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REVIEW ARTICLE

Lentigo Maligna: Review of Salient Characteristics and Management

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Abstract Lentigo maligna is a melanocytic neoplasm, often regarded as 'melanoma in situ,' which may progress to lentigo maligna melanoma. Lentigo maligna clinically presents as a pigmented, asymmetric macule that originates on the head and neck and spreads slowly. The preferred method for diagnosing lentigo maligna is excisional biopsy. Histology shows proliferation of atypical melanocytes at the epidermal–dermal junction in small nests or single cells. The differential diagnosis includes solar lentigo, seborrheic keratosis, lichen planus-like keratosis, pigmented actinic keratosis, and melanocytic nevus. Stains used in diagnosis include hematoxylin and eosin, HMB-45, MART-1/Melan-A, Mel-5, and S-100. Surgical excision is the preferred treatment for lentigo maligna. Second-line techniques include medical (topical imiquimod) and destructive therapy.

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1 Introduction

Lentigo maligna is a pre-malignant melanocytic neoplasm, which originates on chronically sun-exposed skin, particularly the head and neck. Its progression leads to lentigo maligna melanoma, one of the four common subtypes of malignant melanoma. Forms of lentigo maligna that may progress to lentigo maligna melanoma in situ are often termed 'melanoma in situ, lentigo maligna type.' Lentigo maligna typically presents as a pigmented 1–3 mm macule. Although lentigo maligna usually occurs in white males with a peak incidence in the sixth and seventh decades of life, lesions have also been diagnosed in the second and third decades [1–3]. Diagnosis and treatment of lentigo maligna remain complex, as the recurrence rate is quite high (2–50%). In this article, we review the history, clinical presentation, histology, diagnosis, and management of lentigo maligna. The primary database utilized for this article was PubMed. The search terms used included 'lentigo maligna,' 'lentigo maligna melanoma,' and 'melanoma in situ'. These phrases were combined with the following terms: 'diagnosis,' 'pathology,' 'histopathology,' and 'treatment.' On the basis of the results, more specific terms were combined with the above, which included 'digital epiluminescence microscopy,' 'Mohs micrographic surgery,' 'geometric excision,' 'and 'spaghetti technique.'

2 Historical Descriptions

Lentigo maligna was first described by Sir John Hutchinson in 1892 as an "infective senile freckle." From Latin, 'lentigo' translates to 'freckle' and 'maligna' translates to 'the potential to become malignant.' Lentigo maligna has been termed 'lentigo melanosis,' 'Hutchinson's melanotic

freckle,' 'senile freckle,' 'precancerous non-nevoid melanocytoma,' and 'circumscribed precancerous melanosis.' Dubreuilh further defined lentigo maligna in 1894 when he documented four cases as 'lentigo malin des vieillards,' which translates to 'lentigo maligna of the elderly' [4].

3 Clinical Presentation

Lentigo maligna is a slowly growing neoplasm. It clinically presents as an asymmetric macule, which slowly spreads centrifugally with increasingly irregular borders (Figs. 1, 2). The lesion often varies in pigmentation, with shades of tan to black, and usually begins on the face or neck. Its presentation can be subtle with indistinct margins. Net-like black pigmentation is often found on this lesion. Early diagnosis is difficult; lentigo maligna can be confused with lentigo simplex and solar lentigo. Lentigo maligna follows a two-dimensional horizontal growth pattern restricted to the dermal–epidermal junction. Involvement of the dermal component marks the transition between lentigo maligna (confined to the epidermis) and lentigo maligna melanoma (dermal invasion). Once lentigo maligna progresses to invasive lentigo maligna melanoma, its prognosis is determined by the tumor thickness [5].

