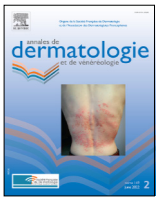
Annales de Dermatologie et de Vénéréologie 152 (2025) 103342

Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com/en



Original article

Radiation therapy on lentigo maligna: A single-centre retrospective study on 91 patients

D. Canu [a], R. Kabore [b], O. Cogrel [a], A. Lamoureux [b], E. Gerard [b], N. Ouhabrache [c], M. Beylot-Barry [a,d,*]

[a] Department of Dermatology Hôpital Saint-André CHU de Bordeaux Bordeaux France
[b] INSERM Bordeaux Population Health Research Centre UMR1219 Université de Bordeaux Bordeaux France
[c] Department of Radiotherapy Hôpital Haut-Lévêque CHU de Bordeaux Pessac France
[d] Bordeaux Institute of Oncology – UMR 1312 Université de Bordeaux Bordeaux France

ARTICLE INFO

Article history:
Received 23 August 2023
Accepted 3 July 2024
Available online 4 March 2025

Keywords:
Melanoma
Lentigo maligna
Radiotherapy

ABSTRACT

Background: Lentigo maligna (LM) is a melanoma subtype that occurs on sun-damaged skin in the elderly. Dermal invasive melanoma developing from LM is called LM melanoma (LMM) and has the same prognosis as other melanoma subtypes. The standard treatment for LM is surgery, which offers the lowest risk of recurrence. Alternatives exist, however, including radiotherapy (RT).
Objective: Describe a real-life cohort of patients with LM/LMM treated with RT and assess prognostic factors for recurrence.
Method: This is a retrospective monocentric real-life study conducted in Bordeaux University Hospital. All LM or LMM patients treated with RT between 2009 and 2020 were included. RT was administered using a superficial or orthovoltage X-ray (kV) with a dose of 40 Gy in 10 fractions over 5 weeks.
Results: Ninety-one patients were included: 67 LM and 24 LMM. Sixty-four patients were female, the mean age was 77 (range: 50 96) in LM group, and 80 (range: 56–98) in LMM group. The mean duration of post-RT follow-up was 25.1 months (range: 0–100). Fourteen recurrences were observed (15.4%): 10 in LM group (14.9%) and 4 in LMM group (16.7%). Most recurrences occurred in the irradiation field: 8/10 in LM group, and 2/4 in LMM group. Recurrences were more frequent in men (6/27 vs 8/64) and on the eyelid area (4/14) compared to others locations. The risk of recurrence was also higher in patients with at least one prior treatment failure (8/36 (22.2%) vs 6/55 (10.9%)). There were significantly fewer recurrences for patients who had achieved a complete response at 3 months compared to those with a partial response (7.1% vs 28.6%, $p = 0.0159$).
Conclusion: Radiotherapy is a therapeutic alternative to surgery to be considered for selected patients with LM.

1. Introduction

Lentigo maligna (LM) is a form of melanoma *in situ* that occurs in the vast majority of cases on sun-damaged skin, especially on the face and neck, and mainly affects the elderly. The diagnosis of LM is based on clinical and dermoscopic features, and is confirmed by biopsy and histological analysis. Dermal invasive melanoma developing from LM is called LM melanoma (LMM). Although the transformation/evolution of LM to LMM is slow, the estimated risk of developing an LMM in this manner in one's lifetime is 5%, with the same prognosis as other melanoma subtypes [1–3]. The recent development of confocal microscopy now allows more precise delineation of the LM and more sensitive monitoring after treatment in order to detect recurrences [4]. The "gold standard" treatment for LM is surgery, which has the lowest risk of recurrence, ranging from 6.8% with conventional surgery to less than 2% with Mohs micrographic surgery [5]. However, the size of the lesion, its location and the advanced age of the patient can make surgery challenging. Moreover, some patients may refuse surgery for cosmetic or functional reasons, making it necessary to propose alternative solutions. Non-surgical treatment for LM mainly includes radiotherapy (RT), topical imiquimod and laser. The nature of these therapies implies limits on their ability to ensure that the entire tumour is treated, that areas of invasion are excluded, and that completely healthy margins are maintained. RT is described as one of the most effective technique, with a mean

* Corresponding author at: Department of Dermatology, Hôpital Saint-André, CHU de Bordeaux, 1 rue Jean Burguet, 33000 Bordeaux, France.
E-mail address: marie.beylot-barry@chu-bordeaux.fr (M. Beylot-Barry).

https://doi.org/10.1016/j.annder.2025.103342
0151-9638/

recurrence rate of 11.5% [6]. It is proposed as curative treatment or as adjuvant treatment when the surgical margins are affected. The decision to use RT must be made in a multidisciplinary meeting, ideally in the presence of the patient. RT allows acceptable local control of LM, with an excellent cosmetic outcome. However, studies describing RT for the treatment for LM are heterogeneous, describing the use of Grenz ray (<20 kV), superficial X-rays, orthovoltage or electron therapy. The aim of our study was to describe in real life, use of RT in patients with LM or LMM and to assess prognostic factors for recurrence.

