



REVIEW

# Topical Treatment of Melanoma In Situ, Lentigo Maligna, and Lentigo Maligna Melanoma with Imiquimod Cream: A Systematic Review of the Literature

Silvia Vaienti · Paolo Calzari · Gianluca Nazzaro

Received: May 30, 2023 / Accepted: July 27, 2023 / Published online: August 24, 2023  
© The Author(s) 2023

## ABSTRACT

**Introduction:** The classical management of melanoma is surgery, but this can be challenging because of several factors, such as age, body area, lesion size, among others. Topical imiquimod may be a therapeutic option for the treatment of melanoma in situ and lentigo maligna melanoma due to its efficacy, tolerability, and non-invasiveness. The purpose of this systematic review is to assemble current evidence on the treatment of non-metastatic melanoma with topical imiquimod.

**Methods:** The PubMed/MEDLINE and Cochrane Library databases were searched as the primary sources using the main search terms “imiquimod” combined with “lentigo maligna” and “melanoma” with the command “AND.” Articles were identified, screened, and

extracted for relevant data, following the PRISMA guidelines.

**Results:** A total of 87 studies covering 1803 lesions treated with imiquimod cream were identified and included in this systematic review. Forty-nine studies were case reports, 16 were retrospective analyses, 13 were open label trials, six were case series; one study was a controlled randomized trial, one was a randomized trial, and one was a single-arm phase III trial. Because of the high number of low-evidence studies, the overall risk of bias resulted high. In 55 studies, imiquimod 5% was used in monotherapy as the primary treatment; only in one study was imiquimod 3.75% introduced. In most cases, the topical treatment was applied once daily, with the exception of nine cases where an increased daily dosage was prescribed. The total duration of the treatment regimen was extremely variable and depended on body area and tolerability, with differences among patients of the same study. In six studies, imiquimod was used as neoadjuvant therapy before the surgical excision, and in 11 studies it was used after surgery as complementary or adjuvant therapy. In total, 1133 of the 1803 (62.8%) lesions were reported to be cleared after the treatment, taking into account that not all of the patients completed the treatment. Of these 1133 lesions, histological clearance was achieved in 645 (56.9%) lesions and clinical clearance only was achieved in 490 (43.2%) lesions; relapse occurred in 107 lesions.

---

S. Vaienti  
Section of Dermatology and Venereology,  
Department of Medicine, University of Verona,  
Verona, Italy

P. Calzari  
Department of Pathophysiology and  
Transplantation, University of Milan, Milan, Italy

G. Nazzaro (✉)  
Dermatology Unit, Foundation IRCCS, Ca' Granda  
Ospedale Maggiore Policlinico, Via Pace 9, 20122  
Milan, Italy  
e-mail: Gianluca.nazzaro@gmail.com

**Conclusions:** The heterogeneity of the studies included in this systematic review precludes the drawing of any relevant conclusions regarding the application of imiquimod. Its efficacy in melanoma in situ and lentigo maligna melanoma has been demonstrated, but further evidence from controlled studies concerning the modalities is missing.

**Keywords:** Melanoma; Lentigo maligna; Imiquimod; Skin cancer; Oncology; Systematic review

### Key Summary Points

The classical management of melanoma is surgery, but it can be challenging because of several factors, such as age, body area, lesion size, among others.

The purpose of this systematic review is to assemble current evidence on the treatment of non-metastatic melanoma with topical imiquimod.

A total of 87 studies covering 1803 lesions were included in this systematic review, of which 49 were case reports, 16 were retrospective analysis, 13 were open label trials, six were case series; one was a controlled randomized trial, one a randomized trial, one was a single-arm phase III trial. Because of the high number of low-evidence studies, the overall risk of bias was high.

Of the 1803 lesions, 1133 (62.8%) cleared after the treatment and 107 lesions relapsed. The efficacy of imiquimod cream in melanoma in situ and lentigo maligna melanoma was demonstrated, but uniform evidence regarding the modalities of treatment is lacking.

## INTRODUCTION

Melanoma is a malignant tumor originating from melanocytes. It can involve every tissue where there are melanocytes (cutis, mucosae, conjunctiva, uvea, meninges, etc.), but the cutis is the most frequently affected area [1, 2]. For example, cutaneous melanoma (CM) is classified according to assessment of the infiltration of the melanoma in situ (MIS), whether atypical melanocytes are confined to the epidermis, and whether there is invasive melanoma in which cancerous cells invade dermis and other structures. In turn, invasive melanoma can be classified into four clinic-pathological subtypes: superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM) [1, 3].

Lentigo maligna (LM) and LMM represent a continuous spectrum. LM is a slow-growing melanoma in situ that appears mostly in UV-exposed regions, such as the face [4]. LMM is an invasive melanoma with LM elements and the metastatic potential of melanoma [5]. The classic management of non-invasive melanoma is surgery, but this approach can be challenging in some cases or non-realizable. For example, the lesion may be close to important anatomical structures, show unclear margin, or be very large; in these situations, reaching the surgical radicality can be difficult [6]. Furthermore, many patients are elderly with comorbidities, and the surgical approach may not be the best choice [7, 8]. In these situations, a non-surgical treatment, such as radiotherapy [9], cryotherapy [10], laser [11], or topical imiquimod [12], may be useful. At the present time, topical imiquimod is used to treat LM, MIS, and, more rarely, LMM as an off-label therapy [13–17]. The registered use is for adults affected by small non-nodular basal cell carcinomas, actinic keratoses, and warts on the anogenital area [18].

High-quality evidence supporting the role of imiquimod as primary therapy is lacking, but a number of retrospective analyses and trials have demonstrated how this drug can be a good alternative to surgery. This option could be considered in selected cases not eligible for

surgery or radiotherapy, or for incompletely excised tumors. Another use could be as neoadjuvant, adjuvant, or complementary therapy [7, 19]. However, topical imiquimod should be chosen with caution for younger patients affected by LM because this patient population has a higher lifetime risk of developing LMM than older patients ( $\geq 65$  years) [20].

Imiquimod is a synthetic drug belonging to the imidazoquinolone family [21] and initially developed as an antiviral [22, 23], although its antiviral action has never been demonstrated. In contrast, the antitumoral activity of imiquimod was discovered in pre-clinical models [24]. Further, its chemical properties, such as hydrophobicity and small size ( $M_r = 240.3$ ) allow imiquimod to penetrate the epidermal barrier, making it a perfect molecule for topical use [25]. Imiquimod stimulates the innate immune system, acting primarily on cutaneous dendritic cells (DC) that are able to respond to low concentrations of drugs [26–29]. This activation of DC activation seems to be mediated by the interaction between imiquimod and Toll-like receptors (TLRs) 7 and 8, resulting in activation of nuclear factor-kappa B (NF- $\kappa$ B) and the consequent production of pro-inflammatory cytokines, such as interferon alpha (IFN $\alpha$ ), tumor necrosis factor alpha (TNF $\alpha$ ), and other important cytokines with a strong Th1-weighted cellular response. The outcome is an activation and immigration of cytotoxic T cells. Imiquimod also induces 2'5'-oligoadenylate synthase with subsequent stimulation of NK cells and the induction of perforin in cytotoxic T cells. Both of these mechanisms may increase the antitumoral activities of imiquimod [24]. Imiquimod can also bind the adenosine receptor (AR). When activated, AR can suppress the translation of pro-inflammatory cytokines, thereby downregulating the immune response. Imiquimod, by blocking AR, impedes a negative feedback mechanism that limits inflammation, improving the immunity response to cancer [28, 29]. Finally, the topical use of imiquimod increases the expression of cell death receptor CD95 (Fas) 57 and decreases the expression of antiapoptotic protein with an increase of tumor cell apoptosis. This pro-apoptotic activity can

be direct or indirect, with the former effect depending on drug concentration and the latter appearing to be mediated by TLR activation [25].

The adverse effects associated with imiquimod are primarily due to its mechanism of action. The most common adverse effects are local erythema, burning, edema, and crusts [30]. The development of alterations in skin pigmentation, such as post-inflammatory hyper and hypopigmentation, are also possible [31]. In their study, Di Bartolomeo et al. observed the formation of perifollicular blue gray dots after 12 weeks of treatment with imiquimod 5% [32]. These authors speculated that these structures corresponded to dermal melanophages activated by the imiquimod-related inflammatory process [33]. Hypopigmentation or vitiligo-like depigmentation may also be observed. The latter, unlike the classic forms of vitiligo, can show spontaneous repigmentation [34]. Furthermore, halo nevi could occur in areas outside the sites of imiquimod cream application [34, 35]. Moreover, some patients can experience constitutional symptoms due to cytokine release, but these are self-limiting [20].

It is necessary to pay attention to the use of imiquimod near sensitive structures such as the eyes. Murchinson et al. reported the use of imiquimod 5% on a lesion near the right eye, with subsequent chemosis of the lateral palpebral conjunctiva, a decrease of visual acuity, diffuse punctate keratopathy, and corneal edema [36]. All of these adverse effects were resolved by interrupting the topical treatment with imiquimod and using petroleum jelly, cool compresses, and ophthalmic erythromycin. After 1 month, a small crusting area remained on the cheek, without residual melanosis. The visual acuity was 20/30 on the right eye with a clear cornea and without chemosis. In another study, Conforti et al. [37] treated a LM close to the conjunctiva without severe side effects, using a combination of topical steroid and hyaluronic acid eye-drops. These authors concluded that conjunctival inflammation can be easily treated without permanent ocular side effects and for that reason the use of imiquimod 5% is safe in the periorbital area. On the other hand, the corneal edema caused by imiquimod

5% could induce fibrosis and lymphohistiocytic infiltrate with a consequent compression of lymphatic vessels and the development of lymphoedema that can potentially persist for years, as reported by Tio et al. [31]. Therefore, in order to limit adverse effects, it is important to adapt the number of weeks of imiquimod application based on the patient's inflammatory reaction [31].

Here we report the results of a systematic review that was initiated in order to assemble current evidence on the treatment of non-metastatic melanoma with topical imiquimod, to better understand the modalities, and to propose a non-invasive option in patients who are not eligible for surgery.

## MATERIALS AND METHODS

This systematic literature review was conducted using PubMed/MEDLINE and Cochrane Library as primary sources. All articles in these databases up to March 2023 were considered, with the last search date being 16 March 2023. The main search terms were “imiquimod” combined with “lentigo maligna” and “melanoma” with the command AND.

All articles in English on the efficacy of imiquimod for the treatment of LM, MIS, and LMM in human subjects were included. Articles identified in the search on invasive melanoma (except for LMM), melanoma metastasis, and non-melanoma skin cancer were excluded, as were articles on molecular and *in vitro* studies. Previous reviews were also excluded, but the respective bibliography of each identified review was used to identify articles that may have been missed in the primary search. Commentaries were also excluded.

Articles were identified, screened, and extracted for relevant data in accordance with the PRISMA guidelines [38] by two reviewers who worked independently. The articles included case reports, case series, open label trials, retrospective analyses, clinical trials, and randomized studies. Case reports and old references were included because of the suboptimal evidence on the topic.

