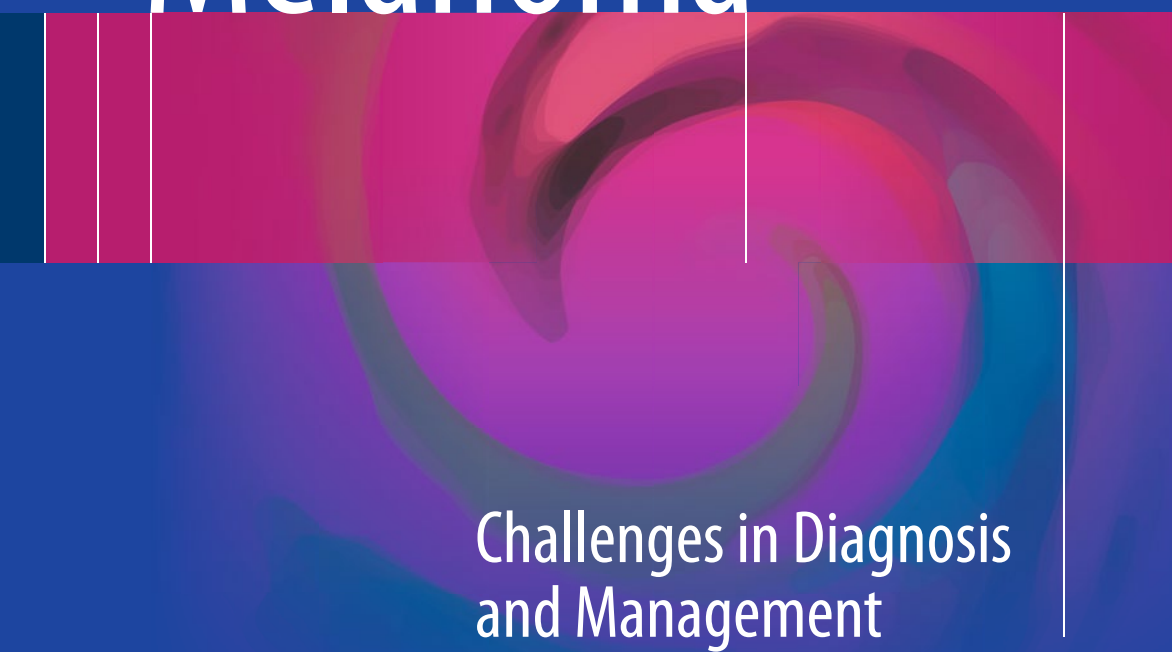
Kishwer S. Nehal · Klaus J. Busam
Editors

Lentigo Maligna Melanoma



Challenges in Diagnosis and Management

Springer

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ISBN 978-3-319-43785-9 ISBN 978-3-319-43787-3 (eBook)
DOI 10.1007/978-3-319-43787-3

Library of Congress Control Number: 2016958455

Printed on acid-free paper

This Springer imprint is published by Springer Nature

Foreword

I am honored and delighted to be asked to write the foreword for the first comprehensive textbook on lentigo maligna melanoma. There has been much written about melanoma, but the subtype of lentigo maligna melanoma remains a confusing entity for many. Interestingly, even the basic behavior and natural history of this neoplasm is still not well understood. Some erroneously consider lentigo maligna a premalignant lesion, while others question the need for treatment. The management debate is further complicated when anatomic and cosmetic issues surrounding the sensitive locations in the head and neck region are added into the mix.

It is important for clinicians to understand that although melanoma of the lentigo maligna subtype follows the American Joint Committee on Cancer (AJCC) staging for melanoma, there are unique features of this melanoma subtype that necessitate a thorough understanding of all facets of the disease process. Only recently, the American Academy of Dermatology and the National Comprehensive Cancer Network clinical practice guidelines recognized that management of this melanoma subtype may require a modified approach given its ill-defined clinical presentation, frequent partial biopsy, and irregular subclinical extension compared to other melanoma subtypes. Experts like Drs. Kishwer Nehal and Klaus Busam appreciate the inherent clinical, histological, and management differences in lentigo maligna melanoma, but that knowledge and experience is not widely known across critical specialties that manage this malignancy.

