



# Effectiveness of 5% Topical Imiquimod for Lentigo Maligna Treatment

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**Lentigo maligna (LM) is treated to prevent progression to lentigo maligna melanoma (LMM). Surgery is the gold standard, but an alternative treatment is off-label topical imiquimod. The aim of this study was to evaluate the effectiveness of 5% topical imiquimod treatment for lentigo maligna. In the period 2007–2017 57 patients with lentigo maligna were treated with off-label topical imiquimod once daily for 12 weeks. Complete clinical clearance was observed in 48 patients (84.2%) and partial clearance in 3 patients (5.3%). Three patients (5.3%) showed no response and another 3 patients (5.3%) stopped treatment due to side-effects. After 4.5 years, during follow-up, one patient developed a lentigo maligna melanoma, which was subsequently excised. Treatment with topical imiquimod resulted in complete clearance of lentigo maligna in 48 out of 57 patients (84.2%). Topical imiquimod is an acceptable treatment option for patients with lentigo maligna who prefer topical treatment to surgery or radiotherapy.**

*Key words:* lentigo maligna; topical imiquimod; melanoma.

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Lentigo maligna (LM) is considered a type of melanoma *in situ*. It is prevalent in a predominantly elderly population with a fair skin type. LM typically occurs on chronic sun-exposed skin, such as the head and neck area, where critical anatomical structures are located. Elderly patients often have multiple comorbidities and, as a consequence, clinical management may be challenging. Several studies have shown an increased incidence of LM over recent decades (0.54 LM/100,000 patient years to 1.99 LM/100,000 patient years) (1–4). Treatment of LM is recommended in order to prevent progression to lentigo maligna melanoma (LMM), which can metastasize. The true progression rate is unknown, but a recent epidemiological study describing 10,545 LM and 124 LMM patients reported that the cumulative risk of LMM developing after a LM on any location after 25 years is 2.0–2.6%. The progression of individual lesions could not be evaluated in this study (1).

According to the current European Consensus Guideline (5), surgical excision is the gold standard for

## SIGNIFICANCE

Lentigo maligna is treated to prevent progression to lentigo maligna melanoma. The current treatment of choice for lentigo maligna is surgical excision. Topical imiquimod is an alternative option. In this study, topical imiquimod treatment was successful in 84.2% of patients with lentigo maligna.

treatment of LM. Alternative treatment options, such as off-label topical imiquimod 5%, radiotherapy, or watchful waiting, are mentioned in the guideline, but there is no recommendation on their application (5). Surgical excision of larger lesions can result in disfiguring scars or functional impairment, and radiotherapy could potentially cause secondary malignancies or radiodermatitis (6, 7). Off-label topical imiquimod has the advantage of providing a good cosmetic outcome and it is easy to use for elderly patients (8).

The reported response rate to off-label topical imiquimod for LM varies between 37.0% and 78.6% (9–12). This wide range of response rates could be due to the use of different treatment regimens.

A survey performed by our group among 415 dermatologists in Europe showed that non-surgical options are used quite often. Of the respondents, 17.0% indicated that they use radiotherapy, 30.6% topical imiquimod, and 19.6% watchful waiting when treating LM patients >70 years of age (13).

Patients with LM have been treated with off-label topical imiquimod 5% since 2007. The patients recruited for this cohort between 2007 and 2012 have been described previously by Kirtschig et al. (8), who treated 27 patients with topical imiquimod, of whom 20 (74%) showed complete clinical and histological clearance with a mean follow-up of 39 months. The current study expands this cohort with 30 additional patients with LM treated between 2012 and 2017.

The aim of this study was to analyse all patients with LM treated prospectively with off-label topical imiquimod at our centre between November 2007 and December 2017, in order to evaluate the effectiveness of this treatment. Data were collected retrospectively by reviewing clinical records.

## METHODS

Patients were usually referred to our academic referral centre when they were not eligible for surgical treatment or did not want

surgical treatment. Often these patients were referred specifically for treatment with off-label topical imiquimod. All patients were informed about the advantages and disadvantages of excision, radiotherapy, off-label topical imiquimod, and watchful waiting. A shared decision for treatment was made depending on the location of the lesion, comorbidity of the patient, feasibility of the treatment option, and the patient's preference. If off-label topical imiquimod was chosen, informed consent was obtained prior to treatment. If watchful waiting was chosen, patients were offered check-up appointments for clinical revision every 3 months. When clinical or dermoscopic changes were seen during these check-up appointments, the treatment options were discussed again.