For each study the following items were considered: epidemiologic features of patients; diagnosis (LM/MIS/LMM); number of treated lesions; localization of lesions; diagnostic method (histology/clinical); protocol of treatment; margins of the lesions included in treated area; response after the treatment, specifying the verification method (complete/partial/none; histology/clinical/other); time of long-term follow-up (as range or average time); and number of relapses, specifying the verification method (histology/clinical/other) at the time of the long-term follow-up. Missing data were classified as “not recorded” or “not applicable.”

The quality of the enrolled studies was appraised using the revised Cochrane risk-of-bias tool for randomized controlled trials (RCTs) [39] and the overall risk of bias for each study was judged as low, high, or of some concern.

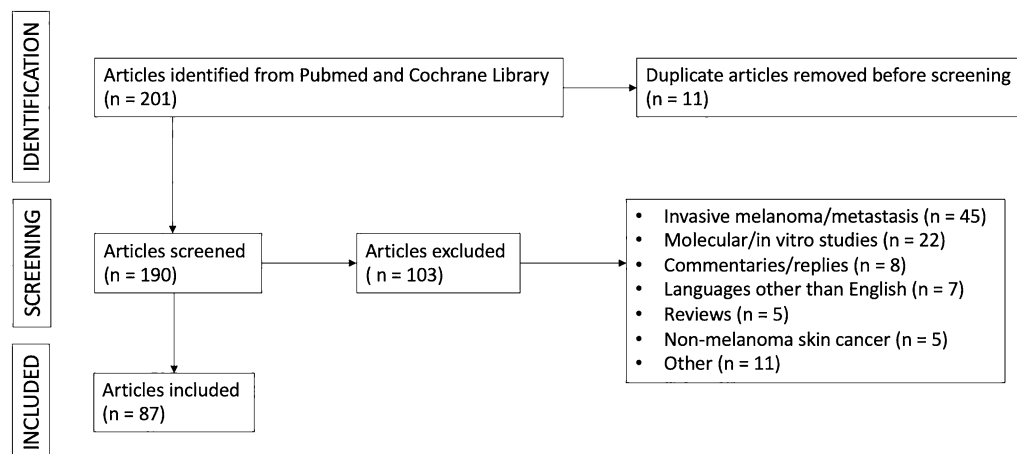
This systematic review is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## RESULTS

A total of 87 studies covering 1803 lesions treated with imiquimod cream were included in this review. The selection process is shown in Fig. 1.

The main features of the selected studies are reported in Table 1. Of the selected studies, 49 were case reports, 16 were retrospective analysis, 13 were open label trials, six were case series; one was a RCT, one a randomized trial, one a single arm phase III trial. Because of the high number of low-evidence studies, the overall risk of bias resulted high.

In the included studies, age was expressed as range, mean, or median, depending on the individual study. A median age was not always available. The lowest and highest age was 33 [82] and 96 years [96], respectively; the lowest and highest mean age was 60 [43] and 80 years [113], respectively. Most of the patients selected for imiquimod treatment were elderly and, presumably, with comorbidities. The latter was often not reported in the studies analyzed. Some young patients were also selected for



**Fig. 1** Flow chart of the selection of the studies included in the review

imiquimod treatment, especially where difficulties were encountered with a surgical approach regarding body localization of the lesion, i.e., genital area [16, 94].

In all cases the initial diagnosis of LM/MIS/LMM was histologically confirmed through punch biopsies, partial excision, or excision with positive margins, with one exception [63] which was confirmed with videodermoscopy. Only four studies reported on the treatment of LMMs [88, 101, 110, 112, 117].

The majority of the lesions were located on the head/neck area; the remaining body areas treated included limbs, extremities, back, thorax, and genitals. The lesions treated were not only the first diagnosis, but also relapses and results of incomplete previous surgeries.

In 55 studies, imiquimod 5% was used as monotherapy in the primary treatment; only in one study was imiquimod 3.75% introduced into the treatment regimen [115]. In most cases, the topical treatment was applied once/daily; the exceptions were ten cases [12, 41, 59, 64, 87, 90, 97, 103] where an increased dosage per day was applied. In four cases [17, 59, 90, 97], the authors of the study required patients to apply imiquimod cream in occlusion. The ranges of number of days/weeks of treatment and the total duration of the treatment regimen were extremely variable (1–7 days/weeks and 1–60 weeks, respectively) and depended on the body area and the tolerability of the patient, with differences among patients in the same

study as well. Some authors reported the number of patients who did not complete the treatment [43, 75, 77, 85] and/or who had a therapeutic break during the treatment protocol [16, 17, 50, 56, 68, 86, 93].

In six studies [44, 60, 75, 80, 93, 99], imiquimod was used as neoadjuvant therapy before the surgical excision, and in 11 studies [34, 45, 52, 54, 56, 83, 84, 86, 101, 105, 109] imiquimod was used after the surgical, possibly serial, excision with partial or with positive margins, respectively as complementary or adjuvant therapy (in some cases not all the population of the study did the surgical procedure). In one study [112], monotherapy and adjuvant therapy were compared. In another study [113], adjuvant, complementary, and monotherapy were compared. Finally, in one study [117] adjuvant and monotherapy were compared.

In ten studies [60, 69, 86, 95, 96, 99, 107, 109, 114, 117], topical retinoids (tazarotene, tretinoin) were added to the topical treatment with imiquimod with different modalities (before/after/at the same time of the treatment or only in case of insufficient inflammatory response). In one case [77], the neoadjuvant therapy with imiquimod only was compared to neoadjuvant therapy with imiquimod + tazarotene. In three [58, 59, 112] and two studies [81, 91], imiquimod was associated with cryotherapy and with laser therapy, respectively.

**Table 1** Results of literature search

Reference	Type	$N_p$	$N_i$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Ahmed and Berth-Jones [40] (2000)	CR	1	1	88	LM: forehead	H	Darkest area: imiquimod 5% once/d 3 $\tau$ /w for the first 4 w then daily, alternate days or 3 $\tau$ /w if inflammation for 7 m	NR	Complete (H)	9 m	0 (C)
Borucki and Metzger [17] (2003)	CR	1	1	73	LM: cheek	H	Whole area: same regimen as for the darkest area for the last 3 m Imiquimod 5% under occlusion for 12 h 3 $\tau$ /w for 4 w, 2 w break, then once/w for 8 w	1	Complete (H)	4 m	0 (C)
Chapman et al. [41] (2003)	CR	1	1	55	LM: cheek	H	Imiquimod 5% once-twice/d for 3 m	NR	Complete (H)	NR	NR
Epstein [42] (2003)	CR	1	1	90	LM: cheek	H	Imiquimod 5% once/d alternate days for 5 w	NR	Complete (C)	18 m	0 (C)
Fisher et al. [30] (2003)	CR	1	2 (primary lesion + recurrence)	87	LM: cheek	H	Primary lesion: imiquimod 5% once/d 3 $\tau$ /w for 14 w Recurrence: NR	NR	Primary lesion: Partial/none (H). Recurrence: complete (H)	17 m (recurrence)	0 (C)
Naylor et al. [43] (2003)	OLT	30	30	42–91 $\mu$ (male) = 69 $\mu$ (female) = 60	LM: head (26), upper extremity (3), thorax (1)	H	Imiquimod 5% daily for 12 w (Note: only in 28 cases was the treatment completed)	2	Complete: 26 (H) None: 2 (H)	12 m	0 (C)
Fleming et al. [44] (2004)	OLT	6	6	42–79	LM: face (5), forearm (1)	H	Imiquimod 5% once/d 7 $\tau$ /w for 6 w + surgical excision (5-mm margins)	1	Complete: 1 (H) Partial: 3 (H) None: 1 (H)	NA	NR

**Table 1** continued

Reference	Type	$N_p$	$N_i$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Kupfer-Bessagnet et al. [45] (2004)	CR	2	2	80–88	LM: cheek, ear	H	Partial surgery (case 1) + imiquimod 5% once/d 3 $\tau$ /w for 12–16 w	NR	Complete (H)	13–14 m	0 (C)
Michalopoulos et al. [46] (2004)	CR	1	1	62	LM: cheek	H	Imiquimod 5% once/d 5 $\tau$ /w for 4 w, then 2–3 $\tau$ /w for 12 w	NR	Complete (H)	9 m	0 (C)
Muñoz et al. [47] (2004)	CR	1	1	83	MIS: neck	H	Imiquimod 5% once/d 7 $\tau$ /w for 1 week, then twice–3 $\tau$ /w for 4 m	NR	Complete (H)	4 m	0 (C)
Powell et al. [48] (2004)	OLT	12	12	47–86 $\mu = 63.25$	LM: cheek (7), nose (2), forehead (2), preauricular (1), temple (1)	H	Imiquimod 5% once/d 3 $\tau$ /w overnight for 6 w $\pm$ daily for 6 w	2	Complete: 10 (H) None: 2 (H)	median = 6 m	0 (C)
Powell and Russell Jones [49] (2004)	CR	2	2	61–79	Amelanotic LM: cheek	H	Imiquimod 5% once/d 3 $\tau$ /w overnight for 12 w	Whole cheek	Complete (H)	9–18 m	0 (C)
Kamin et al. [50] (2005)	CR	1	1	69	LM: retroauricular	H	Imiquimod 5% once/d 5 $\tau$ /w for 24 w, 4 w break, then daily for 5 $\tau$ /w for 12 w	NR	Complete (H)	12 m	0 (C)
Wolf et al. [51] (2005)	OLT	5	6	67–80 $\mu = 73.8$	LM (5), amelanotic LM (1): forehead (2), infraorbital (1), cheek (1), nose (1), shoulder (1)	H	Imiquimod 5% once/d 7 $\tau$ /w overnight for 5–13 w	0.5–1	Complete (H)	3–18 m	0 (C)
Lonsdale-Eccles et al. [52] (2006)	CR	1	1	68	MIS: vulva	H	Partial surgical excision + imiquimod 5% once/d alternate-day for 4 m	NR	Complete (C)	18 m	0 (C)
Micantonio et al. [53] (2006)	CR	1	1	78	LM: zygomatic	H	Imiquimod 5% once/d 5 $\tau$ /w for 12 w	NR	Complete (H)	24 m	0 (C)