With the aging population at increased risk for the development of cutaneous malignancies related to ultraviolet radiation exposure, we will be tasked with providing patient-centered, high-quality care to an even larger number of patients with lentigo maligna melanoma. When you add to this burden younger patients presenting with this malignancy, the management dilemmas are compounded even further. Drs. Nehal and Busam have invited experts from multiple fields, including dermatology, dermatologic surgery, dermatopathology, plastic surgery, radiation oncology, and ophthalmic oncology—all the specialties who encounter patients with lentigo maligna melanoma—to share their invaluable insight and experience regarding this challenging malignancy. This multidisciplinary approach is critical and

much needed to navigate the complexities and pitfalls associated with lentigo maligna melanoma management.

Lentigo Maligna Melanoma: Challenges in Diagnosis and Management guides the reader from epidemiology to clinical and histologic diagnosis to surgical and nonsurgical management options. The challenges are thoughtfully explored in each chapter including diagnostic and treatment dilemmas and pitfalls and followed by practical techniques to overcome these hurdles. The fact that a chapter is dedicated to patient preference and quality of life speaks volumes to the contemporary and well-balanced nature of this text. Furthermore, the importance of long-term follow-up to critically assess the current literature and design future studies on lentigo maligna melanoma cannot be emphasized enough, as only such rigor will improve our understanding of varied treatment outcomes. The text concludes with complex case studies which again highlight the challenges encountered in lentigo maligna melanoma.

The reasons to have a dedicated text on lentigo maligna melanoma are compelling. *Lentigo Maligna Melanoma: Challenges in Diagnosis and Management* truly fulfills the practice gaps and is a wonderful contribution to the melanoma literature. For any practitioner encountering lentigo maligna melanoma, I consider this book to be essential reading. The reader will gain a comprehensive understanding of up-to-date principles of care for this increasingly common neoplasm. The logical and evidence-based approach presented here will guide clinicians from multiple specialties with treatment paradigms to truly optimize patient care.

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Acknowledgments

We first and foremost would like to thank our fellow colleagues and authors whose dedication to the field of lentigo maligna melanoma inspired this endeavor. Their collective wisdom has been indispensable in the compilation of this multidisciplinary text. It is our hope that their expertise and scholarship will serve as a vital resource for clinicians.

We also wish to acknowledge our skin cancer team at Memorial Sloan Kettering Cancer Center. At the helm, Dr. Allan Halpern, Service Chief of Dermatology, has always encouraged clinical and academic excellence and supported our professional growth. We are privileged to work with Dr. Halpern whose leadership has been instrumental in our group's success. There are so many other colleagues and coworkers who also play a critical role in our multidisciplinary skin cancer program on a daily basis; we are truly indebted to their commitment to outstanding and compassionate patient care.

We would like to recognize the tremendous efforts of several key players in this project. Dr. Karen Connolly's dedication and countless hours reviewing and editing the manuscripts with us were essential for a cohesive and comprehensive text. For Christa Mathew it was a labor of love. She handled all logistics with confidence and grace to ensure the highest-quality work. Despite seemingly impossible deadlines, administrative support provided by Danielle Ruffini, Ashley Gandham, and Miriam Amilcar allowed our team to succeed. We are grateful to Desiree Kingston for her dedication and for providing many of the high-quality images presented in this book. We are thankful to Grant Weston whose encouragement and persistence made this idea for a lentigo maligna text a reality. In addition, Michael Wilt and the Springer publishing team's attention to detail and professionalism streamlined this process for us.

It cannot be left unsaid that we are deeply appreciative of our families who made personal sacrifices—accommodating our schedules many times, graciously forfeiting time spent with them in order to complete this project. Their encouragement and support were invaluable. For these reasons, we have chosen to dedicate this book to them.

