**Melanoma**

**Alternative Therapies**

**Nonsurgical Treatments for Lentigo Maligna**

James M Grichnik MD PhD  
Director, Scully-Welsh Cancer Center  
Indian River Medical Center  
grichnik@IRMC.CC

---

**DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY**

James M. Grichnik M.D. Ph.D.  
Alternative Therapies  
Major Shareholder & Founder  
DigitalDerm, Inc (MoleMapCD®)  
Consultant  
ClearView, Galileo, Novartis, Castle Biosciences, Caliber ID

---

**Nonsurgical Treatments**

- Surgical excision is the standard of care for all primary cutaneous melanomas
- When surgery not an option, comorbidities/preferences, for lentigo maligna alternative therapies may be considered.
- Limitations need to be clearly discussed

**Limitations of nonsurgical treatment modalities**

- Risk of missing and undertreating invasive melanoma by not microstaging the primary lesion
- Higher local recurrence rates because of a lack of margin control
- Absence of long-term, randomized, controlled comparative studies

---

**Nonsurgical Treatments (Table V)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiquimod</td>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>Cryosurgery</td>
<td>C</td>
<td>III</td>
</tr>
</tbody>
</table>

C/III = consensus, opinion, case studies, or disease oriented evidence
Imiquimod

- Off-label use of topical imiquimod has been proposed as an alternative treatment to surgery, and an adjunctive modality after surgical excision.
- Studies are limited by highly variable treatment regimens and lack of long-term follow-up with an average of approximately 18 months.

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. JAAD 2015;73(2):205-12

- 347 tumors from 45 studies
- Clinical clearance rate 78.3% (95% CI, 73.6-82.9%)
- Histologic clearance rate 76.2% (95% CI, 71.4-81.0%)
- Clinical recurrence was 2.3% (95% CI, 0.5-4.2%), with a mean follow-up of 34.2 ± 11.8 months
- Treatment with 60 total applications was associated with a higher histologic clearance (odds ratio, 8.4 [95% CI, 2.9-24.1])
- Treatment with 5 applications per week was associated with a higher histologic clearance (odds ratio, 6.0 [95% CI, 2.4-14.7])

Time to local recurrence lentigo maligna: Implications for future studies. Connolly KL et al JAAD 2016 1247-8

- 100 76 LM/41LMM Mean time for 4 local recurrence 5.9 years (range 1.9 to 8.9)

Imiquimod 5% cream as primary or adjuvant therapy for melanoma in situ, lentigo maligna type. Swetter SM, Chen FW, Kim DD, Egbert BM. JIAD 2015 1047-52

- 63 LM/LMM cases were identified in 61 patients, mean (SD) age 71.1 (12.4) year
- 58 were analyzed for local recurrence. Imiquimod was used as primary therapy in 22 of 63 (34.9%) and adjuvant therapy in 41 of 63 (65.1%) for mean duration of 11.7 (range 2-60) weeks.
- Fifty cases (86.2%) demonstrated clinical clearance at mean (SD) follow-up of 42.1 (27.4) months:
  - 72.7% primary at 39.7 (23.9) months
  - 94.4% adjuvant at 43.1 (28.9) months.

A systematic review on the role of imiquimod in lentigo maligna and lentigo maligna melanoma: need for standardization of treatment schedule and outcome measures. Ti D et al. JEADV 2016; 1-7

- Clinical clearance was seen in 369 of 471 patients (78.5%).
- Histological clearance was present in 285 of 770 (77%) patients.
- LMM was diagnosed in nine (1.8%) patients 3.9 months (range 0–11 months) post-treatment.
- 6–7 applications/ week had a 6.47 greater odds (P = 0.017) of resulting in complete clinical clearance compared to 1–4 applications/ week.
- 6–7 applications/week showed a 8.85 greater odds (P = 0.003) of resulting in histological clearance compared to 1–4 applications.
- Applying imiquimod >60 times during a treatment period of 12 weeks (range 4–36) showed a 7.75 greater odds (P = 0.001) of resulting in histological clearance compared to <60 total applications.
Topical imiquimod with vs without tazarotene, 22% (8 of 37) of lesions vs 36% (15 of 42) of lesions showed residual LM on staged excisions.

Did not reach statistical significance ($P=.17$).

No recurrences noted with a mean follow-up period of 42 months.