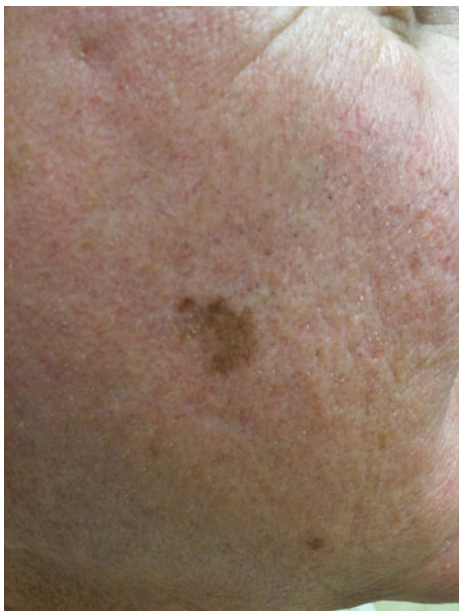

Fig. 1 Lentigo maligna. This asymmetric, variably pigmented macule on the cheek of this patient is consistent with lentigo maligna. Note the net-like black pigmentation

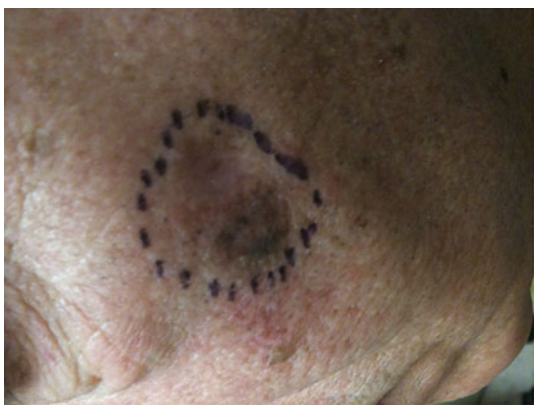

Fig. 2 Lentigo maligna prior to excision. This is another lentigo maligna lesion, presenting as a hyperpigmented macule with irregular borders on the cheek

4 Diagnosis

The preferred method for diagnosing lentigo maligna is excisional biopsy. If limited by the size of the lesion, shave and punch biopsies can also be utilized, but these techniques have a greater risk of sampling error. Another technique is a fusiform incisional biopsy measuring at least 5 mm in depth and spanning the center of the tumor [6]. Biopsy of the darkest portion of the lesion yields a more definitive diagnosis.

4.1 Histopathology

Lentigo maligna has traditionally been challenging to diagnose, since it is difficult to distinguish non-malignant atypical melanocytic hyperplasia from melanoma in situ in chronically sun-damaged skin [7]. As such, the histological differential for this lesion is broad and includes solar lentigo, early lesions of seborrheic keratosis, lichen planus-like keratosis, pigmented actinic keratosis, and melanocytic nevus. Debate also exists in the characterization of lentigo maligna as a 'melanoma in situ.' Some pathologists believe that lentigo maligna is a melanoma precursor, while others call it a true melanoma in situ on the basis of the number of atypical melanocytes and their pattern of arrangement within the basal epidermis [8].

The most reproducible histological parameter that is used to confirm a diagnosis of lentigo maligna is proliferation of atypical melanocytes at the epidermal–dermal junction in small nests or single cells, coupled with underlying photodamage. Disagreement exists about the utility of several additional histological features in diagnosing lentigo maligna, given the overlap between sun-induced changes to the skin. These histological characteristics include bridging of rete pegs, epidermal atrophy, extension of melanocytes into periadnexal structures, extensive underlying solar necrosis, melanocyte atypia, the presence of an inflammatory dermal infiltrate, and

non-uniform pigmentation or distribution of melanocytes [9]. A multi-center comparative study examining melanocytes in sun-exposed skin identified a high density and confluence of melanocytes, superficial follicular extension, and moderate cytologic atypia. That study suggested that melanocytes along the follicular epithelium and increased melanocyte density and confluence cannot by themselves be diagnostic of lentigo maligna. The presence of other histological criteria, such as nesting, vertical stacking, or pagetoid spread, help to more accurately distinguish lentigo maligna from the melanocytic features of sun-damaged skin. Furthermore, the extent of pagetoid spread can differentiate lentigo maligna from malignant melanoma: minimal pagetoid spread into the epidermis distinguishes lentigo maligna from superficial spreading melanoma [10].