Finally, to our patients—it is our privilege to care for you. We would like to thank Ronald Schwartz for his support and encouragement in making this project happen. Our desire to continually improve the standard of patient care for lentigo maligna is the reason this book was written.

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Part I
Introduction

Chapter 1
Introduction

Karen L. Connolly, Klaus J. Busam, and Kishwer S. Nehal

We are privileged to present *Lentigo Maligna Melanoma: Challenges in Diagnosis and Management*, the first authoritative, comprehensive text focusing solely on this often misunderstood skin cancer. Of the main subtypes of melanoma including superficial spreading, nodular, and acral lentiginous, lentigo maligna (LM) has been at the center of discussion and debate in recent years with confusion and misconceptions surrounding this entity. First described by Hutchinson as Hutchinson's melanotic freckle, LM was considered an infectious process in the late nineteenth century. Two centuries later, misconceptions regarding LM persist, with some still considering this lesion premalignant. LM is recognized by the American Joint Committee on Cancer as a form of melanoma in situ, with lentigo maligna melanoma (LMM) referring to its invasive counterpart. LM must be taken seriously, as potential evolution to a deeply invasive LMM can lead to metastasis and death. For these reasons, a comprehensive text on LM is a necessary and timely contribution. The purpose of this text is to clarify misconceptions and describe the latest techniques used by experts for diagnosis and management of LM and LMM.

In this book we explore the entire spectrum of LM and LMM through the expertise of leaders in the field. First, we will define the extent of the problem by examining the latest data on epidemiology and natural history. Unique characteristics of LM distinguishing it from other melanoma subtypes are outlined, emphasizing that LM must be considered a distinct entity with specific clinical and pathologic features

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_1

that impact treatment. Challenges in the clinical diagnosis of LM are frequent given its often subtle appearance. We will evaluate utilization of established and more novel technologies such as dermoscopy and reflectance confocal microscopy to aid in the diagnosis of LM. LM is also known to present a challenge histologically, given its development on severely sun-damaged skin which mimics the trailing edge of the malignancy itself.

LM and LMM often present as large lesions involving cosmetically and functionally important facial structures including the eyelid, which necessitates careful consideration of the treatment approach. Specialized techniques for surgical management including staged excision and Mohs micrographic surgery are explored along with unique pathology dilemmas when evaluating LM surgical specimens. Experienced authors who use the various surgical techniques share their expertise and critical assessment of advantages and limitations of each approach which continues to be hotly debated within the dermatologic surgery field. Furthermore, important considerations for challenging facial reconstruction following surgical removal of LM are evaluated.

The shared decision-making process and quality of life for patients with LM and LMM has received increased attention of late, given an emphasis on patient-centered care. In this context, alternative treatments to surgery such as radiation have become a part of the patient discussion. The advent of newer therapeutic options with topical treatments also offers exciting possibilities for nonsurgical management. Finally, special issues unique to the follow-up of LM including characteristics of locally recurrent disease are examined. This text concludes with case studies of LM and LMM that illustrate many of the complexities and challenges that present in a clinical practice.

From pathophysiology and risk factors to optimizing technology for diagnosis, to the latest treatment modalities, LM management requires a comprehensive and thoughtful approach. We trust that the knowledge, insight, and expertise shared by our experienced authors will benefit clinicians at all levels of practice. With the prime demographic of the elderly increasing in number worldwide, the expected incidence of LM and LMM continues to increase. It is therefore essential that dermatologists, pathologists, plastic surgeons, head and neck surgeons, surgical oncologists, ophthalmologists, radiation oncologists, and primary care physicians have a thorough understanding of this disease process. The authors sincerely hope that this LM text providing a comprehensive approach to the diagnostic and management dilemmas will optimize the care of all our patients.