Table 1 continued

Reference	Type	N <sub>p</sub>	N <sub>t</sub>	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, n (verification method)
Du Plessis [54] (2007)	CR	1	1	70	LM: forehead	H	Imiquimod once/d 5 t/w for 6 w	NR	Complete (C)	3 y	0 (C)
Hopson et al. [55] (2007)	CR	1	1	67	LM: cheek	H	Imiquimod 5% once-twice/d for 5 w, 1 m break, then imiquimod 5% once/d for 4 w	NR	Complete (H)	3 m	0 (C)
Spenny et al. [56] (2007)	RA	12	12	54–83	LM: nose (4), cheek (6), lip (1), forehead (1)	H	± Surgical excision (margins involved)	NR	Complete: 6 (H), 4 (C)	9–48 m	NR
Van Meurs et al. [57] (2007)	CR	1	1	49	LM: forehead	H	Imiquimod 5% once/d 2–7 t/w for 7–44 w (± break)	2	Partial: 2 (H)	9 m	1 (H)
Basukas et al. [58] (2008)	CR	1	1	78	LM: cheek	H	Imiquimod 5% once/d 7 t/w for 6 w + cryotherapy (one session, 2 cycles 20'' each) + imiquimod 5% once/d 7 t/w for 6 m	1	Complete (H)	26 m	0 (C)
Buetiker et al. [59] (2008)	OLT	32	34	50–95 μ = 75	LM: cheek (14), eyelid (4), nose (8), temple (3), ear (3), zygomatic (1), neck (1)	H	Imiquimod 5% (± occlusion) once-twice/d for 2–20 w ± cryotherapy (one session, 2 cycles 2'' each)	0	Complete: 28 (C), 6 (H)	5–31 m	0 (C)
Cotter et al. [60] (2008)	RA	40	40	49–92 μ (male) = 72 μ (female) = 68	LM: cheek (14), nose (6), temple (5), scalp (5), ear (3), extremity (2), trunk (2), chin (1), forehead (1), neck (1)	H	Imiquimod 5% once/d 5 t/w or daily for 12 w ± 0.1% tazarotene gel once during the weekend after the first month in the absence of erythema + staged excision (margins 2 mm)	2	Complete: 30 (H) Partial/none: 10 (H)	12–34 m	0 (C)
Craythorne et al. [61] (2008)	OLT	8	8	50–92 μ = 67.25	LM: nose (3), forehead (1), cheek (2), scalp (1), ear (1)	H	Imiquimod 5% once/d 5 t/w or daily for 6–12 w	1	Complete: 1 (H), 6 (C) None: 1 (H)	2–63 m	2 (H)

**Table 1** continued

Reference	Type	N <sub>p</sub>	N <sub>i</sub>	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, n (verification method)
De Troya Martín et al. [62] (2008)	CR	2	2	89–93	LM: ear, chin	H	Imiquimod 5% once/d 5–7 t/w for 12 w	NR	Complete (H)	36 m	0 (C)
Micali et al. [63] (2008)	CR	2	2	39–48	LM: nose (2)	H (case 1) C (case 2)	Imiquimod 5% once/d 5–7 t/w overnight for 16 w	0.5	Complete (VD)	30 m	0 (C)
Mahoney et al. [64] (2008)	CR	7	7	55–78 $\mu = 67$	LM: cheek (2), nose (2), temple/lower lid (2), scalp (1)	H	Imiquimod 5% once/d 5–7 t/w for 12 w In case of insufficient inflammatory response: twice/d 5 t/w or once/d 7 t/w	0.5–1	Complete (H)	12–25 m	0 (C)
Ramsdell and Zeitouni. [65] (2009)	CR	1	1	84	LM: left side of the face (cheek, eyelid, forehead)	H	Imiquimod 5% once/d 3 t/w for 3 m for most of the lesions, for 5 months for a persistent focus on the cheek, and an additional 7 months for the eyelid	NR	Complete (H)	> 36 m	0 (C)
Missal et al. [66] (2009)	CR	2	2	59–82	LM: scalp, cheek	H	P1: Imiquimod 5% once/d 5 t/w for 2 w, then 3 t/w for 4 w, then 5 t/w for 8 w P2: Imiquimod 5% once/d 5 t/w for 13 w	2	Complete (H)	19–21 m	0 (C)
Powell et al. [67] (2009)	RA	48	48	44–90 $\mu = 70.6$	LM (46) and amelanotic LM (2): NR	H	Imiquimod 5% once/d 3 t/w overnight for 6–10 w In case of insufficient inflammatory response at w4: daily for further 6 w	2	Complete: 20 (C), 17 (H) None: 9 (C)	25–72 m	0 (C)
Ventura et al. [68] (2009)	CR	1	1	80	LM: cheek	H	Imiquimod 5% once/d 7 t/w for 4 w, 1 w break, then imiquimod 5% daily for 12 w	NR	Complete (H)	12 m	0 (C)

Table 1 continued

Reference	Type	$N_p$	$N_t$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Woodmansee et al. [69] (2009)	CR	1	1	71	LM: forehead	H	First treatment: Tazarotene 0.1% gel for 2 w, then imiquimod 5% once/d 7 $\tau$ /d for 6–8 w Recurrence: imiquimod 5% once/d 3 $\tau$ /w for 8 w	1	Complete (H)	NA	1 (H)
Martires et al. [70] (2010)	CR	1	1	60	Amelanotic LM: nose	H	Imiquimod 5% once/d overnight for 30 d	NR	None (H)	NA	NA
Demirci et al. [71] (2010)	CS	5	5	62–82 $\mu = 73$	LM: eyelid + cantus (3), eyelid + cantus + cheek (1), cantus (1)	H	Imiquimod 5% once/d 5–7 $\tau$ /w overnight for 1–22 w	1	Complete: 2 (C) Partial: 3 (C)	0–33 m	0 (C)
Missal et al. [120] (2010)	CS	14	15	-	LM: cheek (5), nose (4), neck (2), scalp (3), cantus (1)	H	Imiquimod 5% once/d 5–7 $\tau$ /w for 12–20 w	NR	Complete (H)	1–32 m	0 (C)
Sadownik et al. [72] (2010)	CR	1	1	72	MIS: vulva	H	Imiquimod 5% once/d 3 $\tau$ /w for 6 w	0	Complete (H)	10 m	0 (C)
Van Meurs et al. [73] (2010)	OLT	10	10	48–90 $\mu = 65$	LM: nose (4), cheek (3), forehead (2), chin (1)	H	Imiquimod 5% once/d 3–5 $\tau$ /w or daily overnight for 6–13 w	2	Complete: 9 (H) None: 1 (H)	11–56 m	3 (C), 1 (H)
Costa et al. [74] (2011)	CR	1	1	82	LM: cheek	H	Imiquimod 5% once/d 7 $\tau$ /d for 31 d	NR	Complete (C)	NR	NR

**Table 1** continued

Reference	Type	$N_p$	$N_i$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Ly et al. [75] (2011)	OLT	43	48	48–83 $\mu = 69$	LM: head and neck	H	Imiquimod 5% once/d 5 $\tau$ /w for 12 w (including rest period if excessive inflammation) + surgical excision within (5 mm margin)	1	Complete: 20 (H) Partial: 18 (H)	NR	NR
O'Neill et al. [76] (2011)	CR	1	1	52	LM: canthus + conjunctiva	H	4 courses of imiquimod 5% once/d 5 $\tau$ /w overnight for 6 w over 2 years	NR	Complete (C)	36 m	0 (C)
Hyde et al. [77] (2012)	RT	90	Group 1: 47 Group 2: 44	35–92 $\mu = 68.2$	LM: body area	H	Group 1: imiquimod 5% once/d 5 $\tau$ /w for 3 m <i>Note: only in 42 cases the treatment was completed</i> Group 2: imiquimod 5% once/d 5 $\tau$ /w (Monday-Friday) + tazarotene 0.1% gel 2 $\tau$ /w (Saturday and Sunday) <i>Note: only in 37 cases the treatment was completed</i>	1	Group 1 Complete: 27 (H) None: 15 (H) Group 2: Complete: 29 (H) None: 8 (H)	$\mu = 42$ m	0 (C)
Lapresta et al. [78] (2012)	CR	1	1	67	Amelanotic LM: nose	H	+ staged excision (margins 2 mm) after 2 months after the end of the treatment $\pm$ additional staged excision	NR	Complete (H)	18 m	0 (C)

Table 1 continued

Reference	Type	$N_p$	$N_f$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Prescott et al. [79] (2012)	CR	1	1	68	MIS: vagina	H	Imiquimod 5% once/w for the first month, then twice/w for the second month, then three t/w for the third and fourth months	NR	Complete (C)	18 m	0 (C)
Wong et al. [80] (2012)	RA	27	32	42–87 $\mu = 72.4$	LM: cheek, ear, nose, periorbital, neck, temple, scalp, arm  <i>Note: 5 patients were treated for LM in two areas, non-specified which</i>	H	Imiquimod 5% once/d 3–7 t/w. One or two cycles. Clinical judgment was used to determine treatment cessation $\pm$ wide excision	1	Complete: 20 p(H) None: 7 (H)	$\mu = 3.4$ y	0 (C)
De Vries et al. [81] (2013)	OLT	12	12	50–85 $\mu = 66.6$	LM: cheek (5), nose (5), temporal (1), forehead (1)	H	Er:YAG laser + imiquimod 5% once/d for 5 d/w for 4–8 w	2	Complete: 12 (C)	10–53 m	0 (C)
Alarcon et al. [82] (2014)	OLT	20	12	33–90 $\mu = 76.5$	LM: buccal (14), nose (3), scalp (1), forehead (1), periorbital (1)	H	Imiquimod 5% once/d for 3–5 d/w for 8 w	1	Complete: 15 (H) Partial/None: 5 (H)	23–62 m	0 (C)
Sue et al. [83] (2014)	CR	2	2	81–83	MIS: foot	H	Surgical excision of invasive acral melanoma with positive margins (focus of residual MIS) + Imiquimod 5% once/d 3 t/w for 8–12 w. Two cycles for case 2	NA	Complete: 1 (H) Partial: 1 (H)	4 y (case 1)	0 (C)
Fan et al. [84] (2015)	CR	1	1	75	MIS: cheek	H	Surgical excision (margins involved) + imiquimod 5% once/d 5–3 t/w for 9 m	NR	Complete (C)	NR	NR
Kirttschig et al. [85] (2015)	OLT	27	27	44–82 $\mu$ (male) = 69 $\mu$ (female) = 71	LM: body area NR	H	Imiquimod 5% once/d (up to 3 t/d) 3–7 t/w for 12 w  <i>Note: only in 24 cases the treatment was completed</i>	1–2	Complete: 24 (H)	12 m	1 (C)

**Table 1** continued

Reference	Type	$N_p$	$N_i$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Pandit et al. [86] (2015)	RA	22	22	52–92 $\mu = 70.95$	MIS: cheek (5), forehead (2), eyelid (1) eyelid + nose (1), nose (3), scalp (2), foot (2), ear (1), upper limb (2), neck (1), hand (1), lip (1)	H	Surgical excision (margins involved) + imiquimod 5% once/d 5 $\tau/w$ for at least 12 w If insufficient inflammatory response: Imiquimod 5% + tazarotene/tretinoin 0.1% once/d 5 $\tau/w$ for 2 w, then Imiquimod 5% once/d 5 $\tau/w$ and tazarotene/tretinoin 0.1% once/d twice/ $w$	NR	Complete: 21 (H) Partial: 1 (H)	6–53 m	0 (C)
Savarese et al. [87] (2015)	CR	1	1	85	MIS: foot	H	If exaggerated inflammatory response: 2 w break then imiquimod 5% once $\tau/d$ 3 $\tau/w$	NR	Complete (C)	NR	NR
Swerter et al. [88] (2015)	RA	61	63 (5 cases excluded)	$\mu = 71$	LM/LMM: preauricular/cheek (12), scalp (8), forehead/temple/eyebrow/eyelid (8), trunk (7), lip/chin/jawline/submentum (5), arm (5), nose (4), neck (4), leg (3), ear (1), face NOS (1), hand, foot (1)	H	Imiquimod 5% once/d 3–7 $\tau/w$ for 2–60 w	2	Complete: 50 (C) Partial: 8 (H)	2–106 m	0 (C)
Elia et al. [89] (2016)	CS	12	12*	65–88 $\mu = 77$	MIS: peritocular	H	Imiquimod 5% once/d 3–7 $\tau/w$ for 1–10 w	1	Complete (H)	Median = 1.5y	0 (C)
Gaurschi et al. [90] (2016)	OLT	89	89	36–93 $\mu = 72.5$	LM: facial (84), arm/neck/shoulder (5)	H	Imiquimod 5% ( $\pm$ occlusion) once-twice/d 7 $\tau/w$ until weeping erosion developed	0	Complete: 84 (C)	Median = 4, 8 y	16 (C)