Patients were instructed to apply topical imiquimod to the lesion daily with a 1–2-cm margin for a total of 12 weeks. The aim was to achieve at least 10 weeks of inflammation. Patients had a check-up appointment every 4 weeks. Depending on the inflammatory reaction, the treatment schedule was adapted. If the inflammation was “too intense” (erythema and erosion of the skin was seen outside the application area), patients were instructed to apply imiquimod 3 times a week, and if the inflammatory response was “too mild” (no erythema or erosions of the skin were seen) patients were instructed to apply imiquimod twice daily (8, 14). The treatment protocol for off-label topical imiquimod for LM was reviewed and consented by the ethics committee of Vrije Universiteit Medical Center.

Some patients had received other treatment prior to topical imiquimod, by excision, cryotherapy, or radiotherapy. Such lesions were regarded as recurrent. Previous biopsies taken elsewhere were sent to the pathology department for revision by an experienced dermatopathologist, to confirm the diagnosis of LM. All samples were examined using haematoxylin and eosin and Melan-A (MART-1) staining. LM was histologically defined as a proliferation of atypical melanocytes along the basal cell layer of the epidermis, with possible extension into hair follicles and ascension of melanocytes. Post-inflammatory hyperpigmentation (PIH) was defined by the presence of melanophages in the dermis without proliferation of atypical melanocytes (15).

After treatment, if no residual pigmentation was visible with the naked eye or by dermoscopy a lesion was deemed completely clinically clear. Lesions were classified as partially clear if pigmentation was reduced in comparison with pre-treatment photographs, but still visible macroscopically or by dermoscopy.

When a lesion did not change at all, the patient was classified as a non-responder.

After completion of treatment, patients were invited for a check-up visit every 6 months. Clinical assessment included comparison with previous dermoscopic and photographic documentation. During follow-up, if a patient showed pigmentation at the treated site at any time, a 3-mm punch biopsy was performed to investigate whether the pigmentation was PIH or residual LM.

A sub-analysis of our cohort was performed to determine whether there was a difference between a total of ≤60 applications or >60 applications.

*Statistical analysis*

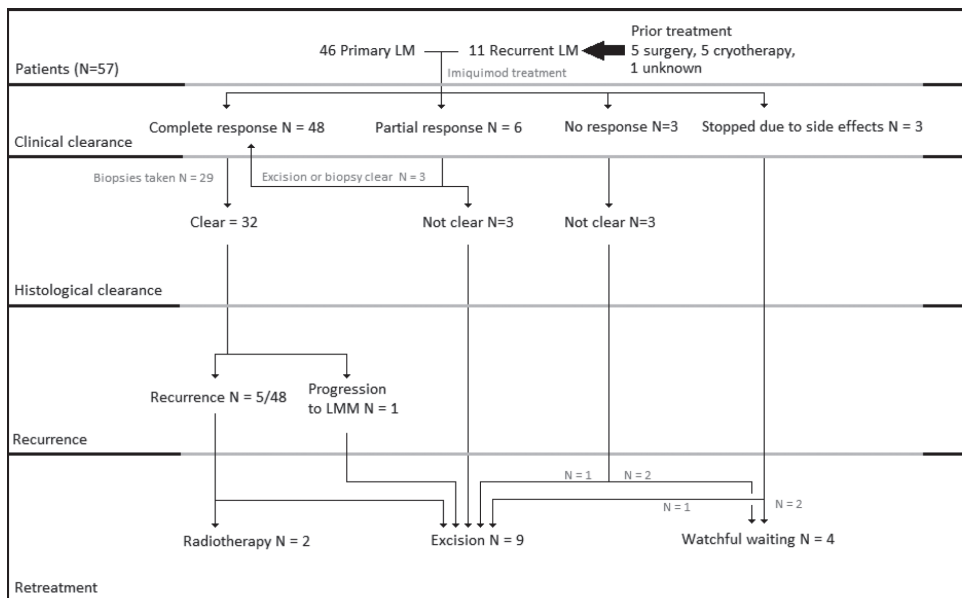
Data were analysed using descriptive statistics with SPSS (version 22.0; IBM Co.  $\chi^2$  tests were used for sub-analysis of the difference between ≤60 applications and >60 applications in total.

**RESULTS**

A total of 57 patients with histologically proven LM were treated with topical imiquimod between 2007 and 2017.

Of the 57 treated patients, 24 were men (42.1%) and 33 were women (57.9%), with a mean ± standard deviation (SD) age of 76 ± 10.6 years. There was a median (interquartile range; IQR) follow-up of 36 (24–60) months. Most lesions were located on the nose (n=23) or cheek (n=20), some on the forehead (n=8), the temple (n=3), the chin (n=1), the cutaneous upper lip (n=1) and the earlobe (n=1) (Fig. 1). The lesions had a median (IQR) longest diameter of 15 mm (10–23 mm). Of the 57 patients, 46 had primary lesions (80.8%) and 11 had recurrent lesions (19.2%). The patients with recurrent LM were treated surgically (n=5), by cryotherapy (n=5) or by an unknown modality (n=1) prior to treatment with topical imiquimod.