2. Patient and methods

2.1. Study design and patient recruitment

This retrospective monocentric study was conducted in Bordeaux University Hospital. All patients with LM or LMM treated with RT between 2009 and 2020 in the RT department were included. RT treatment was decided after a multidisciplinary meeting involving at least surgeon, radiotherapist and oncodermatologist for patients with lesion requiring complex surgical reconstruction either due to its size or location or both, or when surgery was refused by the patient. The following baseline data were retrieved from medical files: histology, sex, age, location of LM, previous treatments, RT technical information (energy, applicator), clinical response assessed at 3 months (complete response (CR), partial response (PR), no response), side effects, overall duration of follow-up after RT and recurrences (inside or outside the irradiation field, cutaneous or extra-cutaneous). In our study, the quality of the response was clinically defined; CR corresponded to the absence of residual pigmentation. In case of suspected clinical or dermoscopic recurrence, a biopsy was performed. This, post-RT recurrence was defined as positive skin histology or the presence of one or more metastatic lesions on imaging. For our cohort, clinical follow-up was usually every 6 months.

2.2. Radiation therapy

RT was administered using a superficial or orthovoltage X-ray (kV) with a dose of 40 Gy in 10 fractions of 4 Gy, 2 days per week, for 5 weeks. A clinical margin of 1 cm was used for all patients.

2.3. Statistical analysis

We performed a descriptive analysis of patients, tumours and treatment characteristics according to LM and LMM groups. Qualitative variables were described by frequency, and quantitative variables by mean and standard deviation. We performed a chi-squared test to identify factors associated with recurrence. When the test conditions were not met, we performed Fisher's exact test or the Freeman-Halton test. The significance level was $p \leq 0.05$. Analysis was performed using SAS software, version 9.4.

3. Results

3.1. Patient characteristics

Ninety-one patients were included (Table 1): 67 LM (73.6%) and 24 LMM (26.4%). The majority of patients were women: The mean ages were 77 (range: 50–96) for LM and 80 (range: 56–98) for LMM. LM was located on the cheek more often than LMM (54.2% vs. 43.3%, respectively). RT was performed more often on the nose (32.8%) and the palpebral area (17.9%) in LM group than in LMM group (both 8.3%) ($p = 0.0002$). Regarding lesion size, 33 patients (49.2%) in LM group and 16 patients (66.6%) in LMM group required an applicator wider than 4 cm ($p = 0.1189$). In LMM group, the mean Breslow was 1.13 mm (range: 0.1–12). A 96-year-old patient with a 12 mm Breslow underwent RT after incomplete surgery on her ear.

RT was more frequently used as first-line treatment in LM group than in LMM group (67.2% vs 20.8%). It was used as second-line treatment after failure of another therapy (mainly Mohs surgery or imiquimod) in 20 patients (29.8%) in LM group, and 17 patients (70.8%) in LMM group ($p = 0.0002$). Among these patients, 2 patients in each group had RT as adjuvant, following incomplete surgery. The duration of post-RT follow-up was similar in the 2 groups, of 25.1 months (range: 0–100).

Overall tolerance of the treatment was good; the most frequent side effect was immediate grade II radiation dermatitis (Fig. 1), which was common, occurring in 73.6% of all cases (67/91). Only 7 patients (7.7%) had grade III radiation dermatitis.

3.2. Clinical response

At 3 months after the end of RT, out of the 78 patients evaluable at this time, all but one was in CR or RP: 42 and 35 respectively (Figs. 1 and 2). The CR rate was 44.8% ($n = 30$) in the LM group and 50% ($n = 12$) in the LMM group; for PR it was respectively 40.3% ($n = 27$) and 33.3% ($n = 8$). There were significantly fewer recurrences for patients with CR at 3 months compared to those with PR (7.1% vs 28.6%, $p = 0.016$). The response extent (complete or partial) could not be assessed in 13 patients.