Table 1 continued

Reference	Type	$N_p$	$N_I$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Greveling et al. [91] (2016)	RA	35	35 (12 form court)	$\mu = 71$	LM: Nose (15), cheek (12), forehead (4), temporal (1), preauricular (1), lip (1), leg (1)	H	2940-nm erbium-doped yttrium aluminium garnet laser or 10,600-nm CO <sub>2</sub> laser + imiquimod 5% once/d 5 t/w for 6 w	2	Complete (C)	Median 42 m IQR [13–38 m]	6 (C)
Kai et al. [92] (2016)	OLT	40	40	–	LM: facial	NR	Imiquimod 5% once/d 5 t/w for 4 w  In case of insufficient inflammatory response at w4: imiquimod 5% once/d 5 t/w for 4 w	NR	Complete: 27 (H) Partial: 11 (H)	> 5 y (for 18/27 patients)	0 (CM)
Marsden et al. [93] (2016)	Single Arm phase II trial	28	28	65–79 $\mu = 72$	LM: cheek (11), nose (7), ear (4), forehead (4), scalp (2), neck (1)	H	Imiquimod 5% once/d 3–7 t/w for 6 w with 7 d break if poor tolerance + surgical excision with 5 mm margins	2	Complete: 10 (H) Partial/None: 17 (H)	NA	NA
Napolitano et al. [94] (2016)	CR	1	1	34	MIS: penis	H	Imiquimod 5% once/d 5 t/w for 7 w	NR	Complete (H)	8 m	0 (H)
Menzies et al. [95] (2017)	CR	1	1	82	LM: nose	H	Imiquimod 5% once/d 5 t/w for 6 w then imiquimod 5% once/d 7 t/w for 8 w + tazarotene gel once/d for 4 w + imiquimod 5% once/d 7 t/w for 8 w	NR	Complete (H)	30 m	0 (C)
Park et al. [96] (2017)	RA	12	12	67–96 $\mu = 79$	MIS: cheek (4), jaw (1), nose (2), back (1), scalp (1), temple (1), preauricular (1), ear (1),	H	± Pretreatment with topical 0.1% tazarotene cream (once/d for 2 weeks) Imiquimod 5% once/d 5 t/w (Monday-Friday) for 6–12 w	NR	Complete: 11 (H), 1 (C)	1.6–12.6 y	2 (H)

**Table 1** continued

Reference	Type	$N_p$	$N_i$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Scalvenzi et al. [16] (2017)	CR	1	1	38	MIS; penis	H	Imiquimod 5% once/d 3 t/w for 5 w, 4 w break, then imiquimod 5% once/d 2 t/w for 4 w	NR	Complete (H)	18 m	0 (C)
Astorino et al. [97] (2018)	CR	2	2	83–85	LM: nose, zygomatic	H	Imiquimod 5% 1 dose twice/d (12.5 mg in 250 mg cream during the morning and in occlusion during the evening 12 h/24) 5 t/w, at alternate w, for 5 w (3 of treatment and 2 of stop)	NR	Complete (C)	24–36 m	0 (C)
Brand et al. [98] (2018)	OLT	34	34	38–87 $\mu = 69$	LM: head (32), other (2)	H	Imiquimod 5% once-twice/d for 8–108 d	NR	Complete: 33 (CM) None: 1 (H)	NR	7 (CM)
Donigan et al. [99] (2018)	RA	334	345 (294/345 recurrence)	$\mu = 67$	LM: other face (206), nose (52), ear (39), neck/trunk/upper extremity (18), scalp (16), lip (9), periocular (5)	H	Imiquimod 5% once/d 5 t/w overnight for 2 to 3 m If insufficient response: razarotene 0.1%, gel twice weekly + staged excisions beginning with 2-mm margins	2	Complete: 119 (H) Partial: 51 (H)	$\mu = 5.5$ y Lost to follow up: 37 p (39 lesions)	12 (H) 2/12 evolution to invasive melanoma
Kim et al. [34] (2018)	CR	1	1	69	LM: cheek	I	Partial surgical excision + imiquimod 5% once/d 3 t/w for 3 m (only 15 applications because of inflammation)	NR	Complete (H)	5 y	0 (C)

Table 1 continued

Reference	Type	$N_p$	$N_t$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Tio et al. [31] (2018)	CS	3	3	66–69 $\mu = 68$	LM: cheek	H	Imiquimod 5% once/d 7 t/w for 8 w If insufficient response: Imiquimod 5% up to 3 t/d 7/w If exaggerated inflammatory response: imiquimod 5% once/d 3 t/w	1–2	Complete (H)	NR	NR
Veratch et al. [100] (2018)	CR	1	1	75	MIS: vulva	H	Imiquimod 5% once/d once/w for 8 w then twice/w for 18 m	NR	Partial (H)	NR	NR
Hamilko de Barros et al. [101] (2019)	CR	1	1	87	LMM: zygomatic	H	Partial surgical excision + 1st cycle: Imiquimod 5% once/d for 6 w + 2nd cycle: Imiquimod 5% once/d for 12 w	Whole check	Complete (C)	1 y	0 (D)
Lackey et al. [102] (2019)	CR	1	1	86	LM: scalp	H	Imiquimod 5% 6 t/w for 12 w	0	Complete (C)	17 m	0 (C)
Papanikolaou et al. [103] (2019)	RA	33	33	50–93 $\mu = 75$	LM: head and neck	H	Imiquimod 5% once/d 5 t/w for 6 w $\pm$ imiquimod 5% twice/d 7 t/w for 6 w $\pm$ imiquimod 5% twice/d, 7 t/w for 10 w or until inflammation	1	Complete: 13 (C), 9 (H) Partial: 7 (H) None: 4 (C)	$\mu = 4.1$ y	0 (D)

Note: treatment was stopped earlier by 4 patients

**Table 1** continued

Reference	Type	$N_p$	$N_i$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Tio et al. [104] (2019)	RA	57	57	$\mu = 76$	LM: nose (23), cheek (20), forehead (8), temple (3), chin (1), upper lip (1), earlobe (1)	H	Imiquimod 5% once/d 7 $\tau$ /w for 12 w (at least 10 w) If exaggerated inflammatory response: Imiquimod 5% up to 3 $\tau$ /d If insufficient response: imiquimod 5% twice/d 7 $\tau$ /w <i>Note: treatment was stopped earlier by 3 patients</i>	1–2	Complete: 29 (C), 22 (H) Partial: 3 (H) None: 3 (C)	5–55 m	6 (C/H)
Tsay et al. [105] (2019)	RA	16	16	41–84	LM: cheek (7), eyelid (3), nose (2), temple (2), ears (1), supraclavicular (1)	H	Surgical excision (partial or with margins involved) + Imiquimod 5% once/d 3–5 $\tau$ /w for 6 weeks (from the begin of the inflammation)	NR	Complete: 13 (H) None: 3 (H)	NA	NA
Bartenjev et al. [106] (2020)	CR	1	1	80	LM: forehead	H	Imiquimod 5% once/d 6 $\tau$ /w for 6 w	NR	Complete (C)	9 m	0 (C)
O'Hern et al. [107] (2020)	CR	1	1	69	MIS: penis	H	Tretinoin 0.1% cream once/d 7 $\tau$ /w for 2 weeks+ imiquimod 5% cream 5 $\tau$ /w for 12 w	NR	Complete (C)	20 m	0 (C)
Lobo and Templeman. [108] (2020)	CR	1	1	88	LM: nose	H	Imiquimod 5% once/d 6 $\tau$ /w for 12 w	NR	Complete (C)	12 m	0 (C)

Table 1 continued

Reference	Type	$N_p$	$N_i$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Chambers et al. [109] (2021)	RA	103	103	38–92 $\mu = 69$	LM: head/neck (95), torso (4), extremities (4)	H	± Surgical excision (partial or margins involved) ± Pretreatment with topical 0.1% tazarotene cream (once daily for 2 weeks) Imiquimod 5% once/d 5 $\tau$ /w (Monday–Friday) for 12 w	NR	Complete: 96 (H) Partial: 4 (H) None: 3 (H)	0.08–17.1 y	8 (H)
Corneli et al. [110] (2021)	CR	2	2	85–81	LMM: cheek, temporal	H	Serial surgical excision + imiquimod 5% once/d 7 $\tau$ /w for 6 w	NR	Complete (C)	10–12 m	0 (C)
Fuchs et al. [111] (2021)	CR	1	1	69	MIS: vulva and urethra	H	Imiquimod 5% once/d 3–5 $\tau$ /w for 16 w	NR	Complete (C)	4 y	1 (H)
Kwak et al. [112] (2021)	RA	95	95	$\mu = 68.4$	LM and LMM: head and neck (84), other (11)	H	(1) Monotherapy Imiquimod 5% once/d 4 $\tau$ /w for 12 w ± cryotherapy (2) Adjuvant Surgical excision (margins included or clear but close/dysplastic) + Imiquimod 5% once/d 4 $\tau$ /w for 12 w ± cryotherapy	NR	Complete: 39 (C), 26 (H)	Median = 38 m	Group 1: 5 (H) Group 2: 5 (H)

**Table 1** continued

Reference	Type	$N_p$	$N_i$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Lallas et al. [113] (2021)	RA	149	149	Group 1 a: $\mu = 73$ Group 1b: $\mu = 69$ Group 2: $\mu = 67$ Group 3: $\mu = 80$	LM: cheek (76), ear (68), nose (21), forehead (13), scalp (12), orbital (7), temple (6), perioral (6)	H	(1) Adjuvant surgical excision in clinical narrow margins (< 5 mm, subgroup 1a) or wider margins ( $\geq 5$ mm, subgroup 1b); histopathologically assessed as clear of tumor + imiquimod 5% once/d 7 t/w for 6–13 weeks (2) Complementary surgical excision in clinical narrow margins (< 5 mm), histopathologically assessed as involved + imiquimod 5% once/d 7 t/w for 6–13 weeks (3) Primary: imiquimod 5% once/d 7 t/w for 6–13 weeks	NR	Group 1: NA Group 2: NA Group 3: Complete: 40 (C) Partial: 12 (C) None: 4 (C)	NA	Group 1: 4 (H) Group 2: 2 (H) Group 3: NA
Nahm et al. [114] (2021)	CR	1	2	66	MIS: upper limb	H	1/5 packet of imiquimod 5% cream, one drop of 5-fluorouracil 2% solution, and 1/5 of a pea-sized quantity of tretinoin 0.1% cream with a bandage overnight (30 applications within a 42-day period) He completed his treatment protocols over 30 days	NR	Complete (C)	NR	NR

