Carbon Dioxide Laser Treatment for Lentigo Maligna

A Retrospective Review Comparing 3 Different Treatment Modalities

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Objective: To assess outcomes in managing primary lentigo maligna through surgical excision, radiation therapy, and carbon dioxide laser ablation.


Results: Seventy-five patients aged 39 to 93 years (mean age, 64.8 years) were included in the study; 73 patients chose treatment. Twenty-seven patients were treated with surgical excision, 31 patients with radiation therapy, and 15 patients with carbon dioxide laser ablation. The median follow-up times were 16.6 months for surgical excision, 46.3 months for radiation therapy, and 77.8 months for carbon dioxide laser ablation ($P < .001$). Recurrence rates by treatment modality were 4.2% (1 of 27) for surgical excision, 29.0% (9 of 31) for radiation therapy, and 6.7% (1 of 15) for carbon dioxide laser ablation.

Conclusions: A trend toward lower recurrence rates with surgical excision and carbon dioxide laser ablation was identified, but the results were not statistically significant. Carbon dioxide laser ablation may have a role as an alternative treatment for lentigo maligna among patients in whom standard treatments, such as surgical excision and radiation therapy, are declined or carry significant morbidity.

Arch Facial Plast Surg. 2011;13(6):398-403

Lentigo maligna (LM), or melanoma in situ, is a common premalignant skin lesion involving atypical melanocytes confined by the epithelial basement membrane. This lesion is typically seen in older populations with a history of chronic sun damage and is commonly located in the head and neck region. Lentigo maligna melanoma (LMM) as it invades beyond the basement membrane. When matched for depth of invasion, LMM has the same prognosis as other subtypes of melanoma. Weinstock and Sober estimated the lifetime risk of LM progressing to LMM as 5%, and it is primarily for this reason that ablative treatment is recommended.

The accepted criterion standard for treatment of LM is surgical excision. This is achieved with single-stage surgery, multiple planned stages, or Mohs micrographic surgery. The National Institutes of Health-recommended surgical margins of 0.5 cm from the pigmented border have been challenged by several authors. Margins as wide as 18 mm were required in some series for histologic clearance. The recurrence rates following surgical excision range from 7% to 45%. For large LM lesions, the challenge lies in the reconstruction of the subsequent defect, particularly in the head and neck region. Older populations with multiple comorbidities are at an increased risk for surgical complications. Considering these factors, the morbidity of surgical management must be weighed against the likelihood of progression to invasive disease using an alternative treatment modality.

Numerous superficial destructive or ablative treatment modalities have been described for LM with the advantages of decreased morbidity and improved aesthetic outcome, particularly when dealing with larger lesions. These treatment modalities include radiation therapy, cryotherapy, dermabrasion, azelaic acid, and laser ablation. New immunomodulatory therapies using topical imiquimod have shown promising results in the treatment of malignant skin lesions.

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clearance. The presence of atypical cells in the deep adnexal structures is a potential source of recurrence and may not be completely destroyed using these modalities. A primary dilemma is that occult invasive foci may be present in 16% to 50% of LM lesions.14

Laser ablation has been described in several case series. Q-switched ruby, Nd:YAG, argon, alexandrite, and carbon dioxide lasers have been associated with variable outcomes and with high recurrence rates.15-20 Theoretically, lasers targeting pigment would not include non-melanocytic lesions, which would be a source of recurrence.21 The depth of ablation in globally ablative therapies, such as carbon dioxide laser, would need to address the deep adnexal structures located in the deep reticular dermis and superficial subcutaneous plane as a source of potential recurrence.

At the London Regional Cancer Program (LRCP), the treatment modalities used include surgical excision, radiation therapy, and carbon dioxide laser ablation. The objective of this review was to assess outcomes in managing primary LM through surgical excision, radiation therapy, and carbon dioxide laser ablation. To our knowledge, this review presents the largest series using carbon dioxide laser ablation as a modality with 5-year follow-up results.