Chapter 2
Epidemiology and Natural History

H. William Higgins and Martin A. Weinstock

Introduction

Originally, some viewed lentigo maligna (LM) as a form of melanoma in situ (MIS); others viewed it as a form of melanocytic dysplasia, yet others as a hybrid category [1–3]. Since then, LM has been re-categorized as a subtype of MIS occurring on chronically sun-damaged skin. It has the potential to progress from an in situ tumor to an invasive tumor, known as lentigo maligna melanoma (LMM).

Lentigo malignas are recognized by the World Health Organization and the Surveillance, Epidemiology, and End Results Program as a type of MIS. However, there are some clinicians and scientists who advocate that LM actually embodies a distinct histologic entity compared to MIS [4–6]. LM has different epidemiologic characteristics, risk factors, and clinical features compared to MIS. Once LM progresses to LMM, it has a similar prognosis and course compared to other types of invasive melanomas when adjusted for the thickness of the tumor [7–11]. This chapter will specifically address the epidemiology and characteristics of lentigo maligna and lentigo maligna melanoma.

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_2

Incidence

Globally, LM and LMM are thought to account for 4–15 % of all melanomas. Because they most commonly presents on the head and neck areas, it makes up an even higher proportion of head and neck melanomas, approximately 10–26 % [8, 12].

Lentigo maligna is typically found on sun-exposed skin, with cumulative UV exposure serving as a known risk factor for development of this malignancy. As such, populations living in southern latitudes compared to northern latitudes tend to have a higher incidence of LM. In Australia, the incidence is estimated at 1.3 cases/100,000 person-years [13]. In the United States, incidence is estimated at 0.8 cases/100,000 person-years [14]. The incidence can be further stratified based on latitude, with Hawaii and parts of California showing a higher incidence than northern states of the United States [12]. However, in a study of Olmsted County, Minnesota, the incidence rate of 13.7 cases/100,000 person-years was disproportionately high compared to other population-based studies of the United States [15]. This may be a reflection of the high population of individuals living in that area with fair Fitzpatrick skin types.

The mean age of presentation for LM/LMM is 66–72 years. Comparatively, the mean age of presentation of non-lentigo maligna melanoma is 45–57 years [8, 12, 16, 17]. The incidence of LM/LMM has also been increasing over the past few decades [8, 12, 15, 18]. In young people between ages 45–64, one study found a 52 % increase in the incidence of LM [12]. Data from Olmsted County, Minnesota, show a doubling of the incidence of LM from 2.2 cases/100,000 person-years between 1970 and 1989 to 13.7 cases/100,000 person-years between 2004 and 2007 [15].

The reported incidence of LM may be influenced by several factors, namely the substantial variation in extent of skin examinations between providers, with increased likelihood of skin examination of sun exposed skin compared to non-sun exposed skin, and the role of attention to facial appearance awareness. Incidence is also difficult to interpret, as some lesions are not visible and detected only incidentally. Furthermore, the ambiguity of definition of the lesion leads some pathologists to report LM as MIS and others to report them as LM.

Risk Factors

This increase in incidence of LM/LMM has been attributed to increasing sun exposure practices and longer life expectancies with increased cumulative sun exposure. One study in Australia found that LM occurs more commonly on the side of the driver's head and neck in men, compared with the passenger side in women. Based on an Australian traffic database, the authors also concluded that during that time period, there were more male drivers than female drivers. Comparatively, females tended to be on the passenger side of the vehicle [19]. Similarly, cumulative sun exposure as a major risk factor for development of LM is supported by the observation that this tumor rarely develops in patients younger than 30 years, and that

Table 2.1 Risk factors for lentigo maligna / lentigo maligna melanoma

Age
Chronically sun exposed areas of sun-damaged skin
Number of lentigenes
Number of AKs
History of previous keratinocyte carcinomas

incidence of LM increases with age [15]. Additionally, LM occurs most commonly in lighter skin types and is rare in darker skin types. Thus, LM cases occur most often in Caucasians compared to blacks.

