000002241. PMID: 27351470.
58. Navarrete-Dechent C, Aleissa S, Ariyan C, Busam KJ, Nehal KS. Melanoma in situ margins: 9 mm for ALL cases may not be appropriate. *J Am Acad Dermatol.* 2019. DOI:10.1016/j.jaad.2019.05.104
59. Adalsteinsson JA, Stoj VJ, Algzlan H, Swede H, Torbeck RL, Ratner D. Limitations in the literature regarding Mohs surgery and staged excision for melanoma: A critical review of quality and data reporting. *J Am Acad Dermatol.* 2023;88(2):404-413. DOI: 10.1016/j.jaad.2021.02.091. PMID: 33872715.
60. Swetter SM, Chen FW, Kim DD, Egbert BM. Imiquimod 5% cream as primary or adjuvant therapy for melanoma in situ, lentigo maligna type. *J Am Acad Dermatol.* 2015;72(6):1047-1053. DOI: 10.1016/j.jaad.2015.02.008. PMID: 25791801.