Table 1 continued

Reference	Type	$N_p$	$N_t$	Age (years)	Diagnosis and body area	Diagnosis (method)	Protocol	Margins (cm)	Clearance (verification method)	Long-term follow-up (time)	Recurrence, $n$ (verification method)
Rovesti et al. [115] (2021)	CR	1	1	90	LM: scalp	H	Imiquimod 5% once/d 5 r/w for 4 m, then Imiquimod 3.75% once/d 5 r/w for 4 m	NR	Complete (C)	NR	NR
Misiak-Galazka et al. [116] (2022)	CR	1	1	82	LM: cheek	H	Imiquimod 5% once/d 5 r/w for 5 w, 3 cycles	1–2	Complete (C)	24 m	0 (C)
Poveda-Montoyo et al. [117] (2022)	CS	13	14	48–84 $\mu = 69.5$	LM and LMM: nose (6), cheek (4), temple (2), back (1), upper lip (1)	H	(1) Monotherapy Imiquimod 5% once/d 7 r/w for 5–11 w $\pm$ tazarotene gel 0.05%	1	Complete (C)	$\mu = 66.4$ m	2 (C)
Soenen et al. [118] (2022)	CRT	40	21 (+ 19 with placebo)	$\mu = 60.5$	LM: face, neck, or scalp	H	(2) Neoadjuvant Imiquimod 5% once/d 7 r/w for 5–11 w $\pm$ tazarotene gel 0.05% + narrow excision	NR	Complete: 13 (H)	NA	NA
Ishioka et al. [119] (2022)	CS	6	6	–	LM: face (3), scalp (2), back (1)	H	Imiquimod 5% once/d 6 r/w for 12 w	NR	Complete (CM)	NA	NA
Seyed Jafari et al. [12] (2023)	RA	114	114	38–93 Median = 72	LM: cheek (49), nose (32), temporo-auricular (14), forehead (6), orbital (5), other face/head areas (3), other (5)	H	Imiquimod 5% once-twice/d until weeping erosion (1–55 w)	NR	Complete: 111 (C) None: 3 (C)	15–168 y	23 (H)

For each study the following items were considered: number of treated lesions; diagnosis (LM/MIS/LMM) with the body area; diagnostic method (histology/clinics); protocol; margins of the lesions included in treated area; response after the treatment specifying the verification method (complete/partial/none; histology/clinical/other); time of long-term follow-up (as range or average time); number of relapses specifying the verification method (histology/clinical/other) at the time of the long-term follow-up. If data were missing, we classified them as "not recorded" or "not applicable".

C Clinically confirmed, CM confirmed with confocal microscopy, CR case report, CRT controlled randomized trial, CS case series, H histologically confirmed, LM lentigo maligna, M month(s), MIS melanoma in situ,  $\mu$  average, NA not applicable,  $N_t$  number of lesions,  $N_p$  number of patients, NR not recorded, OLT open label trial, P patient(s), RA retrospective analysis, RT randomized trial,  $t$  times,  $w$  week(s),  $y$  year(s)

In 30 studies, the application of imiquimod was extended beyond the lesions with margins of between 0.5 and 2 cm. In two studies [49, 101] on LM of the cheek, the treatment was applied onto the whole cheek. In four cases [59, 72, 90, 102], the treatment was applied only on the lesion, excluding the margins. In all other studies, these data were not reported.

In 23 studies, clearance after the treatment was checked with a clinical and/or dermoscopic examination; in the other studies, the patient populations were re-biopsied, at least partly, depending on the patient's consent. In total, 1133 out of 1803 (62.8%) lesions were reported to be cleared after the treatment, taking account that not all the patients completed the treatment and that, in some cases, patients who did not complete the treatment were included in the final analysis. Of the 1133 lesions, histological clearance was achieved in 645 (56.9%) lesions and clinical clearance only was achieved in 490 (43.2%) lesions. For 34 lesions, the initial clearance was tested with the confocal microscopy [98, 119] and (1 case) with videodermoscopy [63].

In most cases the long-term follow-up was mainly clinical, with time ranges extremely variable (0–17.1 years [109]). In two studies, the long-term follow-up was realized with reflectance confocal microscopy [92, 98] and in 22 studies it was realized with biopsy and histological examination. Seventy-one studies reported data on recurrence; in total, 107 lesions relapsed.

Seventeen studies [16, 53, 62, 63, 68, 74, 80, 90, 97, 98, 101, 103, 108, 115–117, 119] mentioned the importance of the (video)dermoscopy for diagnosis and follow-up and to guide the biopsies. In addition, seven studies [74, 82, 92, 98, 100, 118, 119] mentioned or used the reflectance confocal microscopy.

Finally, in two studies [90, 109], the authors made a disease-free survival analysis.

## DISCUSSION

Existing data suggest that imiquimod has a therapeutic effect on non-invasive melanoma and LMM. However, as mentioned in the

“Introduction”, the level of evidence is generally low and the patient populations of individual studies are small. The largest patient population was described in the study by Donigan et al. [99], which was a retrospective medical record review of 334 patients (mean age 67 years) with 345 biopsy-confirmed LM tumors, of whom 294 were recurrences. These patients were treated with neoadjuvant 5% imiquimod cream for a mean of 2.5 months, with or without 0.1% tazarotene gel, prior to conservatively staged excisions beginning with 2-mm margins. A mean of 1.2 surgical stages with a mean margin of 3.5 mm were required to clear the tumor. Residual LM was present in 18% of specimens cleared with stage 1. Thirty-two patients had a complete clinically response to imiquimod prior to staged excision. Thirty-seven patients (39 tumors) were lost to follow-up, and seven of them died. The mean length of follow-up for the remaining 297 patients was 5.5 years. There was a recurrence rate of 3.9%, with a mean time to recurrence of 4.3 years.

Also, there are no comparative studies between the classic surgical treatment, or radiotherapy, and treatment with imiquimod. As previously stated, the main disadvantage of this systematic review is the inclusion of several case reports/series, which make the risk of bias higher. However, we expressly applied broad inclusion criteria in order to include as many studies as possible with the aim to represent the state-of-the-art of this topic and its evolution during the years.

Despite the limited number of studies, imiquimod treatment appears in several international guidelines for the management of LM, such as European Association of Dermato Oncology (EADO) [122], American Academy of Dermatology (AAD) [123], and Italian Association of Medical Oncology (AIOM) [124]. In particular, in the EADO and AIOM guidelines, imiquimod 5% is proposed as a potential alternative to surgery in patients not eligible for radiotherapy or surgery. In the AAD guidelines, imiquimod 5% treatment is proposed as second-line treatment in the primary or adjuvant setting (strength of recommendation B, level of evidence II/III). Moreover, in a 2018 survey sent to the members of European Association of

Dermatologists and Venereologists (EADV), the most common treatment for LM patients was surgery (97.6% of respondents), followed by topical imiquimod (49.7% of respondents), with the latter treatment suggested predominantly for elderly patients [7].

The first aspect to consider when considering topical imiquimod for the treatment of non-invasive melanoma is the extreme heterogeneity in the protocols, the extension of the treatment to margins, the modality of verifying the clearance, and the follow-up. In addition, the lesions treated and the characteristics of the patients in the studies were very heterogeneous. In those studies with more than one patient, LM/MIS/LMM, first diagnosis/relapses, and patients with/without previous treatment were not distinctly considered. Because of the absence of a stratification of the groups, our final analysis is indicative only, but it cannot be precise and conclusive concerning the modality of the treatment. The same limitation holds for the time of follow-up, which was often non-uniform among patients of the same study with very wide time ranges. For this reason, we are unable to draw conclusions on the time of relapse and its association with patients, the type of lesion, and the treatment protocol.

Another aspect to consider is the response rate to the treatment. First, it is necessary to note that most of the non-responders were reported in studies with a large sample, whereas this was rarer for case reports and case series, indicating a bias of selection. Second, in most studies, the response was assessed as the level of inflammation, implementing the dosage, or adding other therapies (topical retinoids, cryotherapy) in the case of insufficient response. These variables explain, at least partially, the variability of the treatment regimen.

The topical application of imiquimod was generally well tolerated by patients, and the irritant adverse effects rarely led to a premature interruption of the therapy. However, strict follow-up of the patient is mandatory to adjust the dosage and ensure patient compliance to the treatment and the clearance of the lesion. In summary, imiquimod therapy must be personalized for the patient being treated. Also, the total duration of the treatment and its

implementation from the first appearance of inflammation, as well as the need for a post-treatment biopsy remain unclear. With regard to the latter aspect, a recurrent issue involves the residual hyperpigmentation at the end of the treatment, linked to residual neoplastic cells or to melanophages and melanin. Indeed, this clinical aspect makes it difficult to assess an incomplete clearance and often leads to a post-treatment surgery. The actual evidence does not lead to avoidance of a final biopsy or surgery in these cases, but some authors raised the importance of non-invasive methods, such as dermoscopy [16, 53, 62, 63, 68, 74, 80, 90, 97, 98, 101, 103, 108, 115–117, 119] and confocal microscopy [74, 82, 92, 98, 100, 118, 119], with the latter preferable in terms of histopathological criteria [121] but less available in daily practice. Treatment with imiquimod is non-invasive, but at the present time an initial biopsy to ensure that the melanoma is non-invasive is mandatory and a biopsy when there is suspicion of partial/absent response or relapse are preferred.

One of the most crucial aspects in studies concerns recurrence. In particular, the timing of the follow-up varies among studies and among patients of the same study. Furthermore, the data on relapse in these studies were not always specified. Currently available data do not allow any evaluation of the relapse rate.

## CONCLUSIONS

The efficacy of local imiquimod cream to treat non-invasive melanoma, and LMM in some cases, has been demonstrated, but the heterogeneity of the included studies precludes the drawing of a firm conclusion. In addition, uniform evidence concerning the modalities of treatment is lacking. At the present time, this kind of therapy cannot substitute for the classical surgical treatment, but it can be considered for the treatment of patients of advanced age, systemic diseases that contraindicate surgical procedures, large lesions, and lesions occurring in difficult anatomic locations. Also, imiquimod can be associated with the surgical procedure as neoadjuvant, adjuvant, or complementary

treatment to avoid large flaps and skin grafts. An accurate post-treatment assessment is mandatory, including clinical-dermoscopic examination, examination with the confocal microscopy, if possible, and a histologic follow-up, if deemed necessary. Identification of eligible patients for which this non-invasive treatment can represent a better option compared to the conventional treatments, the protocol, and the timing of the follow-up remain the main challenges for the future.