4.2 Staining Techniques

Hematoxylin and eosin (H&E) staining is one method that has been employed to help evaluate the surgical margins of lentigo maligna via light microscopy. It has been reported that H&E evaluation of lentigo maligna is 100 % sensitive and 90 % specific. Excellent-quality sections and experienced reviewers are critical to the success of this technique, which has been shown to yield greater than 90 % survival at 5-year follow-up [11].

Several immunohistochemical stains are used to aid diagnosis of lentigo maligna in frozen sections during Mohs micrographic surgery and other surgical techniques. The advent of immunostaining has substantially decreased the skepticism regarding Mohs micrographic surgery—once a controversial approach for treating lentigo maligna. The immunostains most commonly used include HMB-45, MART-1, Melan-A, Mel-5, and S-100. These immunostains are regarded as advantageous to the traditional H&E approach because they better distinguish lentigo maligna from benign melanocyte proliferation on chronically sun-damaged skin. Immunohistochemistry also better differentiates residual lentigo maligna from benign post-excisional melanocytic scarring [12].

MART-1/Melan-A is currently regarded by several groups as the most beneficial in identifying atypical melanocytes in frozen sections. Studies of MART-1 in melanoma chemosurgery have shown that it is typically crisp and with less background staining than MEL-5 and preferable to HMB-45 for better staining consistency [11].

However, MART-1 has many disadvantages. MART-1 is reported to have superb sensitivity but a lack of specificity, with the implication of incorrectly extending surgical margins into normal tissue. This is due to the fact that most epidermal melanocyte cell surfaces, whether benign or malignant, possess the MART-1 antigen. One group demonstrated that MART-1 stained all pigmented actinic keratoses in their study [13]. Another group found it useful in distinguishing 66 out of 68 pigmented actinic keratoses from melanoma in situ [14]. MART-1 also fails to distinguish benign melanocyte proliferation from melanocyte atypia and follicular involvement characteristic of melanoma in situ. Characteristics typical of photodamaged skin may be wrongly interpreted as a positive margin when using MART-1 immunohistochemistry.

Similarly, it has been shown that another stain, Mel-A, also fails to distinguish between lentigo maligna and chronically sun-damaged skin. One group advocates for the use of control biopsies between the lesion and uninvolved sun-damaged skin of individual patients to account for varying melanocytic characteristics [13].

Furthermore, the drawback of immunohistochemistry is the time constraint. This technique was intended for permanent sections rather than frozen sections. MART-1, in particular, has required a 1-hour protocol (developed by Bricca) to ensure greater specificity of detecting lentigo maligna [15]. Fortunately, newer studies have found that a 19-minute protocol is equivalent to that obtained from MART-1-stained permanent sections [16].

4.3 The Wood's Lamp

Because the true margins of the lesion can extend far past the visible margins, several techniques have been developed to improve margin delineation over visual inspection. The Wood's lamp takes advantage of the property of ultraviolet light to be preferentially absorbed by epidermal melanin, distinguishing it from the surrounding uninvolved tissue. The ability of the Wood's lamp to amplify these differences in pigmentation makes it especially invaluable

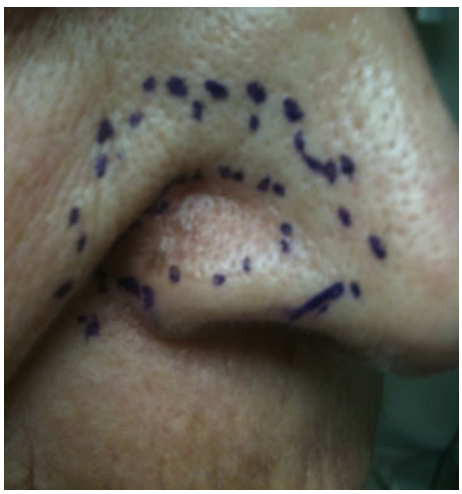

Fig. 3 Lentigo maligna melanoma. This lentigo maligna melanoma extended beyond what was visible to the naked eye. Use of a Wood's lamp allowed accurate margins to be determined in this case