Females also appear to be disproportionately affected, with the ratio of females to males being approximately 1.7:1 [8]. Females also tend to present at a slightly older age than males [8]. Locations on the head and neck most at risk of developing lentigo maligna also differ between men and women. The cheek and nose are equally affected in both genders, whereas scalp and ear locations tend to be common in men compared to forehead locations being more common in women [20–22]. These differences may reflect locations that are more frequently sun exposed based on gender. In older men, the scalp and ears can lack protective coverage compared to women. Conversely, the cheek and nose areas in both genders may be equally exposed to UV rays and thus show a similar incidence of LM.

Additional risk factors are presented in Table 2.1 [23]. Compared to MIS, superficial spreading type, the number of lentigines is one of the strongest risk factors for developing LM. Skin cancer history (number of excised basal and squamous cell carcinomas) is associated with LMM and not with MIS, superficial spreading type. The number of nevi, lifetime severe sunburns, and sunburns before age of 20 were not associated with LMM, whereas these factors are associated with MIS, superficial spreading type. The number of actinic keratosis and Fitzpatrick skin type was associated with both LM and MIS, superficial spreading types [23].

Genetic conditions associated with LM include xeroderma pigmentosum, oculocutaneous albinism, Werner syndrome, and porphyria cutanea tarda [24–29]. These pigmentary or photosensitivity disorders increase the damage produced by ultraviolet radiation, perhaps leading to a quicker accumulation of DNA damage after cumulative sun exposure.

Progression of LM to LMM

LM is a slow-growing lesion that often is diagnosed years after initial presentation. At first, these lesions can be easily misdiagnosed as benign solar lentigines. Occasionally, central regression is seen with extension of the peripheral margin, indicating continued growth and evolution of the lesion [30, 31]. Overall, the lifetime risk of progression from LM to LMM ranges upwards of 5–20 %, and may be increasing with time (Table 2.2) [32–36]. A retrospective epidemiologic study using data from the 1970s estimated risk of progression to be approximately 5 % [36].

Table 2.2 Lentigo maligna: risk of progression vs. incidence of unsuspected invasion

	Author	Database	
Risk of progression from LM to LMM	Weinstock and Sober [36]	Health and nutritional examination survey from 1971–1974; Melanoma clinical cooperative group registry 1972–1977	5 %, age 45 2 %, age 65
Incidence of unsuspected invasion	Penneys [35]	Institutional pathology database, 1980–1987	15 %
	Somach et al. [34]	Institutional pathology database, 1992–1995	20 %
	Hazan et al. [33]	Institutional surgical database, 2000–2006	16 %
	Bousbous et al. [32]	Institutional surgical database, 1997–2008	10 %

Comparatively, studies using databases from single or dual institutions have estimated a risk of progression of up to 20 % [32–35]. Risk factors for transformation from LM to LMM is unclear, although larger size may be associated with diagnosis of LMM [32]. Timeframe for transformation to LMM is uncertain. In some patients, LM can be present for decades without progression to LMM. LM has no associated mortality, whereas prognosis of LMM is similar to other types of invasive melanoma [11].

Role of Genetics

In the past decade, several genes have been associated with development of invasive melanoma, with mutations in BRAF commonly occurring early in the development of melanoma [37]. Discovery of these mutations has been especially groundbreaking due to the array of directed therapies now available for BRAF mutated tumors [38]. BRAF mutations were found in >50 % of LMM in one study which examined 13 LMM [39]. This frequency of mutation was similar to other subtypes of melanoma, including superficial spreading and nodular melanomas [39]. In 6 cases of LMM that lacked BRAF mutations, 1 case (17 %) was found to harbor an NRAS mutation [39]. In a meta-analysis of 36 studies involving BRAF mutations and 31 studies involving NRAS mutations, BRAF mutations were most commonly found in superficial spreading melanoma. More specifically, BRAF mutations were found in 49 % of superficial spreading melanomas compared to 22 % of LMM. This mutation was found to be significantly associated with superficial spreading melanomas. NRAS mutations were found in 17 % of superficial spreading melanomas and 14 % of LMM and was not significantly associated with either superficial spreading melanoma or LMM [40].