## ACKNOWLEDGEMENTS

**Funding.** No funding or sponsorship was received for this study or publication of this article.

**Author Contributions.** Conceptualization: SV and PC. Methodology: SV. Formal analysis: SV. Data curation: SV and PC. Writing—original draft preparation: SV. Writing—review & editing: GN. Supervision: GN.

**Conflict of Interest.** The Authors do not have any conflict of interest to disclose.

**Ethical Approval.** This review is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

**Data Availability.** Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Open Access.** This article is licensed under a Creative Commons Attribution-Non-Commercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated

otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

## REFERENCES

1. Garbe C, Amaral T, Peris K, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: update 2022. *Eur J Cancer*. 2022;170:236–55. <https://doi.org/10.1016/j.ejca.2022.03.008>.
2. Nazzaro G, Passoni E, Pozzessere F, Maronese CA, Marzano AV. Dermoscopy use leads to earlier cutaneous melanoma diagnosis in terms of invasiveness and size? A single-center, retrospective experience. *J Clin Med*. 2022;11(16):4912. <https://doi.org/10.3390/jcm11164912>.
3. Pellegrini C, Botta F, Massi D, et al. MC1R variants in childhood and adolescent melanoma: a retrospective pooled analysis of a multicentre cohort. *Lancet Child Adolesc Health*. 2019;3:332–42.
4. Moehrl M, Dietz K, Garbe C, Breuninger H. Conventional histology vs. three-dimensional histology in lentigo maligna melanoma. *Br J Dermatol*. 2006;154(3):453–9. <https://doi.org/10.1111/j.1365-2133.2005.07068.x>.
5. Juhász MLW, Marmur ES. Reviewing challenges in the diagnosis and treatment of lentigo maligna and lentigo-maligna melanoma. *Rare Cancers Ther*. 2015;3(1):133–45. <https://doi.org/10.1007/s40487-015-0012-9>.
6. Tzellos T, Kyrgidis A, Mocellin S, Chan AW, Pilati P, Apalla Z. Interventions for melanoma in situ, including lentigo maligna. *Cochrane Database Syst Rev*. 2014;12:CD010308. <https://doi.org/10.1002/14651858.CD010308.pub2>.
7. Garbe C, Amaral T, Peris K, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: treatment—update 2022. *Eur J Cancer*. 2022;170:256–84. <https://doi.org/10.1016/j.ejca.2022.04.018>.
8. Hilari H, Llorca D, Traves V, et al. Conventional surgery compared with slow Mohs micrographic surgery in the treatment of lentigo maligna: a retrospective study of 62 cases. *Actas Dermosifiliogr*.

- 2012;103(7):614–23. <https://doi.org/10.1016/j.adengl.2012.08.014>.
9. Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. *Br J Dermatol*. 2002;146(6):1042–6. <https://doi.org/10.1046/j.1365-2133.2002.04750.x>.
  10. Bichakjian CK, Halpern AC, Johnson TM, et al. Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology. *J Am Acad Dermatol*. 2011;65(5):1032–47. <https://doi.org/10.1016/j.jaad.2011.04.031>.
  11. Fikrle T, Divišová B, Šuchmannová J, Pizinger K. The use of 2940-nm ER:YAG laser for the treatment of lentigo maligna. *J Dtsch Dermatol*. 2019;17(4):425–31. <https://doi.org/10.1111/ddg.13814>.
  12. Seyed Jafari SM, Folini-Huesser F, Cazzaniga S, Hunger RE. Long-term follow-up of lentigo maligna patients treated with imiquimod 5% cream. *Cancers*. 2023;15(5):1546. <https://doi.org/10.3390/cancers15051546>.
  13. Guitera P, Waddell A, Paton E, et al. A practical guide on the use of imiquimod cream to treat lentigo maligna. *Australas J Dermatol*. 2021;62(4):478–85. <https://doi.org/10.1111/ajd.13720>.
  14. Mora AN, Karia PS, Nguyen BM. A quantitative systematic review of the efficacy of imiquimod monotherapy for lentigo maligna and an analysis of factors that affect tumor clearance. *J Am Acad Dermatol*. 2015;73(2):205–12. <https://doi.org/10.1016/j.jaad.2015.05.022>.
  15. Rajpar SF, Marsden JR. Imiquimod in the treatment of lentigo maligna. *Br J Dermatol*. 2006;155(4):653–6. <https://doi.org/10.1111/j.1365-2133.2006.07476.x>.
  16. Scalvenzi M, Palmisano F, Russo D, Mascolo M, Costa C. Melanoma of the glans penis successfully treated with topical imiquimod: dermoscopy usefulness in clinical monitoring and review of the literature. *G Ital Dermatol Venereol*. 2017;152(6):663–8. <https://doi.org/10.23736/S0392-0488.16.04789-1>.
  17. Borucki U, Metze D. Topical treatment of lentigo maligna melanoma with imiquimod 5% cream. *Dermatology*. 2003;207(3):326–8. <https://doi.org/10.1159/000073101>.
  18. European Medicines Agency. Aldara. 2018. <https://www.ema.europa.eu/en/medicines/human/EPAR/aldara>. Accessed 8 May 2023.
  19. 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):616–24. <https://doi.org/10.1111/jdv.14085>.
  20. Junkins-Hopkins JM. Imiquimod use in the treatment of lentigo maligna. *J Am Acad Dermatol*. 2009;61(5):865–7. <https://doi.org/10.1016/j.jaad.2009.08.023>.
  21. Vidal D. Topical imiquimod: mechanism of action and clinical applications. *Mini Rev Med Chem*. 2006;6(5):499–503. <https://doi.org/10.2174/138955706776876131>.
  22. Harrison CJ, Jensi L, Voychekovski T, Bernstein DI. Modification of immunological responses and clinical disease during topical R-837 treatment of genital HSV-2 infection. *Antiviral Res*. 1988;10(4–5):209–23. [https://doi.org/10.1016/0166-3542\(88\)90032-0](https://doi.org/10.1016/0166-3542(88)90032-0).
  23. Chen M, Griffith BP, Lucia HL, Hsiung GD. Efficacy of S26308 against guinea pig cytomegalovirus infection. *Antimicrob Agents Chemother*. 1988;32(5):678–83. <https://doi.org/10.1128/AAC.32.5.678>.
  24. Sidky YA, Borden EC, Weeks CE, Reiter MJ, Hatcher JF, Bryan GT. Inhibition of murine tumor growth by an interferon-inducing imidazoquinolinamine. *Cancer Res*. 1992;52(13):3528–33.
  25. Schön MP, Schön M. Imiquimod: mode of action. *Br J Dermatol*. 2007;157(Suppl 2):8–13. <https://doi.org/10.1111/j.1365-2133.2007.08265.x>.
  26. Reiter MJ, Testerman TL, Miller RL, Weeks CE, Tomai MA. Cytokine induction in mice by the immunomodulator imiquimod. *J Leukoc Biol*. 1994;55(2):234–40. <https://doi.org/10.1002/jlb.55.2.234>.
  27. Gibson SJ, Imbertson LM, Wagner TL, et al. Cellular requirements for cytokine production in response to the immunomodulators imiquimod and S-27609. *J Interferon Cytokine Res*. 1995;15(6):537–45. <https://doi.org/10.1089/jir.1995.15.537>.
  28. Megyeri K, Au WC, Rosztochy I, et al. Stimulation of interferon and cytokine gene expression by imiquimod and stimulation by Sendai virus utilize similar signal transduction pathways. *Mol Cell Biol*. 1995;15(4):2207–18. <https://doi.org/10.1128/MCB.15.4.2207>.
  29. Gibson SJ, Lindh JM, Riter TR, et al. Plasmacytoid dendritic cells produce cytokines and mature in response to the TLR7 agonists, imiquimod and

- resiquimod. *Cell Immunol.* 2002;218(1–2):74–86. [https://doi.org/10.1016/s0008-8749\(02\)00517-8](https://doi.org/10.1016/s0008-8749(02)00517-8).
30. Fisher GH, Lang PG. Treatment of melanoma in situ on sun-damaged skin with topical 5% imiquimod cream complicated by the development of invasive disease. *Arch Dermatol.* 2003;139(7):945–7. <https://doi.org/10.1001/archderm.139.7.945>.
31. Tio D, Kirtschig G, Hoekzema R, van Montfrans C. Lymphoedema in patients with lentigo maligna treated with imiquimod: a long-term adverse effect. *Br J Dermatol.* 2018;178(6):1441–2. <https://doi.org/10.1111/bjd.16267>.
32. Di Bartolomeo L, Guarneri F, Moretti G. Treatment of solar lentigo with imiquimod 3.75% cream: a dermoscopic study. *J Cosmet Dermatol.* 2022;21(11):6487–9. <https://doi.org/10.1111/jocd.15177>.
33. Lallas A, Apalla Z, Moscarella E, et al. Extensive regression in pigmented skin lesions: a dangerous confounding feature. *Dermatol Pract Concept.* 2012;2(2):202a08. <https://doi.org/10.5826/dpc.0202a08>.
34. Kim NH, Lee JB, Yun SJ. Development of vitiligo-like depigmentation after treatment of lentigo maligna melanoma with 5% imiquimod cream. *Ann Dermatol.* 2018;30(4):454–7. <https://doi.org/10.5021/ad.2018.30.4.454>.
35. Serrão VV, Páris FR, Feio AB. Genital vitiligo-like depigmentation following use of imiquimod 5% cream. *Eur J Dermatol.* 2008;18(3):342–3. <https://doi.org/10.1684/ejd.2008.0402>.
36. Murchison AP, Washington CV, Soloman AR, Bernardino CR. Ocular effects of imiquimod with treatment of eyelid melanoma in situ. *Dermatol Surg.* 2007;33(9):1136–8. <https://doi.org/10.1111/j.1524-4725.2007.33232.x>.
37. Conforti C, Dell'aquila C, Tognetto D, Zalaudek I, di Meo N. Eyelid lentigo maligna treated with imiquimod 5%: should we fear of ocular side effects? *Dermatol Pract Concept.* 2023;13(1):e2023042. <https://doi.org/10.5826/dpc.1301a42>.
38. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. <https://doi.org/10.1136/bmj.n71>.
39. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898. <https://doi.org/10.1136/bmj.l4898>.
40. Ahmed I, Berth-Jones J. Imiquimod: a novel treatment for lentigo maligna. *Br J Dermatol.* 2000;143(4):843–5. <https://doi.org/10.1046/j.1365-2133.2000.03787.x>.
41. Chapman MS, Spencer SK, Brennick JB. Histologic resolution of melanoma in situ (lentigo maligna) with 5% imiquimod cream. *Arch Dermatol.* 2003;139(7):943–4. <https://doi.org/10.1001/archderm.139.7.943>.
42. Epstein E. Extensive lentigo maligna clearing with topical imiquimod. *Arch Dermatol.* 2003;139(7):944–5. <https://doi.org/10.1001/archderm.139.7.944>.
43. Naylor MF, Crowson N, Kuwahara R, et al. Treatment of lentigo maligna with topical imiquimod. *Br J Dermatol.* 2003;149(Suppl 66):66–70. <https://doi.org/10.1046/j.0366-077x.2003.05637.x>.
44. Fleming CJ, Bryden AM, Evans A, Dawe RS, Ibbotson SH. A pilot study of treatment of lentigo maligna with 5% imiquimod cream. *Br J Dermatol.* 2004;151(2):485–8. <https://doi.org/10.1111/j.1365-2133.2004.05983.x>.
45. Kupfer-Bessagnet I, Guillet G, Misery L, Carre JL, Leroy JP, Sassolas B. Topical imiquimod treatment of lentigo maligna: clinical and histologic evaluation. *J Am Acad Dermatol.* 2004;51(4):635–9. <https://doi.org/10.1016/j.jaad.2004.05.004>.
46. Michalopoulos P, Yawalkar N, Brönnimann M, Kappeler A, Braathen LR. Characterization of the cellular infiltrate during successful topical treatment of lentigo maligna with imiquimod. *Br J Dermatol.* 2004;151(4):903–6. <https://doi.org/10.1111/j.1365-2133.2004.06176.x>.
47. Muñoz CM, Sánchez JL, Martín-García RF. Successful treatment of persistent melanoma in situ with 5% imiquimod cream. *Dermatol Surg.* 2004;30(12 Pt 2):1543–5. <https://doi.org/10.1111/j.1524-4725.2004.30565.x>.
48. Powell AM, Russell-Jones R, Barlow RJ. Topical imiquimod immunotherapy in the management of lentigo maligna. *Clin Exp Dermatol.* 2004;29(1):15–21. <https://doi.org/10.1111/j.1365-2230.2004.01452.x>.
49. Powell AM, Russell-Jones R. Amelanotic lentigo maligna managed with topical imiquimod as immunotherapy. *J Am Acad Dermatol.* 2004;50(5):792–6. <https://doi.org/10.1016/j.jaad.2003.11.057>.
50. Kamin A, Eigentler TK, Radny P, Bauer J, Weide B, Garbe C. Imiquimod in the treatment of extensive recurrent lentigo maligna. *J Am Acad Dermatol.* 2005;52(2 Suppl 1):51–2. <https://doi.org/10.1016/j.jaad.2004.07.047>.