The median (IQR) number of applications of topical imiquimod was 84 in total (77–84 applications). Of the



**Fig. 1. Overview of patients with lentigo maligna (LM) treated with topical imiquimod 5%. LMM: lentigo maligna melanoma.**

57 patients, 10 (17.5%) applied imiquimod  $\leq 60$  times in total. The remaining 47 patients (82.5%) applied imiquimod  $> 60$  times in total (**Table I**).

#### Clinical clearance, histopathological clearance and retreatment

Complete clinical clearance was found in 48 patients (84.2%). Of these patients, 29 underwent a post-treatment 3-mm punch biopsy. All of these biopsies showed PIH and histological clearance of LM. The other 19 patients declined a post-treatment biopsy. They returned for follow-up after treatment.

Partial clinical clearance was found in 6 patients (10.5%). One patient underwent re-excision of the LM lesion without a post-treatment biopsy. Histopathological examination confirmed the presence of residual LM. The remaining 5 patients had a 3-mm punch biopsy performed after treatment. Of these 5 biopsies, 3 showed PIH without residual LM, the 2 other biopsies showed residual LM. The 3 patients with a clear biopsy were added to the total of patients with complete clinical clearance. The 2 patients with a biopsy showing residual LM underwent surgical excision.

Three patients (5.3%) did not respond to treatment. Of these, 2 underwent a biopsy, which showed residual LM in both cases. Both patients declined surgical excision or radiotherapy and opted for watchful waiting. These patients were reviewed clinically every 3 months; so far they have not been re-treated. The third non-responder underwent surgical excision.

Another 3 (5.3%) patients stopped treatment early due to side-effects. Side-effects observed in this study included flu-like symptoms ( $n=11$ ), lymphoedema of the cheek ( $n=3$ ), headache ( $n=7$ ) and a sterile conjunctivitis ( $n=3$ ). The 3 patients who discontinued treatment due to side-effects did not undergo biopsies post-treatment. Residual pigmentation was still visible in these patients. One patient was retreated by excision and referred back to his original dermatologist. The 2 other patients were reviewed clinically every 3 months and have not been re-treated so far (Fig. 1).

#### Recurrence after off-label 5% topical imiquimod

A total of 6 LM recurred (10.5%) after a mean follow-up period of 22.5 months (5–55 months). Recurrences after treatment with topical imiquimod were found on

**Table I. Demographics of patients with lentigo maligna (LM) ( $n=57$ ) treated with off-label 5% topical imiquimod**

Characteristics	
Men/women, $n$ (%)	24 (42.1)/33 (57.9)
Age, years, mean $\pm$ SD	76 $\pm$ 10.6
Follow-up, months, median (IQR)	36 (IQR 24–60)
Primary/recurrent, $n$ (%)	46 (80.8)/11 (19.8)
Longest length of LM, mm, median (IQR)	15 (10–23)
Location, $n$ (%)	
Nose	23 (40.4)
Cheek	20 (35.1)
Forehead	8 (14.0)
Temporal	3 (5.4)
Chin	1 (1.7)
Cutaneous lip	1 (1.7)
Earlobe	1 (1.7)
Total applications of imiquimod, median (IQR)	84 (77–84)
Patients who applied imiquimod $< 60$ times, $n$ (%)	10 (17.5)
Patients who applied imiquimod $> 60$ times, $n$ (%)	47 (82.5)

SD: standard deviation; IQR: interquartile range.

the chin ( $n=1$ ), forehead ( $n=2$ ), cutaneous upper lip ( $n=1$ ), cheek ( $n=1$ ) and earlobe ( $n=1$ ). In 2 of 6 patients, recurrences were found after 5 months. Both patients had recurrent LM following surgery or cryotherapy, prior to treatment with topical imiquimod. In the other 4 patients recurrences were seen after 10, 29, 31 and 55 months. The patient who showed recurrence after 55 months initially presented a histologically proven, primary LM on her left earlobe. After treatment a biopsy showed no residual LM, and check-ups were performed every 6 months. No recurrence was seen, but after 4.5 years she reported repigmentation at the treated site. A biopsy showed LMM (Breslow thickness 0.4 mm, T1aN0M0), which was subsequently surgically excised. This patient was checked regularly for 2 years after excision and, to date, she has not developed local recurrence or metastasis. All 6 patients with recurrent LM were offered alternative treatment; 4 patients opted for excision and 2 for radiotherapy (**Table II**).

#### Subanalysis

A subanalysis showed no significant difference in complete clinical clearance rates between patients who applied imiquimod  $\leq 60$  or  $> 60$  times in total ( $p=0.24$ , data not shown).