While BRAF is one of the most common mutations in melanomas, it is worth noting that several studies with larger sample sizes have shown that the majority of LM lesions tend not to exhibit any known mutation. Mutated specimens of LM demonstrated

BRAF abnormalities ranged from 0–54 % of cases examined [39, 41–50]. A major limitation of these studies is the limited sample sizes, with the majority of studies examining <10 lesions. In LM lesions with a confirmed BRAF mutation, the BRAF V600K mutation was more prevalent than the BRAF V600E mutation, and was found in 16 % and 5 % of lesions, respectively [41].

Future Direction

Current research is under way to better delineate the epidemiologic risk factors and characteristics that help to distinguish LM from MIS. Beyond clinical factors, pathologic features unique to LM may also help to further clarify and separate this diagnosis from MIS. Genetic factors may also be helpful in the future to assist with differentiating these two lesions.

Conclusion

Our understanding of the epidemiology of LM continues to evolve. Risk factors for LM compared to non-LM melanoma are well studied, with several risk factors differing between the two conditions. However, it remains unclear why some lesions progress from LM to LMM whereas others stay indolent for decades as LM. The current era of genetics research in melanoma brings renewed hope for elucidating the underlying mechanism for the development of LM.

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Part II
Clinical and Pathologic Diagnosis

Chapter 3
Clinical Diagnosis

Ashley Sullivan and Timothy Wang

Introduction

Lentigo Maligna (LM) represents in situ melanoma that develops in chronically sun-damaged skin—often on the face of elderly patients. The term LM is used when the lesion is confined to the epidermis and does not contain invasive disease, whereas the term Lentigo Maligna Melanoma (LMM) is reserved for those lesions that have developed an invasive component.

LM typically presents as an asymptomatic macule or patch with irregular borders and pigmentation on the face or neck of an elderly fair skinned patient. Diagnosis of LM is often delayed due to its slow growth and the fact that many benign but similar appearing lesions also develop in these patients. To diagnose LM, physicians must have a high index of suspicion and be able to recognize a lesion that "stands out" within a background of mottled hyperpigmentation and photodamage.

LM can be difficult to treat because the lesions often extend beyond (and sometimes far beyond) the clinically evident margin. Moreover, histopathologically, the margin of LM can be difficult to define as up-regulated atypical melanocytes are often found as the background in chronically sun damaged skin. As with all melanomas but in LM especially, it must be understood that within a single lesion, the depth of invasion can vary. In other words, single lesions can contain both in situ and invasive disease. Since lesions of LM are typically larger at the time of diagnosis, invasion can easily be missed or underestimated due to sampling error.

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_3

Clinical Diagnosis

Patient Demographics

Although the clinical presentation of LM can vary somewhat by skin type, LM is predominantly found in patients with Fitzpatrick skin types I–III. In a 10-year retrospective analysis of 7712 cases of LM from the National Cancer Data Base (NCDB), 7185 (93.1 %) patients were White non-Hispanic, 35 (0.5 %) patients were African-American non-Hispanic, 63 (0.8 %) patients were Hispanic any race, and 429 (5.6 %) were patients that did not identify with one of the above races [1].

Furthermore, both men and women have been shown to have similar incidences of LM. Out of 7712 cases in the NCDB study, 4613 (59.8 %) patients were male and 3091 (40.1 %) were female [1]. In a separate study from Denmark, the incidence of LM was 1.5 cases/100 000 person-years for women and 1.4 cases/100,000 person-years for men between 2009 and 2011 [2]. Additionally, the location of LM can vary within each sex. In a recent retrospective study including 201 histopathologically proven facial and non facial LMs, location on the cheek was significantly associated with the female gender (P = .001), whereas a significant male predominance was found for a location on the scalp (P = .025) and the cartilaginous area on the ear (P = .025) [3].

Lastly, LM is more commonly seen in older patients. The median age in the NCDB study was 67.5 years for the LM subtype [1]. A similar finding was noted in a retrospective study of 201 facial and extra facial LM with the median age being 69.51 ± 12.26 years [3].