51. Wolf IH, Cerroni L, Kodama K, Kerl H. Treatment of lentigo maligna (melanoma in situ) with the immune response modifier imiquimod. *Arch Dermatol*. 2005;141(4):510–4. <https://doi.org/10.1001/archderm.141.4.510>.
52. Lonsdale-Eccles AA, Morgan JM, Nagarajan S, Cruickshank DJ. Successful treatment of vulval melanoma in situ with topical 5% imiquimod cream. *Br J Dermatol*. 2006;155(1):215–7. <https://doi.org/10.1111/j.1365-2133.2006.07297.x>.
53. Micantonio T, Fargnoli MC, Peris K. Usefulness of dermoscopy to monitor clinical efficacy of imiquimod treatment for lentigo maligna. *Arch Dermatol*. 2006;142(4):530–1. <https://doi.org/10.1001/archderm.142.4.530-b>.
54. du Plessis PJ. Lentigo maligna successfully treated with imiquimod. *South Afr J Surg*. 2007;45(2):72.
55. Hopson B, Richey D, Sajben FP. Treatment of lentigo maligna with imiquimod 5% cream. *J Drugs Dermatol*. 2007;6(10):1037–40.
56. Spenny ML, Walford J, Werchniak AE, et al. Lentigo maligna (melanoma in situ) treated with imiquimod cream 5%: 12 case reports. *Cutis*. 2007;79(2):149–52.
57. van Meurs T, van Doorn R, Kirtschig G. Recurrence of lentigo maligna after initial complete response to treatment with 5% imiquimod cream. *Dermatol Surg*. 2007;33(5):623–6. <https://doi.org/10.1111/j.1524-4725.2007.33129.x>. (discussion 626–627).
58. Bassukas ID, Gamvroulia C, Zioga A, Nomikos K, Fotika C. Cryosurgery during topical imiquimod: a successful combination modality for lentigo maligna. *Int J Dermatol*. 2008;47(5):519–21. <https://doi.org/10.1111/j.1365-4632.2008.03562.x>.
59. Buettiker UV, Yawalkar NY, Braathen LR, Hunger RE. Imiquimod treatment of lentigo maligna: an open-label study of 34 primary lesions in 32 patients. *Arch Dermatol*. 2008;144(7):943–5. <https://doi.org/10.1001/archderm.144.7.943>.
60. Cotter MA, McKenna JK, Bowen GM. Treatment of lentigo maligna with imiquimod before staged excision. *Dermatol Surg*. 2008;34(2):147–51. <https://doi.org/10.1111/j.1524-4725.2007.34031.x>.
61. Craythorne EE, Lawrence CM. Observational study of topical imiquimod immunotherapy in the treatment of difficult lentigo maligna. *Clin Med Oncol*. 2008;2:551–4. <https://doi.org/10.4137/cmo.s690>.
62. de Troya-Martín M, Frieyro-Elicegui M, Fúnez Liébana R, Aguilar Bernier M, Fernández-Canedo NI, Blázquez SN. Lentigo maligna managed with topical imiquimod and dermoscopy: report of two cases. *Dermatol Surg*. 2008;34(11):1561–6. <https://doi.org/10.1111/j.1524-4725.2008.34322.x>.
63. Micali G, Lacarrubba F, Nardone B, Nasca MR. Videodermatoscopy of lentigo maligna treated with imiquimod. *J Drugs Dermatol*. 2008;7(11):1077–80.
64. Mahoney MH, Joseph MG, Temple C. Topical imiquimod therapy for lentigo maligna. *Ann Plast Surg*. 2008;61(4):419–24. <https://doi.org/10.1097/SAP.0b013e31816714c8>.
65. Ramsdell AM, Zeitouni N. Long-term follow-up of a hemifacial lentigo maligna treated using 5% imiquimod. *Dermatol Surg*. 2009;35(2):287–90. <https://doi.org/10.1111/j.1524-4725.2008.34426.x>.
66. Missall TA, Fosko SW. The use of imiquimod to minimize the surgical defect when excising invasive malignant melanoma surrounded by extensive melanoma in situ, lentiginous type. *Dermatol Surg*. 2009;35(5):868–74. <https://doi.org/10.1111/j.1524-4725.2009.01146.x>.
67. Powell AM, Robson AM, Russell-Jones R, Barlow RJ. Imiquimod and lentigo maligna: a search for prognostic features in a clinicopathological study with long-term follow-up. *Br J Dermatol*. 2009;160(5):994–8. <https://doi.org/10.1111/j.1365-2133.2009.09032.x>.
68. Ventura F, Rocha J, Fernandes JC, Pardal F, Brito C. Topical imiquimod treatment of lentigo maligna. *Case Rep Dermatol*. 2009;1(1):78–81. <https://doi.org/10.1159/000249151>.
69. Woodmansee CS, McCall MW. Recurrence of lentigo maligna and development of invasive melanoma after treatment of lentigo maligna with imiquimod. *Dermatol Surg*. 2009;35(8):1286–9. <https://doi.org/10.1111/j.1524-4725.2009.01227.x>.
70. Martires KJ, Capaldi L, Pattee SF, Maloney ME, Bordeaux JS. Failed treatment of amelanotic lentigo maligna with imiquimod followed by pigment production. *Arch Dermatol*. 2010;146(9):1047–8. <https://doi.org/10.1001/archdermatol.2010.237>.
71. Demirci H, Shields CL, Bianciotto CG, Shields JA. Topical imiquimod for periocular lentigo maligna. *Ophthalmology*. 2010;117(12):2424–9. <https://doi.org/10.1016/j.ophtha.2010.03.049>.
72. Sadownik LA, Crawford RI. Post-surgical treatment of melanoma in situ of the vulva with imiquimod. *J Obstet Gynaecol Can*. 2010;32(8):771–4. [https://doi.org/10.1016/s1701-2163\(16\)34619-9](https://doi.org/10.1016/s1701-2163(16)34619-9).
73. Van Meurs T, Van Doorn R, Kirtschig G. Treatment of lentigo maligna with imiquimod cream: a long-term follow-up study of 10 patients. *Dermatol Surg*.