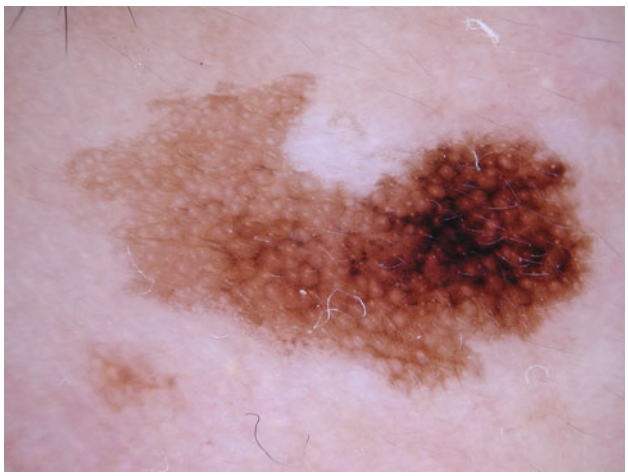

Fig. 4 Lentigo maligna under dermoscopy. The dark rhomboidal structures near hair follicles is highly specific for lentigo maligna when viewed under dermoscopy. Reproduced with permission from Tanaka et al. [18]

in delineating the borders of lentigo maligna, as was the case in the patient presented in Fig. 3 [17].

4.4 Dermatoscopy

Dermatoscopy is the process of viewing skin lesions through a dermatoscope, which is an instrument that magnifies the skin (usually by 10 times) and illuminates non-polarized light upon the lesion being examined. Tanaka has identified four key criteria that are diagnostic for lentigo maligna on dermatoscopy: asymmetrical pigmented follicular openings (which usually develop into rhomboid structures, as seen in Fig. 4), linear pigmented lines forming rhomboidal structures, annular–granular structures, and a gray pseudo-network (perifollicular slate-gray dots and granules) [18]. Two of these characteristics, annular–granular structures and the gray pseudo-network, are also present in regressive areas of solar lentigo/initial seborrheic keratosis, lichen planus-like keratosis, and pigmented actinic keratosis. As such, asymmetrical pigmented follicular openings and rhomboidal structures are regarded as the more specific dermatoscopy criteria. Circles within circles and atypical blood vessels have separately been identified as diagnostic features of lentigo maligna [19].

One group recently identified a 'zig-zag' pattern of incomplete rhomboidal structures of "brown to bluish gray dots and lines arranged in an angulated linear pattern" seen in lentigo maligna. Though the zig-zag pattern is not pathognomonic for lentigo maligna, as it can also appear in pigmented actinic keratosis, the presence of a rough texture in the latter helps distinguish the two lesions [20].

Digital epiluminescence microscopy, also known as digital dermatoscopy and video dermatoscopy, is a technique in which digital images are captured and stored so they can be compared with images captured at future visits. This tool can provide 30-fold magnification of the lesion in question. One study found that use of digital epiluminescence microscopy during surgical excision of lentigo maligna greatly reduced the border size of excised samples, compared with visual inspection. The superior magnification of digital epiluminescence microscopy can differentiate the rete ridge pattern at the dermoepidermal junction of lentigo maligna from the atrophic, flat rete ridges of benign melanocytes [21].

5 Treatment Options

If untreated, lentigo maligna poses the risk of dermal invasion and progression to invasive lentigo maligna melanoma. The percentage of lentigo maligna cases that progress to lentigo maligna melanoma has been estimated to be as low as 5 % and as high as 50 % [22]. Surgical excision remains the preferred treatment for lentigo maligna, but the methods by which excision is undertaken have evolved significantly. The alternatives for individuals with contraindications to surgical excision have also significantly expanded. A proposed therapeutic algorithm for the management of lentigo maligna is outlined in Fig. 5.