METHODS

Medical ethics approval was first obtained through the University of Western Ontario Health Research Ethics Board. Patient records at the LRCP were recalled using the search headings lentigo maligna and melanoma in situ. Patients were included if the diagnosis was made between July 2, 1991, and June 30, 2005. Among 145 identified records, 75 patients met the study inclusion criteria of an LM untreated following pathological diagnosis or excised in the periphery and referred to the tertiary center for surveillance. Patients referred for recurrent lesions were excluded, but it was noted whether they were previously treated at the LRCP. Data on carbon dioxide laser ablation before 2005 were obtained from the records of a sole physician (C.C.M.) now providing laser treatment at the LRCP. If more than 1 lesion was present in a patient, the earliest lesion was treated at the LRCP. If more than 1 lesion was present in a patient, the earliest lesion was treated at the LRCP.

Diagnosis was confirmed histopathologically for LM, with multiple punch biopsy specimens obtained to rule out LMM. Treatment administered was surgical excision, radiation therapy, carbon dioxide laser ablation, or none. Choice of treatment modality was made by a multidisciplinary team (E.Y. and C.C.M. and others) and took into account patient input and patient and tumor factors. The preferred choice of treatment by the multidisciplinary team was surgical excision or radiation therapy. Patients in the carbon dioxide laser ablation group were initially offered both standard treatments. Therefore, treatment of LM with carbon dioxide laser ablation was offered only to patients who refused both surgical excision and radiation therapy.

SURGICAL EXCISION

Surgical excision included single-stage surgery, multiple planned stages, or Mohs micrographic surgery. A single-stage surgical intervention consisted of a completely excised histologic specimen. Multiple planned stages were defined as a single surgical intervention that was followed by a subsequent excision before histologic information was obtained about the margins in the first excision. Surgical excision was considered complete when histologic margins were cleared, typically with 5-mm margins.

RADIATION THERAPY

Radiation therapy was administered using a superficial radiography unit (Orthovoltage T-150 Therapax; Elimpex-Medizintechnik, Moedling, Austria) with a preset dose of 50 Gy in 20 fractions (or its biological equivalent). Radiotherapy was considered complete in the clinical absence of the lesion at 6 months following the last treatment date.

CARBON DIOXIDE LASER ABLATION

Carbon dioxide laser ablation was administered in a single treatment using a laser system with a scanning handpiece (Sharplan 40C with SilkTouch; Sharplan Lasers [UK] Limited, London, England) at 18 W with a 200-mm handpiece continuous-wave mode and repeat delay of 0.2 seconds. A single treatment consisted of multiple passes over the affected area until pinpoint capillary bleeding was observed in all areas. The ablation was tapered over a distance of at least 1 cm from the lesion. Response to carbon dioxide laser ablation was considered complete with the clearance of the pigmented lesion following resolution of posttreatment erythema (typically at 3-4 months). An example of an LM treated with laser therapy is shown in Figure 1.

DATA ANALYSIS

Local recurrence was detected clinically by a radiation oncologist (E.Y.) and a surgeon (C.C.M.) at the institution. If biopsy specimens of suspicious areas were obtained, the pathological information was recorded. The location, treatment, and response of the recurrence were recorded using the same criteria as for the primary lesion. The last known status for each patient was obtained from the last clinical encounter or from the death summary.

Patient records were reviewed to compare outcomes of surgical excision (single-stage surgery and multiple planned stages), radiation therapy, and carbon dioxide laser ablation. Patient demographic information collected included age at diagnosis, sex, and personal and family history of skin lesions and other malignant neoplasms. Clinical and histologic information about each lesion included the pathological diagnosis of LM and the location and size (greatest tumor diameter).

Basic statistics, such as descriptive frequencies and means (SDs), were obtained for patient demographics, clinical lesion characteristics, treatment modalities, and recurrence rates. When appropriate, statistical analysis was performed using analysis of variance and the Kruskal-Wallis test and Fisher exact test (2 tailed). Statistical significance was set at P<.05. The main outcomes of interest were recurrence rates using the 3 modalities. Kaplan-Meier curves were plotted for survival analysis, while the log-rank statistic was used to determine statistical significance of recurrence rates, comparing carbon dioxide laser ablation with nonlaser modalities. Statistical analysis was performed using commercially available software (SPSS version 13; SPSS, Inc, Chicago, Illinois).