3.3. Recurrences

Fourteen recurrences were observed (15.4%): 10 in LM group (14.9%) and 4 in LMM group (16.7%) (Table 1). The mean time to recurrence was 23 months (range: 2–48). Only one patient in LM group had an invasive recurrence (Breslow index = 0.7 mm). Three patients in LMM group developed metastases, including one concomitantly with local recurrence, and one with metastases in transit. Most local recurrences occurred in the irradiation field: 8/10 in LM group and 2/4 in LMM group. There was no difference in the recurrence rate depending on the energy used (< or ≥80 kV).

There were 11 patients with isolated local recurrences (10 *in situ* and one invasive). Metastatic recurrences were only observed in patients of the LMM group: one had skin metastases in transit near the previously irradiated LMM, one had local and metastatic recurrences and one had isolated metastatic recurrences (pulmonary and adrenal glands).

As presented in Table 2, recurrences were more often observed in men (6/27 male patients, 22.2%) than in women (8/64 female patients, 12.5%). The eyelids tended to be most associated with risk of recurrence (4/14, 28.6%), compared to other areas, such as the cheeks (4/42, 9.5%). The risk also seemed to be higher in patients with at least one prior treatment failure (8/36, 22.2%, vs 6/55, 10.9%) and with LM ≤ 4 cm (9/39, 23.1%) compared to those >4 cm (5/49, 10.2%) although this does not reach a statistically significant value.

Patients with isolated local recurrences were treated with surgery ($n = 6$, including the single invasive recurrence), imiquimod ($n = 3$), imiquimod followed by surgery ($n = 1$), RT for a recurrence outside the first radiation field ($n = 1$), and one patient was lost to follow-up.

The patient with LMM and metastases in transit progressed during RT, which led the treatment to be discontinued and it was the only case of initial non-response to RT. Concerning the patient with local and metastatic recurrence, the local recurrence was managed by surgery and no specific treatment for the metastatic recurrence was undertaken in view of his age (90 years). The patient with metastatic recurrence without local recurrence died

Table 1
Characteristics of patients with LM or LMM.

	Total	LM	LMM	*P* value
Total	91	67 (73.63)	24 (26.37)	<0.0001
Age, mean (years)	77.1 [50–98]	76 [50–96]	80 [56–98]	0.1294
Male/Female n (%)				
Male	27 (29.7)	22 (32.8)	5 (20.8)	0.2694
Female	64 (70.3)	45 (67.2)	19 (79.2)	
Location of LM/LMM, n (%)				
Cheek	42 (46.2)	29 (43.3)	13 (54.2)	0.0002**
Nose	24 (26.4)	22 (32.8)	2 (8.3)	
Palpebral	14 (15.4)	12 (17.9)	2 (8.3)	
Other	11 (12.1)	4 (6)	7 (29.2)	
Breslow index, mean (mm)			1.13 [0.1–12]	
Indication of radiotherapy, n (%)				
First-line	50 (54.9)	45(67.2)	5 (20.8)	0.0002**
After failure of previous treatment*	41 (45.1)	20 (29.8)	17 (70.8)	
Including post-surgery R1	4 (4.4)	2 (3)	2 (8.3)	
Radiation applicator, n (%)				
≤4 cm	38 (41.8)	31 (46.3)	7 (29.2)	0.1189
>4 cm	49 (53.8)	33 (49.2)	16 (66.6)	
Not reported	4 (4.4)	3 (4.5)	1 (4.2)	
Early clinical response (3 months), n (%)				
Partial response	35 (38.5)	27 (40.3)	8 (33.3)	0.2538**
Complete response	42 (46.1)	30 (44.8)	12 (50)	
No response	1 (1.1)	0	1 (4.2)	
No data	13 (14.3)	10 (14.9)	3(12.5)	
Early side effects, n(%)				
Radiation dermatitis grade I	14 (15.4)	11 (16.4)	3 (12.5)	0.3339**
Radiation dermatitis grade II	67 (73.6)	50 (74.6)	17 (70.8)	
Radiation dermatitis grade III	7 (7.7)	6 (9)	1 (4.2)	
Not reported	3 (3.3)	0	3 (12.5)	
Skin Recurrences, n (%)	14 (15.4)	10 (14.9)	4 (16.7)	0.7708
Duration of follow-up, mean (months)	25.1 [0–100]	25.8 [0–100]	23 [0–66]	0.6110*

* ttest.
** Fisher's Exact Test.

from disease progression before treatment. This advanced age patient (96 year-old) had initially a 12 mm Breslow LMM, treated with RT after incomplete surgery.

At the time of data collection, 3 patients had died of causes unrelated to LM or LMM.