Location

LM typically occurs on chronically sun-damaged skin. A majority of the cases are located on the face, particularly on the cheeks and nose. In a recent retrospective study including 201 cases of facial and non facial LM, 108 (53.7 %) lesions were located on the cheeks while 30 (15 %) lesions were found on either the cartilaginous or bony parts of the nose [3]. Other common areas include the scalp, periocular region, forehead and neck (Fig. 3.1).

Size

LM is slowly growing, asymptomatic and often occurs in the setting of mottled hyperpigmentation. By the time they are biopsied, they are often larger in size (Fig. 3.2). In a retrospective study by Tiodorovic-Zivkovic et al., 48.8 % of lesions were > 10 mm in diameter at the time of biopsy. Similarly, 49.3 % of LMs biopsied had surrounding freckles, reinforcing the concept that these lesions arise in chronically sun-damaged skin (Fig. 3.3) [3].

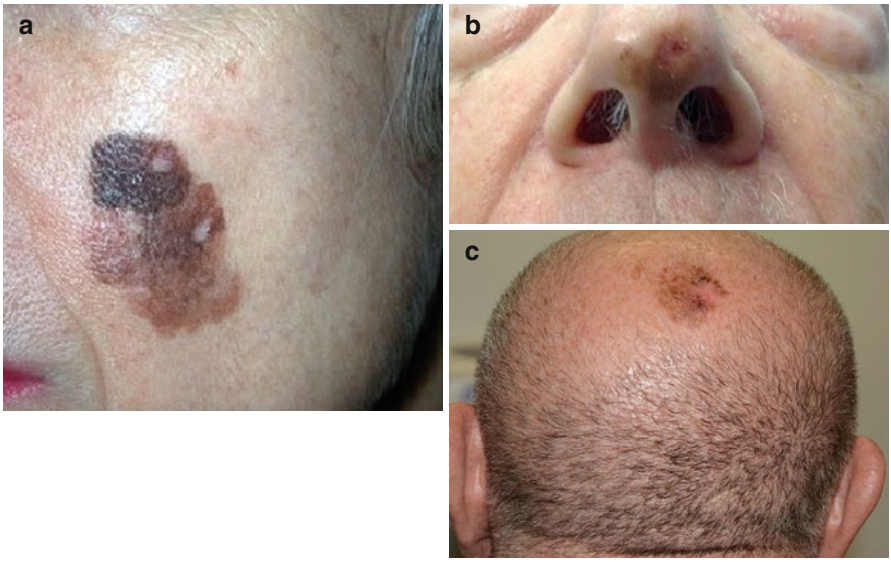

Fig. 3.1 Classic examples of lentigo maligna (**a**) on the cheek in a 60 year old female, (**b**) on the nasal tip in an 83 year old male, (**c**) and on the scalp in a 78 year old male

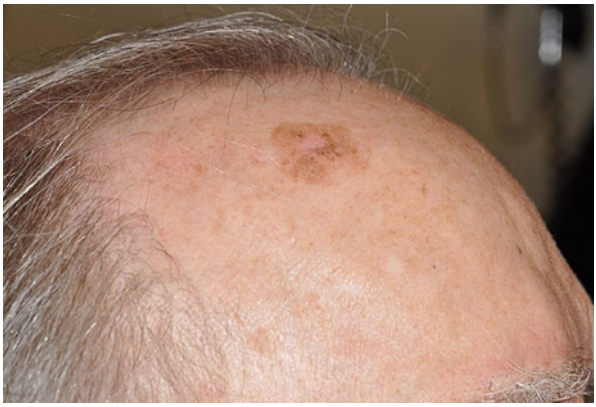

Fig. 3.2 2.5 cm lentigo maligna lesion on forehead

Morphology (Borders and Colors)

Most LMs present as asymmetric brown-black macules or patches with variegated color and irregular borders [4]. The differential diagnosis includes solar lentigo, seborrheic keratosis (Fig. 3.4), lichenoid keratosis, pigmented actinic keratosis, and melanocytic nevus. In a study of 121 melanoma in situ lesions, 92 % were macular. In that same study, 75 % of the melanoma in situ lesions had asymmetric borders [4]. In a study of 186 melanomas of various subtypes (LM, superficial spreading melanoma, desmoplastic melanoma, and nevoid melanoma), light-and dark-brown were the most frequently seen colors [n = 161 (86.6 %) and n = 158 (84.9 %), respectively].