RESULTS

PATIENT DEMOGRAPHICS

Included in the study were 75 patients aged 39 to 93 years (mean [SD] age, 64.8 [13.0] years) at diagnosis. Thirty-one
patients (41.3%) were men, and 44 patients (58.7%) were women. A personal history of having other malignant or precursor lesions was noted in 34 patients (45.3%), the most common being basal cell carcinoma in 16 patients, squamous cell carcinoma in 7 patients, and actinic keratoses in 5 patients. Four patients had had a previous melanoma.

**CLINICAL LESION CHARACTERISTICS**

Most lesions (89.3%; n=67) were located in the head and neck region, with 10.7% (n=8) located on the trunk or extremities. The distribution was 50.7% (n=38) on the right side, 42.7% (n=32) on the left side, and 6.7% (n=5) at the midline (Table 1). The most common locations in the head and neck region were the cheek (58.7% [n=44]) and the nose (9.3% [n=7]). The lesion size, defined as the greatest tumor diameter, was measured in 54 patients, who had a mean (SD) lesion size of 2.63 (1.32) cm.

**TREATMENT MODALITIES**

Of 75 patients, 73 chose treatment with surgical excision, radiation therapy, or carbon dioxide laser ablation. The remaining 2 patients were not documented as having had treatment of their lesions. Twenty-seven patients were treated with surgical excision, 31 patients with radiation therapy, and 15 patients with carbon dioxide laser ablation; their mean (SD) ages at diagnosis were 64.4 (12.8) years, 69.0 (12.2) years, and 56.0 (9.3) years, respectively (P=.004) (Table 2). Before pathological diagnosis of LM, cryotherapy was administered to the lesion of interest in 4 cases, none of which recurred. The median follow-up times were 16.6 months for surgical excision, 46.3 months for radiation therapy, and 77.8 months laser for carbon dioxide laser ablation (P<.001). Recurrence was recorded among 11 patients in the database.

Complications observed among the radiation therapy group included telangiectasia, hypopigmentation, skin erythema, infection, and dry desquamation. All patients in the carbon dioxide laser ablation group had skin erythema for 3 to 4 months, which subsequently resolved. Recurrence rates by treatment modality were 4.2% (1 of 27) for surgical excision, 29.0% (9 of 31) for radiation therapy, and 6.7% (1 of 15) for carbon dioxide laser ablation. No recurrences were found to be LMM in biopsy specimens.

At the time of data collection, 11 patients had died of causes unrelated to LM or melanoma. Kaplan-Meier curves were compared for overall survival and recurrence-free

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**Table 1. Tumor Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Cheek</td>
<td>44 (58.7)</td>
</tr>
<tr>
<td>Nose</td>
<td>7 (9.3)</td>
</tr>
<tr>
<td>Forehead</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Temple</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Ear</td>
<td>3 (4.0)</td>
</tr>
<tr>
<td>Neck</td>
<td>3 (4.0)</td>
</tr>
<tr>
<td>Eyelid</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Chin</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Scalp</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Posterior auricular</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Posterior trunk</td>
<td>3 (4.0)</td>
</tr>
<tr>
<td>Side, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>38 (50.7)</td>
</tr>
<tr>
<td>Left</td>
<td>32 (42.7)</td>
</tr>
<tr>
<td>Midline</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>Maximum tumor diameter</td>
<td>(n=54)</td>
</tr>
<tr>
<td>Mean (SD), cm</td>
<td>2.63 (1.32)</td>
</tr>
</tbody>
</table>

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Figure 1. Lentigo maligna of the right cheek in an 88-year-old woman before treatment (A), immediately following carbon dioxide laser ablation (B), and at 6 months after carbon dioxide laser ablation (C).
survival across modalities and yielded no significant differences (Figure 2). Log-rank analysis of recurrence-free survival between carbon dioxide laser ablation vs non-laser modalities also showed no significant differences (Figure 3). Compared with the other groups, the carbon dioxide laser ablation group had significantly larger lesions (P < .001), a younger patient population (P = .004), and a longer median follow-up time (P < .001) (Table 2).