## DISCUSSION

Our academic outpatient clinic treated 57 patients with LM with off-label topical imiquimod (one application

**Table II. Recurrence of lentigo maligna (LM) after treatment with off-label 5% topical imiquimod**

Case number	Primary or recurrent	Previous treatment	Location	Time to recurrence (months)	Treatment after recurrence
Case 1	Recurrent	Cryotherapy	Cheek	5	Excision
Case 2	Recurrent	Excision	Upper lip	5	Excision
Case 3	Primary	-	Forehead	10	Radiotherapy
Case 4	Primary	-	Forehead	29	Excision
Case 5	Primary	-	Chin	31	Radiotherapy
Case 6	Primary	-	Earlobe	55 (progression to LMM)	Excision

LMM: lentigo maligna melanoma.

daily for 12 weeks) over a 10-year period. This treatment resulted in complete clinical clearance in 84.2% of patients, with a 10.5% recurrence rate during follow-up. One patient (1.8%) treated with topical imiquimod showed progression to LMM after 4.5 years of follow-up. The progression rate of LM to LMM in this study was 1.8%, which is similar to previous studies on topical imiquimod for LM. A systematic review of LM treated with topical imiquimod described 471 treated patients, with only 9 cases progressing to LMM following topical imiquimod (1.9%) (11).

Kai et al. (12) reported a clearance rate of 62.5% ( $n=40$ ). The patients in this study applied topical imiquimod 3 times a week for 6 weeks, followed by 5 times a week for 4 weeks, for a total of 38 applications. Another study by Marsden et al. (9) reported a 37% ( $n=27$ ) histological clearance rate. These patients applied topical imiquimod 5 times a week for 12 weeks; a total of 60 applications. The more intense treatment regimen used in the current study could explain the higher clearance rate observed. This is concurrent with the results of a systematic review, which has shown that the odds ratio of achieving complete clinical clearance is 8 times higher if topical imiquimod is applied >60 times in total (10, 11).

Compared with staged surgical techniques or radiotherapy, topical imiquimod has a higher recurrence rate, at 10.5%. Surgical excision with a 5-mm margin has a recurrence rate of 30% after 5.5 years (16) while staged excision techniques, such as Mohs micrographic surgery or the “spaghetti technique” show a superior recurrence rate of 4–5.9% (1, 17, 18). Radiotherapy has a reported recurrence rate of 5% after 3 years (19). Topical imiquimod, however, has the advantages of being non-invasive, providing a good cosmetic outcome, and being easy to use for elderly patients. To our knowledge, no comparative studies between treatments have been published to date.

To determine the position of topical imiquimod in a treatment algorithm it is necessary to define the primary goal of treatment. Currently, the main treatment goal for LM is to prevent progression to LMM. The true progression rate is unknown, although Greveling et al. reported that the cumulative risk of developing LMM after primary LM is 2–2.6% over a course of 25 years (1). Patients with LM are mostly elderly and have been shown to have a relative survival rate of 104% compared with the general population, while patients with LMM have a relative survival rate of 99% after treatment (1). In contrast, studies on malignant melanoma (non-LMM) showed a relative 5-year survival of 76–83.4% after treatment (20, 21). The current study found no LM- or LMM-related deaths. A previous study on surgical treatment of LM and LMM by Gambichler et al. (22) reported similar findings. In a cohort of 270 patients (124 with LM and 146 with LMM) who were treated surgically they

observed no LM- or LMM-related deaths after a mean follow-up of 55 months.

Swetter et al. (23), have suggested that histological clearance should not necessarily be the gold standard to measure the success of LM treatment. In general, LM develops on actinically damaged skin. In sun-damaged skin, morphologically atypical, but biologically non-malignant, melanocytes may reside at the dermal–epidermal junction and may simulate LM. This makes diagnosis difficult. Histologically these atypical, but non-malignant, melanocytes are indistinguishable from true malignant cells, even with the use of immunostains (MART1/melan-A, SOX10, MiTF and soluble adenylyl cyclase) (23, 24). Thus it is difficult to prove radical excision and, subsequently, striving for histological clearance could lead to large, perhaps unnecessary, defects.

The current study has several limitations. Firstly, patients referred to us for LM are usually elderly, who often do not want to undergo surgical excision. Most of these patients did not want radiotherapy either, because it requires daily travelling to the hospital for several weeks. Therefore, this patient population is prone to selection bias, which may have influenced the study results. Secondly, 11 of our patients had been diagnosed with recurrent LM prior to treatment with topical imiquimod. This may have confounded the response to therapy. Lastly, the usage of single 3-mm punch biopsies for histopathological examination may have led to sampling error in cases of large LMx.

Based on these results, we conclude that off-label topical imiquimod is an acceptable treatment option for patients with large LM lesions and for those who do not want surgical excision or radiotherapy. Future studies should focus on comparing treatment options for LM, and whether histological clearance should be regarded as the most important measure of outcome.

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*The authors have no conflicts of interest to declare.*

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