- 2010;36(6):853–8. <https://doi.org/10.1111/j.1524-4725.2010.01560.x>.
74. Costa MC, Abraham LS, Barcaui C. Lentigo maligna treated with topical imiquimod: dermatoscopy usefulness in clinical monitoring. *An Bras Dermatol*. 2011;86(4):792–4. <https://doi.org/10.1590/s0365-05962011000400028>.
75. Ly L, Kelly JW, O’Keefe R, et al. Efficacy of imiquimod cream, 5%, for lentigo maligna after complete excision: a study of 43 patients. *Arch Dermatol*. 2011;147(10):1191–5. <https://doi.org/10.1001/archdermatol.2011.260>.
76. O’Neill J, Ayers D, Kenealy J. Periocular lentigo maligna treated with imiquimod. *J Dermatol Treat*. 2011;22(2):109–12. <https://doi.org/10.3109/09546630903559798>.
77. Hyde MA, Hadley ML, Tristani-Firouzi P, Goldgar D, Bowen GM. A randomized trial of the off-label use of imiquimod, 5%, cream with vs without tazarotene, 0.1%, gel for the treatment of lentigo maligna, followed by conservative staged excisions. *Arch Dermatol*. 2012;148(5):592–6. <https://doi.org/10.1001/archdermatol.2012.270>.
78. Lapresta A, García-Almagro D, Sejas AG. Amelanotic lentigo maligna managed with topical imiquimod. *J Dermatol*. 2012;39(5):503–5. <https://doi.org/10.1111/j.1346-8138.2011.01358.x>.
79. Prescott LS, Papadopoulos NE, Euscher ED, Watkins JL, Schmeler KM. Topical treatment of recurrent vaginal melanoma in situ with imiquimod: a case report. *Gynecol Oncol Case Rep*. 2012;2(3):92–3. <https://doi.org/10.1016/j.gynor.2012.04.004>.
80. Wong JG, Toole JWP, Demers AA, Musto G, Wiseman MC. Topical 5% imiquimod in the treatment of lentigo maligna. *J Cutan Med Surg*. 2012;16(4):245–9. <https://doi.org/10.1177/120347541201600405>.
81. de Vries K, Rellum R, Habets JMW, Prens EP. A novel two-stage treatment of lentigo maligna using ablative laser therapy followed by imiquimod. *Br J Dermatol*. 2013;168(6):1362–4. <https://doi.org/10.1111/bjd.12157>.
82. Alarcon I, Carrera C, Alos L, Palou J, Malveyh J, Puig S. In vivo reflectance confocal microscopy to monitor the response of lentigo maligna to imiquimod. *J Am Acad Dermatol*. 2014;71(1):49–55. <https://doi.org/10.1016/j.jaad.2014.02.043>.
83. Sue GR, Hanlon A, Lazova R, Narayan D. Use of imiquimod for residual acral melanoma. *BMJ Case Rep*. 2014;2014:bcr2014203826. <https://doi.org/10.1136/bcr-2014-203826>.
84. Fan Q, Cohen S, John B, Riker AI. Melanoma in situ treated with topical imiquimod for management of persistently positive margins: a review of treatment methods. *Ochsner J*. 2015;15(4):443–7.
85. Kirtschig G, van Meurs T, van Doorn R. Twelve-week treatment of lentigo maligna with imiquimod results in a high and sustained clearance rate. *Acta Derm Venereol*. 2015;95(1):83–5. <https://doi.org/10.2340/00015555-1861>.
86. Pandit AS, Geiger EJ, Ariyan S, Narayan D, Choi JN. Using topical imiquimod for the management of positive in situ margins after melanoma resection. *Cancer Med*. 2015;4(4):507–12. <https://doi.org/10.1002/cam4.402>.
87. Savarese I, Papi F, D’Errico A, et al. Acral lentiginous melanoma treated with topical imiquimod cream: possible cooperation between drug and tumour cells. *Clin Exp Dermatol*. 2015;40(1):27–30. <https://doi.org/10.1111/ced.12469>.
88. 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):1047–53. <https://doi.org/10.1016/j.jaad.2015.02.008>.
89. Elia MD, Lally SE, Hanlon AM, et al. Periocular melanoma in situ treated with imiquimod. *Ophthalm Plast Reconstr Surg*. 2016;32(5):371–3. <https://doi.org/10.1097/IOP.0000000000000554>.
90. Gautschi M, Oberholzer PA, Baumgartner M, Gadaldi K, Yawalkar N, Hunger RE. Prognostic markers in lentigo maligna patients treated with imiquimod cream: a long-term follow-up study. *J Am Acad Dermatol*. 2016;74(1):81–87.e1. <https://doi.org/10.1016/j.jaad.2015.08.031>.
91. Greveling K, de Vries K, van Doorn MBA, Prens EP. A two-stage treatment of lentigo maligna using ablative laser therapy followed by imiquimod: excellent cosmesis, but frequent recurrences on the nose. *Br J Dermatol*. 2016;174(5):1134–6. <https://doi.org/10.1111/bjd.14330>.
92. Kai AC, Richards T, Coleman A, Mallipeddi R, Barlow R, Craythorne EE. Five-year recurrence rate of lentigo maligna after treatment with imiquimod. *Br J Dermatol*. 2016;174(1):165–8. <https://doi.org/10.1111/bjd.14311>.
93. Marsden JR, Fox R, Boota NM, et al. Effect of topical imiquimod as primary treatment for lentigo maligna: the LIMIT-1 study. *Br J Dermatol*. 2017;176(5):1148–54. <https://doi.org/10.1111/bjd.15112>.
94. Napolitano M, Annessi G, Didona D, Didona B. Multifocal melanoma in situ of the penis treated

- with topical Imiquimod. *J Eur Acad Dermatol Venereol.* 2016;30(3):458–60. <https://doi.org/10.1111/jdv.12835>.
95. Menzies S, Mc Menamin M, Barry R. Lentigo maligna successfully treated with combination therapy of topical tazarotene and imiquimod. *Clin Exp Dermatol.* 2017;42(4):468–70. <https://doi.org/10.1111/ced.13053>.
96. Park AJ, Paul J, Chapman MS, Samie FH. Long-term outcomes of melanoma in situ treated with topical 5% imiquimod cream: a retrospective review. *Dermatol Surg.* 2017;43(8):1017–22. <https://doi.org/10.1097/DSS.0000000000001115>.
97. Astorino S, Astorre P, Pasquini P, Di Nunno D, Pellegrini F, Paolino G. Imiquimod 5% cream in occlusion, for the treatment of lentigo maligna: a new scheme of short cycles and the need for clinical trials. *Dermatol Ther.* 2019;32(1):e12757. <https://doi.org/10.1111/dth.12757>.
98. Brand FL, Seyed Jafari SM, Hunger RE. Confocal microscopy and lentigo maligna: an in vivo pilot study for the assessment of response to imiquimod therapy. *Dermatology.* 2019;235(2):150–5. <https://doi.org/10.1159/000495034>.
99. 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):885–9. <https://doi.org/10.1001/jamadermatol.2018.0530>.
100. Veraitch O, Lewis F, Craythorne E, Calonje E, Nath R. Management of vulval melanoma in situ with imiquimod. *Br J Dermatol.* 2019;180(4):947–8. <https://doi.org/10.1111/bjd.17433>.
101. Hamilko de Barros M, Conforti C, Giuffrida R, Seabra Resende FS, Di Meo N, Zalaudek I. Clinical usefulness of dermoscopy in the management of lentigo maligna melanoma treated with topical imiquimod: a case report. *Dermatol Ther.* 2019;32(5):e13048. <https://doi.org/10.1111/dth.13048>.
102. Lackey AE, Glassman G, Grichnik J, McDonald J, Correa-Selm L. Repigmentation of gray hairs with lentigo maligna and response to topical imiquimod. *JAAD Case Rep.* 2019;5(12):1015–7. <https://doi.org/10.1016/j.jdc.2019.09.014>.
103. Papanikolaou M, Lawrence CM. Long-term outcomes of imiquimod-treated lentigo maligna. *Clin Exp Dermatol.* 2019;44(6):631–6. <https://doi.org/10.1111/ced.13896>.
104. Tio DCKS, van Montfrans C, Ruijter CGH, Hoekzema R, Bekkenk MW. Effectiveness of 5% topical imiquimod for lentigo maligna treatment. *Acta Derm Venereol.* 2019;99(10):884–8. <https://doi.org/10.2340/00015555-3241>.
105. Tsay C, Kim S, Norwich-Cavanaugh A, Hsia HC, Narayan D. An algorithm for the management of residual head and neck melanoma in situ using topical imiquimod: a pilot study. *Ann Plast Surg.* 2019;82(4S Suppl 3):S199–201. <https://doi.org/10.1097/SAP.0000000000001840>.
106. Bartenjev MS, Isaković-Vidović S, Bartenjev I. Topical imiquimod for management of recurrent lentigo maligna melanoma in situ. *Acta Dermatovenerol Croat.* 2020;28(1):34–7.
107. O'Hern K, Chambers M, Ryan C, Chapman MS. In lieu of penectomy: complete resolution of penile melanoma in situ with topical imiquimod and tretinoin. *Int J Dermatol.* 2021;60(8):e297–9. <https://doi.org/10.1111/ijd.15261>.
108. Lobo Y, Templeman R. Conservative treatment of lentigo maligna with topical imiquimod 5% cream: a case report. *Dermatol Online J.* 2020;26(7):13030/qt5tc7c9w7.
109. Chambers M, Swetter SM, Baker C, Saunders E, Chapman MS. Topical imiquimod for lentigo maligna: survival analysis of 103 cases with 17 years follow-up. *J Drugs Dermatol.* 2021;20(3):346–8. <https://doi.org/10.36849/JDD.5660>.
110. Corneli P, Moscarella E, Di Brizzi EV, et al. Serial excision and imiquimod for lentigo maligna melanoma: a proposal for a combined treatment. *Ital J Dermatol Venereol.* 2021;156(Suppl. 1 to No. 6):3–4. <https://doi.org/10.23736/S2784-8671.18.06168-0>.
111. Fuchs E, Khanijow A, Garcia RL, Goff BA. Imiquimod treatment of vulvar melanoma in situ invading the urethra. *Gynecol Oncol Rep.* 2021;38:100875. <https://doi.org/10.1016/j.gore.2021.100875>.
112. Kwak R, Joyce C, Werchniak AE, Lin JY, Tsibris HC. Clinical and histologic features associated with lentigo maligna clearance after imiquimod treatment. *J Dermatol Treat.* 2022;33(4):1995–9. <https://doi.org/10.1080/09546634.2021.1962001>.
113. 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):675–7. <https://doi.org/10.1111/bjd.20407>.
114. Nahm WJ, Gwillim EC, Badiavas EV, et al. Treating melanoma in situ during a pandemic with telemedicine and a combination of imiquimod,

- 5-fluorouracil, and tretinoin. *Dermatol Ther.* 2021;11(1):307–14. <https://doi.org/10.1007/s13555-020-00473-w>.
115. Rovesti M, Zucchi A, Feliciani C, Satolli F. Case of large lentigo maligna melanoma of the scalp treated with 5% and 3.75% Imiquimod. *An Bras Dermatol.* 2021;96(5):565–8. <https://doi.org/10.1016/j.abd.2020.08.025>.
116. Misiak-Galazka M, Czuwara J, Galazka A, Czaplicka A, Rudnicka L. Lentigo maligna on a difficult location of the face treated with 5% imiquimod: a case report of 2-year follow-up. *Dermatol Ther.* 2022;12(2):599–604. <https://doi.org/10.1007/s13555-021-00667-w>.
117. Poveda-Montoyo I, Álvarez-Chinchilla P, Schneller-Pavelescu L, Hispán-Ocete P, Bañuls-Roca J. Series of fourteen cases of topical imiquimod 5% in lentigo maligna: treatment modalities and clues for detecting recurrences. *Actas Dermosifiliogr.* 2022;113(4):407–12. <https://doi.org/10.1016/j.ad.2021.07.018>.
118. Soenen A, Vourc’h M, Khammari A, et al. Change in lentigo maligna score assessed by in vivo reflectance confocal microscopy after 1 month of imiquimod treatment for lentigo maligna management. *J Am Acad Dermatol.* 2022;86(5):1042–8. <https://doi.org/10.1016/j.jaad.2021.03.077>.
119. Ishioka P, Costa LL, Maia M. Practical application of laser reflectance confocal microscopy in the follow-up of patients with lentigo maligna undergoing treatment with imiquimod. *An Bras Dermatol.* 2022;97(4):520–2. <https://doi.org/10.1016/j.abd.2021.01.008>.
120. Missall TA, Hurley MY, Fosko SW. Lentiginous melanoma in situ treatment with topical imiquimod: need for individualized regimens. *Arch Dermatol.* 2010;146(11):1309–10. <https://doi.org/10.1001/archdermatol.2010.338>.
121. Mataca E, Migaldi M, Cesinaro AM. Impact of dermoscopy and reflectance confocal microscopy on the histopathologic diagnosis of lentigo maligna/lentigo maligna melanoma. *Am J Dermatopathol.* 2018;40(12):884–9. <https://doi.org/10.1097/DAD.0000000000001212>.
122. 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):208–50. <https://doi.org/10.1016/j.jaad.2018.08.055>.
123. Associazione Italiana Oncologia Medica (AIOM). Linee guida “Melanoma” edizione 2020. 2020. [https://www.aiom.it/wp-content/uploads/2020/10/2020\\_LG\\_AIOM\\_Melanoma.pdf](https://www.aiom.it/wp-content/uploads/2020/10/2020_LG_AIOM_Melanoma.pdf). Accessed 20 July 2023.
124. 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):1476–84. <https://doi.org/10.1111/jdv.14850>.