4. Discussion

Alternative treatments are relevant in LM since surgery is not always possible and the Mohs micrographic surgery technique is not available in all centres. Ellison et al. showed that to obtain 97% healthy margins with surgery, a margin of 1 to 1.5 cm should be used during conventional surgery, which represents a considerable loss of substance when lesions – especially large ones – are located on the face [5]. This may represent limitation according to size and location or both of LM, especially in advanced age patients who are the main population group concerned.

Management of LMM with RT requires a technique allowing very superficial irradiation (penetration of a few millimetres) – most often on the face, which is difficult with conventional linear accelerators. The use of superficial or orthovoltage X-rays is then necessary, but these techniques are not available in all centres. In the literature, recurrence rates after RT were higher than for surgery. However, the comparison with surgery must be made with caution, as patients undergoing RT often had unfavourable characteristics such as comorbidities, larger lesions or areas difficult to remove with adequate margins. Their prognosis in terms of recurrence risk was therefore probably not the same. The recurrence rate following RT in our study (15.4%) was comparable to rates found in reviews on the subject [6–8]. The place and modalities of RT in the management of LM are not yet well established, without comparative studies on different irradiation techniques used. Hedblad et al. [9] described treatment with superficial energy RT (Grenz ray) in 593 patients with LM (from 1990 to 2009) in 3 circumstances – first-line treatment, after partial excision and adjuvant post-surgery treatment – with different recurrence rates: 17.1%, 9.9% and 3.5%, respectively. The 10-year follow-up of a portion of this same cohort (LM/LMM treated between 2005 and 2007) was recently published [10]. Of the 159 patients initially selected, 62 died, but only three from metastatic progression. Of the 68 remaining patients, only 2 (3%) had a recurrence of their LM and 9 (13%) presented another melanoma or LM/LMM.

Doses used for the irradiation of LM in the literature were also heterogeneous. Fogarty et al. [11] recommended superficial RT rather than Grenz ray for LM and LMM, allowing deeper penetration, and particularly to the skin annexes. These were, therefore, the techniques we used for our cohort. The recent study by Drakensjö et al. reported the high efficacy of Grenz ray (97% of cure rates) [10].

In our study, surprisingly, we observed more recurrences of the smallest lesions. This can be partially explained by the fact that there was a predominance of palpebral lesions (23.1%, $n = 9$), which tend to have a higher recurrence rate (4 out of 14 cases; 28.6%) or

Fig. 1. A patient before (a–c), during (d), in the final stage with radiation dermatitis grade II (e) and 3 months after radiotherapy (f).

Fig. 2. Before (a) and 3 months after (b) radiotherapy.

which can be more difficult to treat (because of necessary protection of the eyeball and possible damage to the mucous side of the eyelid).

In our study, the clinical response at 3 months after RT (PR or CR achieved in all assessable patients but one) made it possible to estimate the risk of recurrence. Indeed, a complete clinical response at 3 months was a good prognostic factor found in our study with less recurrence. Patients with early PR should be monitored more carefully, residual pigmentation should also raise suspicion of persistent LM, which may explain the higher recurrence rate in these patients, even though it remains low.

Rather than an alternative to surgery in the therapeutic strategy of LM, imiquimod seems to be used more as adjuvant or neoadjuvant therapy, to limit the loss of substance, rather than a true alternative to surgery. Maude et al. showed that imiquimod reduced the LM surface (4.6–3.1 cm^2) significantly ($p < 0.001$) more compared to the placebo (3.9–4.1 cm^2) [12]. Results obtained with laser are not convincing so far and its use in LM is therefore not recommended [6,13].

The risk with non-surgical methods is the possible omission of an invasive part of the LM not detected in prior biopsies. According to Erickson et al. [14], an invasive component was subsequently revealed when the entire lesion was removed in 22% of cases after an initial diagnosis of LM [3]. This probably explains part of the recurrences of LMM not initially identified, for which superficial RT is insufficient. We decided to include LMMs because this is a real-life study. It is clear that this indication must remain exceptional, and may be discussed in very elderly patients, or for palliative purposes (bleeding, pain, etc.).

The main limitations of our study are its monocentric and retrospective nature and the absence of a comparative group surgically treated in the same period. As previously discussed, however, these

Table 2
Results of univariate analysis of LM/LMM patients with or without recurrence.