5.1 Surgical Modalities

The challenge of excising lentigo maligna is to achieve complete tumor-free margins but with an optimal cosmetic outcome, especially with lesions on the face, head, and neck. Standard excision is insufficient in 50 % of cases [23]. Indeed, the mean total surgical margin required for tumor-free excision is 7.1 mm, suggesting that standard 5 mm surgical margins are inadequate [24]. This large average defect size is likely exacerbated by multiple prior treatments of lesions that interfere with adequate delineation of margins [25]. Multiple surgical techniques have been proposed.

5.1.1 Mohs Micrographic Surgery

Mohs micrographic surgery is a technique that differs from conventional surgical excision because it allows real-time in-clinic assessment of tissue samples. After the Mohs surgeon excises the cancer, the sample is immediately frozen, sectioned (horizontally rather than vertically), and assessed. If the margins of the sample are not clear, the surgeon excises more tissue in subsequent stages until the sample is tumor free. This technique allows a primary tumor mass to be excised completely with minimal loss of normal tissue, as with the patient shown in Fig. 6, who

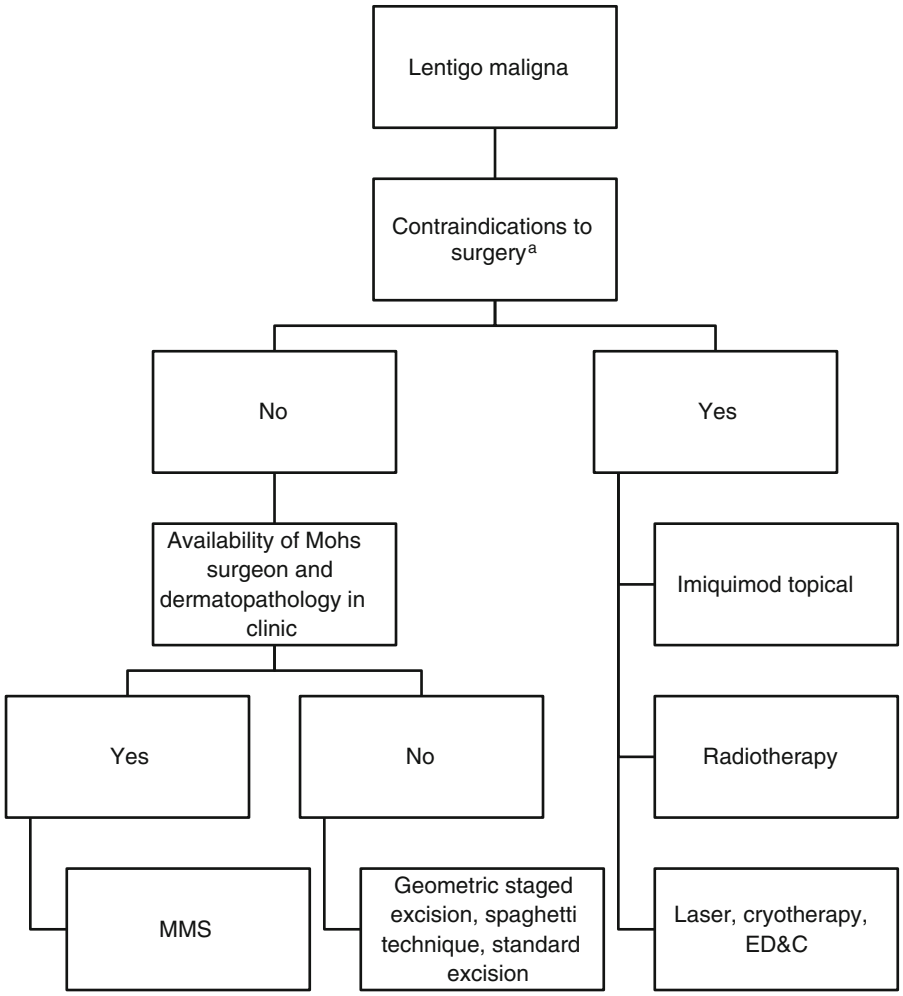

Fig. 5 Treatment of lentigo maligna

Abbreviations: ED&C, electrodessication and curettage; MMS, Mohs micrographic surgery
[a] These include patients who are elderly, large unresectable lesions of the head and neck, and problematic reconstruction.

presented to our clinic. Mohs micrographic surgery is reported to have better cure rates than standard excision. While the recurrence rate after standard excision ranges from 8 to 20 %, the rate after staged Mohs micrographic surgery is only 4–5 % [23].