In this retrospective review, we evaluated recurrence rates in 75 patients with LM. Consistent with previous reviews, LM lesions demonstrated a slight female predominance, a mean patient age of about 60 years, and a common location in the head and neck region.

The recurrence rate following surgical excision found in this study is comparable to rates in the literature. Although surgical excision is established as the gold standard of LM and LMM treatment, complete excision is not always feasible in large lesions of the head and neck. The decision to perform complete excision in the setting of LM, a noninvasive disease, must weigh the benefits of excision against the morbidity of the procedure. Although many superficial ablative modalities have been pro-

Table 2. Comparison of Treatment Modalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgical Excision (n=27)</th>
<th>Radiation Therapy (n=31)</th>
<th>Carbon Dioxide Laser Ablation (n=15)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, mean (SD), y</td>
<td>64.4 (12.8)</td>
<td>69.0 (12.2)</td>
<td>56.0 (9.3)</td>
<td>.004b</td>
</tr>
<tr>
<td>Maximum tumor diameter (n = 16)</td>
<td>1.80 (0.99)</td>
<td>2.63 (1.33)</td>
<td>3.60 (1.03)</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td>Follow-up time, median, mo</td>
<td>16.6</td>
<td>46.3</td>
<td>77.8</td>
<td>&lt;.001c</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>8 (29.6)</td>
<td>25 (80.6)</td>
<td>10 (66.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Complete response, No./total No. (%)</td>
<td>23/27 (92.0)</td>
<td>27 (87.1)</td>
<td>15 (100)</td>
<td>.41</td>
</tr>
<tr>
<td>Complications, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin erythema</td>
<td>0</td>
<td>2 (6.5)</td>
<td>15 (100)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dry desquamation</td>
<td>0</td>
<td>1 (3.2)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Wet desquamation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>1 (3.2)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>0</td>
<td>6 (19.4)</td>
<td>0</td>
<td>.01</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>0</td>
<td>2 (6.5)</td>
<td>0</td>
<td>.68</td>
</tr>
<tr>
<td>Recurrence, No./total No. (%)</td>
<td>1/24 (4.2)</td>
<td>9 (29.0)</td>
<td>1 (6.7)</td>
<td>. . . d</td>
</tr>
<tr>
<td>Died, No. (%)</td>
<td>2 (7.4)</td>
<td>8 (25.8)</td>
<td>1 (6.7)</td>
<td>. . . d</td>
</tr>
</tbody>
</table>

* Kruskal-Wallis test if not otherwise indicated.
  b Analysis of variance.
  c Fisher exact test (2 tailed).
  d Groups were too small to make a valid comparison of time to event.

Figure 2. Kaplan-Meier curves estimating survival by treatment modality. A. Overall survival. B. Recurrence-free survival.

Figure 3. Log-rank plot estimating recurrence-free survival with carbon dioxide laser ablation vs nonlaser modalities.
posed and reviewed, a lack of randomized controlled trials with long-term follow-up data challenges the physician in choosing the appropriate modality.

The recurrence rate herein of 29.0% (9 of 31) in the radiation therapy group was particularly high. In a study of radiation therapy as a treatment modality, Farshad et al24 performed a retrospective analysis of 150 patients treated with grenz (12 kV) or soft (20-50 kV) radiography. One hundred one patients had a minimum 2-year follow-up period, with a mean time to recurrence of 45.6 months and a recurrence rate of 7% when pooling the 2 groups (5 LM recurrences and 2 LMM recurrences [subgroup rates were unavailable]). Their review advocated the use of radiation therapy for first-line treatment as a reasonable alternative to surgical management in older patients, with an acceptable cosmetic result.

Laser ablation has been suggested as an alternative treatment of LM in older patients, among whom the location and size of lesions and medical comorbidities contribute significantly to surgical risk and morbidity. In this retrospective review, the patients treated with carbon dioxide laser ablation had refused surgical excision and radiation therapy; therefore, the selection of patients who underwent carbon dioxide laser ablation is a source of bias within this study. In these patients, the major factor leading to performance of carbon dioxide laser ablation was patient preference following the refusal of standard treatment. Surgical excision was most frequently declined because of the size of the defect and the steps necessary for reconstruction, while radiation therapy was most commonly refused secondary to concerns about comorbidities and the potential complications of treatment. Owing to the somewhat experimental nature of the use of carbon dioxide laser ablation at the time of initial use and the inability to obtain histologic clearance of the lesions, it was believed that randomizing patients would not be ethically sound.