	Total	Recurrence: *n* (%)	*p*
Total	91	14 (15.4)	
No data		9 (9.9)	
Male/Female, n (%)			0.3394
Male	27	6 (22.2)	
Female	64	8 (12.5)	
Type of lesion, n (%)			0.7480*
LM	67	10 (14.9)	
LMM	24	4 (16.6)	
Location, n (%)			0.2561**
Cheek	42	4 (9.5)	
Nose	24	3 (12.5)	
Eyelid	14	4 (28.6)	
Other	11	2 (18)	
Previous treatment, n (%)			0.2337
Yes	36	8 (22.2)	
No	55	6 (11)	
Surgical margins, n (%)			0.1675**
No previous surgery	56	6 (10.7)	
R0	17	5 (29.4)	
R1	18	3 (16.6)	
Radiotherapy, n (%)			
Applicator			0.1485
≤4 cm	39	9 (23)	
>4 cm	49	5 (10.2)	
No data	3	0	
Energy kV			0.9380*
<80	70	11 (15.7)	
≥80	20	3 (15)	
No data	1	0	
Early response (3 months)			0.0159
Partial response	35	10 (28.6)	
Complete response	42	3 (7)	
Not reported	14	0	

* Fisher exact test.
** Fisher-Freeman-Halton test.

treatments probably do not concern the same patients. Moreover, the mean follow-up after radiotherapy is 25.1 months and we cannot exclude late recurrences.

Surgery is the most effective treatment and should be the first option for LM. However, the use of radiation therapy for first-line treatment appears as a reasonable alternative to surgery in selected patients with LM, with a good cosmetic result, few side-effects and a high rate of efficacy with limited rare of recurrences that are mainly *in situ*.

Funding sources

This research did not receive any specific grant.

Statement of ethics

This study protocol was reviewed and approved by the ethics committee of the university hospital of Bordeaux, approval number CER-BDX-2022-22. Patients in this manuscript have given written informed consent to publication and any accompanying images.

Data availability statement:

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Andrew Cowderoy for editing the manuscript.

References

[1] McKenna JK, Florell SR, Goldman GD, et al. Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. Dermatol Surg 2006;32:493–504.
[2] Koh HK, Michalik E, Sober AJ, et al. Lentigo maligna melanoma has no better prognosis than other types of melanoma. J Clin Oncol 1984;2:994–1001.
[3] Gérard E, Cogrel O, Goehrs C, et al. Clinical features associated with the invasive component in lentigo maligna of the head and neck: a retrospective study of 175 cases. Ann Dermatol Venereol 2022;149:258–63.
[4] Elshot YS, Tio DCKS, van Haersma-de With ASE, et al. Lentigo maligna (melanoma): a systematic review and meta-analysis on surgical techniques and presurgical mapping by reflectance confocal microscopy. J Eur Acad Dermatol Venereol 2023;37:871–83.
[5] Ellison PM, Zitelli JA, Brodland DG. Mohs micrographic surgery for melanoma: a prospective multicenter study. J Am Acad Dermatol 2019;81:767–74.
[6] Read T, Noonan C, David M, et al. A systematic review of non-surgical treatments for lentigo maligna. J Eur Acad Dermatol Venereol 2016;30:748–53.
[7] Fogarty GB, Hong A, Scolyer RA, et al. Radiotherapy for lentigo maligna: a literature review and recommendations for treatment. Br J Dermatol 2014;170:52–8.
[8] Hendrickx A, Cozzio A, Plasswilm L, et al. Radiotherapy for lentigo maligna and lentigo maligna melanoma – a systematic review. Radiat Oncol 2020;14(15):174.
[9] Hedblad MA, Mallbris L. Grenz ray treatment of lentigo maligna and early lentigo maligna melanoma. J Am Acad Dermatol 2012;67:60–8.
[10] Drakensjö IRT, Rosen E, Frohm Nilsson M, et al. Ten-year follow-up study of grenz ray treatment for lentigo maligna and early lentigo maligna melanoma. Acta Derm Venereol 2020;100:adv00282.
[11] Fogarty GB, Hong A, Economides A, et al. Experience with treating lentigo maligna with definitive radiotherapy. Dermatol Res Pract 2018;2018:7439807.
[12] Daude M, Dinulescu M, Nguyen JM, et al. Efficacy of imiquimod in the management of lentigo maligna. J Eur Acad Dermatol Venereol 2023;37:1785–91.
[13] Robinson M, Primiero C, Guitera P, et al. Evidence-based clinical practice guidelines for the management of patients with lentigo maligna. Dermatology 2020;236:111–6.
[14] Erickson C, Miller SJ. Treatment options in melanoma in situ: topical and radiation therapy, excision and Mohs surgery. Int J Dermatol 2010;49:482–91.