Confocal microscopy identified 70% of these responders with no false-negative results.

- RCM and histopathology interpretations were concordant in 56 of 63 sites (89%).
- No false negative and 7 false-positive results using RCM
- Sensitivity 100%, specificity 71%, positive predictive value 85%, negative predictive value 100%

Eighty-nine patients with histologically confirmed LM and a median follow-up time of 4.8 years after imiquimod treatment were included

Sixteen patients (18%) relapsed.

Statistically significant indicators of an increased risk of local recurrence included: the total number of melanocytes, the number of basal and suprabasal melanocytes and the number of pagetoid spreading melanocytes.

- Risk of a severe inflammatory reaction
- High cost of treatment
- Low threshold for subsequent biopsy to exclude residual or recurrent disease
Radiotherapy

- Primary radiation therapy for lentigo maligna, with or without prior excision of a nodular component of lentigo maligna melanoma, may be considered when complete surgical excision is not a realistic option.

- 537 patients with LM treated with definitive primary RT with a median reported follow-up time of 3 years.
- 18 recurrences documented in a total of 349 assessable patients (5%). Salvage was successful in the majority of recurrent LM cases by using further RT, surgery or other therapies.
- Progression to LM melanoma (LMM) occurred in five patients (5 of 349, 1.4%) who all had poor outcomes.

Histologic confirmation of tumor clearance after radiation therapy has not been well documented.

Reported clinical recurrence rates after radiation therapy range from 0% to 14% (Review - ~5%).
Cryosurgery

- 30 patients lesions ranged from 1.3 to 4.5 cm in diameter
- Open spray, temp probes -45-50, 3-5mm
- 2 patients recurred (6.6%) - average follow-up 3 years (re-treated with cryosurgery).
- Eleven patients observed for more than 5 years showed no recurrence.

- 10 LM
- 3 short freeze-thaw cycles
- 9 cleared in 2-4 treatments
- Mean follow up 4 years
- Recurrences (macular) in 4 patients (1-9 years later) and 3 cleared with further treatment. Two had subsequent recurrences 2 and 3 years later which responded to cryotherapy were clear to date

- 12 LM patients
- Thermocouples -30 to - 40
- Average follow-up 51.4 months (range 30-80 M)
- LM recurred in 1 patient (8.3%), cryosurgery was administered a second time. No sign of recurrence (18M after 2nd Rx)
- Retrospectively used S-100 immunohistochemical stains and identified intradermal microinvasion in 1 patient, no recurrence within 61 months of follow-up.

- 14 LM, 8 LMM
- LM 6 received 30 s cotton swab method; 8 were treated with a single freeze using liquid nitrogen spray. More aggressive 2x for LMM
- 14 LM, 13 cured, 1 retreated at 3 w and cleared. 2 had hypopigmentation for approximately 3 months. 1 subject developed hypopigmentation which remained 14 months. No recurrences with follow up 7 M -2.5 Y.
- 8 LMM, 6 remitted completely, 2 were retreated at 1 month and responded. No recurrences follow-up of 6 months to 2 years. 2 patients with hypopigmentation 6 and 10 months after cryotherapy; one of these had received a second treatment.

- 20 with LM
- Cryo probe - 50
- Recurrence in 10%
- 42.6 median f/u

- 18 patients with clinical and histopathological Dx of LM
- 2 freeze thaw cycles of liquid nitrogen under local anesthesia. Lesions larger than 2 cm(2) were divided into smaller segments for freezing
- The lesions resolved clinically in all cases
- No recurrence or metastasis detected during a mean follow up of 75.5 months.
- Some patients developed hypopigmented scars

Cryosurgery

- Clinical clearance rate of 60% or higher (to 100%) have been reported
- Data are insufficient to determine a histologic clearance rate.

Recommendations for nonsurgical treatments (Table XIII)

- Nonsurgical therapy for primary cutaneous melanoma should only be considered under select clinical circumstances, when surgical excision is not feasible.
- Alternatives to surgery include topical imiquimod, radiation therapy, cryosurgery, and observation.
- Efficacy of nonsurgical therapies for lentigo maligna has not been fully established.

Observation

- When surgery for lentigo maligna is not possible, observation may also be acceptable.
- Although it is reasonable to assume that therapy aimed at decreasing tumor burden may improve outcome, none of the above-mentioned alternative treatment modalities have been shown to be superior to observation.