Various lasers and combinations have been used to treat LM, including Q-switched ruby, Nd:YAG, argon, alexandrite, and carbon dioxide lasers. However, laser ablation has not been recommended as first-line treatment of LM because of its limited success, high recurrence rates, and lack of prospective controlled studies.1,25 Carbon dioxide laser ablation has been described in several case series. A descriptive study by Koperca17 involved the treatment of 4 patients, with a mean follow-up period of 15 months (range, 11-20 months); no recurrence was observed in any of the patients. However, the review by Zalaudek et al1 described a high recurrence rate of 42.9% at 5 years following carbon dioxide laser ablation. In our retrospective review, 15 patients treated with carbon dioxide laser ablation had a recurrence rate of 6.7% (1 of 15), which is significantly lower than that reported by Zalaudek et al and is comparable to our recurrence rate following surgical excision, with a median follow-up period of longer than 6 years in the carbon dioxide laser ablation group. The lower recurrence rate may be attributed to the ablative technique. The carbon dioxide laser ablation required multiple passes to reach a visual end point of pinpoint capillary bleeding in the entire treatment area. This likely resulted in a deeper level of injury, destroying a greater proportion of cells that would have been a source of recurrence.

Because most surgical excision is performed in the periphery before referral to the LRCP, a tertiary care center, heterogeneity of technique and histopathological examination of excisional biopsy specimens may influence recurrence rates. In addition, patients referred to the LRCP may not be representative of the full spectrum of LM presentation, as many dermatologists, surgeons, and family physicians choose to observe the progress of the lesions. After treatment at the tertiary center, the area of interest would often be followed up by the original referring physician or family physician, which may lead to altered estimates of recurrence rates because there would no longer be documentation in the tertiary center medical records. However, if recurrence occurred, the patient would be referred back to the tertiary center, as it is the only cancer center in the region. As such, one can be reasonably sure that virtually all cases of recurrence are accurately represented within this retrospective review.

The data from our review support the use of carbon dioxide laser ablation to treat LM when surgical excision or radiation therapy is not feasible. However, as with all superficial ablative modalities, data on histologic clearance are unavailable. The physician’s judgment as to the area of maximum thickness within the lesion for biopsy is not infallible and could misdiagnose LMM lesions. This could be potentially devastating for the patient, but close follow-up care ensures that early recurrence or invasion is not missed. The advantage of using carbon dioxide laser ablation over other lasers is that nonmelanocytic lesions will also be ablated. The risk is that melanocytes deep in adnexal structures cannot be treated with laser therapy.

In conclusion, there is a need to develop standardized treatment for LM when surgical excision is not feasible. Numerous superficial ablative and immunomodulatory treatments exist, with no randomized controlled prospective studies definitively supporting the use of one modality over another. However, patient tolerance for a treatment modality and adverse effects may limit its use, regardless of the efficacy. Carbon dioxide laser ablation may have a role as an alternative treatment for LM, although the number of cases is too few to provide evidence of efficacy. In addition, the high 29.0% (9 of 31) recurrence rate among the radiation therapy group herein warrants a review of whether this modality should be used. Carbon dioxide laser ablation may be advantageous because it treats large lesions in cosmetically sensitive regions of the head and neck in a short period, with minimal morbidity. Prospective descriptive studies or controlled trials are recommended to characterize the use and efficacy of carbon dioxide laser ablation as a valid treatment for LM.

Accepted for Publication: May 27, 2011.
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Author Contributions: Dr Moore had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lee, Yu, and Moore. Acquisition of data: Lee and Moore. Analysis and interpretation

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Financial Disclosure: None reported.

Previous Presentation: This study was presented at the 63rd Annual Meeting of the Canadian Society of Otolaryngology–Head and Neck Surgery; May 11, 2009; Halifax, Nova Scotia, Canada.

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