5.1.2 Geometric Staged Excision

Geometric staged excision has an even lower recurrence rate than Mohs micrographic surgery (1.7 %) and allows for complete examination of the peripheral and deep margins of excised specimens. In this technique, a Wood's lamp is used to demarcate the lesion margins. A geometric shape with at least three sides and with a 3–5 mm margin is then drawn around the lesion. Ninety-degree vertical incisions extending to the hypodermis are made along the drawn margins. The geometric shape is then excised, mapped, inked, and sent to the laboratory. The patient is sent home with pressure dressings. When the analysis of the sample is complete, the patient returns to the clinic. If the margins are not clear, additional stages with 3–5 mm margins are taken. If the sample is tumor free, the defect is repaired [26].

5.1.3 The Spaghetti Technique

The spaghetti technique consists of three phases. In phase I, a 2 mm-wide strip of skin (the 'spaghetti') that circumscribes the lentigo maligna lesion is excised with 3–5 mm margins. The strip-like linear defect is immediately sutured together. The 'spaghetti' strand is then analyzed by dermatopathology. The patient returns at a later date once the results are available. If positive, an additional circumferential 'spaghetti' strand is removed with an extra 5 mm margin, followed by closure of the linear defect. The steps are repeated until the final strand is tumor free.

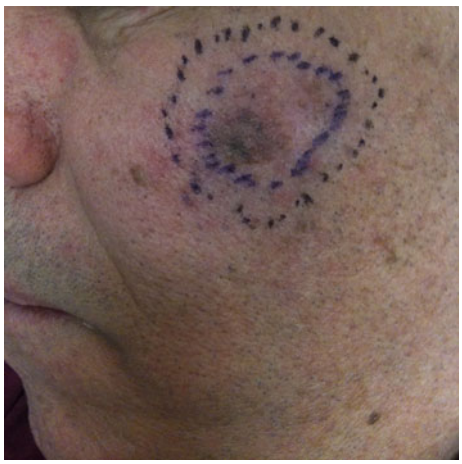

Fig. 6 Lentigo maligna prior to Mohs micrographic surgery. 1–2 mm margins were delineated about the lesion. This tumor was successfully cleared after one stage

Phase II involves resection of the lesion about the outermost peripheral sutured area. The surgeon will subsequently determine the method of reconstruction (via a graft or flap) [27].

Unlike Mohs micrographic surgery, the 'spaghetti technique' does not require specific training of surgeons or pathologists. Its advantage over geometric staged excision is not leaving patients with an open defect for days between visits before final reconstruction. Furthermore, this technique is very tissue sparing. In one study, the mean margin to clearance of lentigo maligna after excision was only 6.6 mm, and in a mean follow-up period of 15-months, 98.3 % of patients had no local recurrence [27].

5.1.4 Special Considerations

It is important to emphasize that standard surgical excision may fail to completely resect the invasive component of lentigo maligna in at least half of all cases. Although standard surgical excision may be insufficient in half of all cases, imaging modalities such as digital epiluminescence microscopy and confocal microscopy have greatly improved outcomes [28]. Confocal microscopy is an imaging modality in which lesions visualized through a microscope are amplified and analyzed so that a two- or three-dimensional image is constructed. This allows lesions to appear with greater resolution and depth. In one study, confocal microscopy was able to detect subclinical disease in 59 % of patients with lentigo maligna lesions that extended beyond the standard 5 mm surgical margin. This changed the management in 73 % of these patients [29]. In instances where residual components remain after standard excision, non-surgical imaging modalities—including medical and destructive—play a strong role.

5.2 Medical Modalities

Surgical excision is the gold standard in the treatment of lentigo maligna. However, non-surgical modalities can be used for a subset of patients. Imiquimod, a topically applied immunomodulator, stimulates toll-like receptors 7 and 8, which enhances innate and acquired immune responses. This leads to activation of nuclear factor κB, which galvanizes the production of inflammatory cytokines such as tumor necrosis factor α, interleukin 12, interferon α, and interferon γ. In addition, cytotoxic T cells are activated, which induce apoptosis in tumor cells [30]. There is no consensus regarding the dosage of imiquimod. The dosage varies from daily to three times weekly for between 2 weeks and 7 months. Although this modality is cosmetically favorable, 12 % of patients in one study had recurrence or no response [31]. In fact, some cases of lentigo maligna treated with imiquimod have progressed to invasive malignant melanoma with satellite lesions [32]. Another disadvantage of topical therapy is the inability to determine tumor resolution with complete certainty. Although surgical excision is cosmetically unfavorable, it allows for histological confirmation of tumor-free margins.

5.3 Radiotherapy

Radiotherapy is a locally destructive technique best used for elderly patients, patients with large facial and neck lesions, patients in whom reconstruction may be problematic, and patients who have a residual tumor after surgical excision. One study of soft X-irradiation treatment of lentigo maligna demonstrated complete resolution in only 88 % of patients [33]. In Toronto, Canada, 86 % of patients treated with radiotherapy had no local recurrence within 5 years [34]. In another review, 14 out of 17 patients with lentigo maligna treated with radiation had no recurrence within 5 years [35]. In the latter two studies, multifractionated radiation at 100–280 kV was delivered at a 5–6 mm depth. One study at the University of Munich in Germany used a direct field superficial X-ray with a total of 100 Gy applied over 10 fractions at a depth of 1.1 mm. Of the 42 patients with lentigo maligna, none had recurrence of the tumor within a mean 23-month follow-up period. Complications included hypo- and hyperpigmentation [36]. Nevertheless, radiation serves as a good alternative for patients in whom surgery is not preferred.

5.4 Other Modalities

Other modalities for the treatment of lentigo maligna include laser ablation, cryotherapy, and curettage and electrodessication. Carbon dioxide laser should be used only if excision is contraindicated (as in elderly patients

with concomitant medical conditions) and if the lentigo maligna lesion has not progressed to lentigo maligna melanoma [37]. Cryotherapy, electrodessication, and other destructive methods are rarely used to treat lentigo maligna, because of their inability to deeply penetrate to periadnexal melanocytes as well as the lack of biopsy-confirmed tumor removal [38].

6 Summary

Lentigo maligna is a slow-growing melanoma in situ, which may progress to lentigo maligna melanoma, one of the four subtypes of malignant melanoma. Lentigo maligna clinically presents as an asymmetric macule originating on the face, head, or neck, and slowly spreads centrifugally with increasingly irregular borders. The preferred method for diagnosing lentigo maligna is excisional biopsy. Histology shows proliferation of atypical melanocytes at the epidermal–dermal junction in small nests or single cells, coupled with underlying photodamage. The differential diagnosis for this lesion is broad: solar lentigo, seborrheic keratosis, lichen planus-like keratosis, pigmented actinic keratosis, and melanocytic nevus. Stains used in diagnosis include H&E, HMB-45, MART-1, Melan-A, Mel-5, and S-100. Wood's lamp and dermatoscopy are also helpful in diagnosis. Dermatoscopy shows asymmetrical pigmented follicular openings, linear pigmented lines forming rhomboidal structures, annular–granular structures, and perifollicular slate-gray dots and granules. Surgical excision is the preferred treatment for lentigo maligna. Techniques include Mohs micrographic surgery, geometric staged excision, and the 'spaghetti technique.' Other modalities include imiquimod, laser ablation, radiotherapy, cryotherapy, and curettage and electrodessication.

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Conflict of Interest Disclosure Statement None of the authors have any conflicts of interest to declare.

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