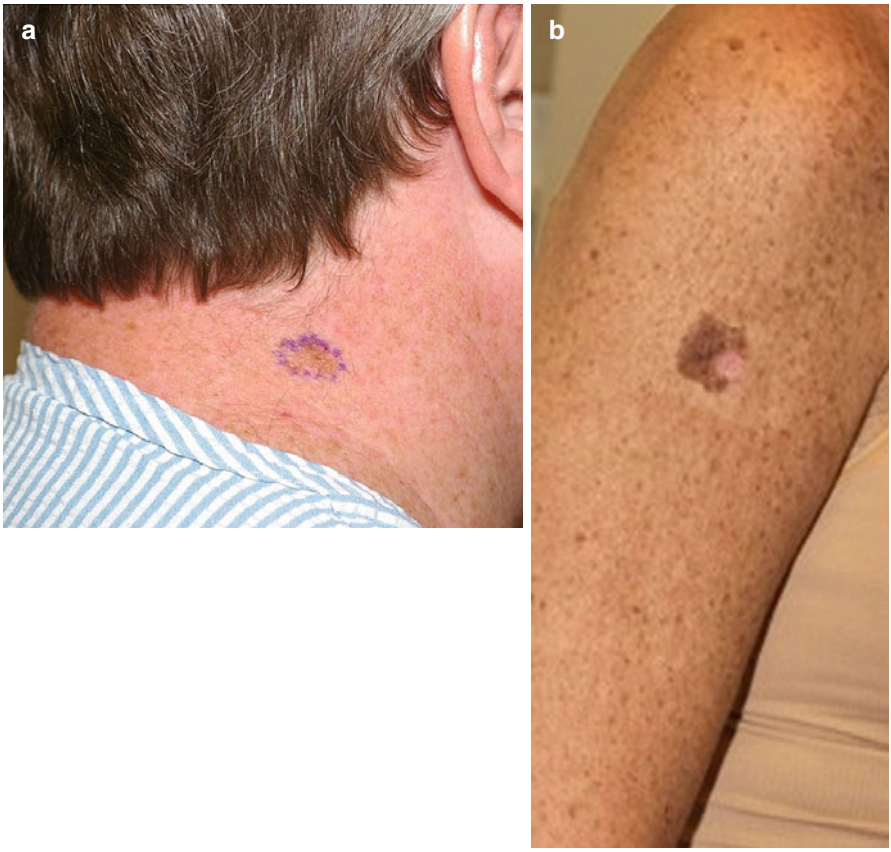

Fig. 3.3 Biopsy proven lentigo maligna surrounded by chronically sun-damaged skin on the (**a**) neck and (**b**) arm

Pink was appreciated in 56 cases (30 %) while white was seen in 10 cases (5.4 %). Melanoma in situ most commonly demonstrated 2 colors [n = 97 (68.3 %)] while 9.9 % showed only 1 color and 21.8 % showed 3+ colors [5]. Infrequently it is even possible for LM/LMM to have an amelanotic presentation as depicted in Fig. 3.5.

ABCDE's of Melanoma

In the early 1980s, a group of dermatologists created an algorithm for detecting melanomas based on their experience at NYU. At that time, melanoma detection was emphasized by **A**symmetry, **B**order irregularity, and **C**olor variegation [6]. This mnemonic has since been expanded to include **D**iameter greater than 6 mm and **E**volution (lesions changing over time). The mnemonic **ABCDE**s of melanoma is commonly used by many physicians to raise melanoma awareness and educate the

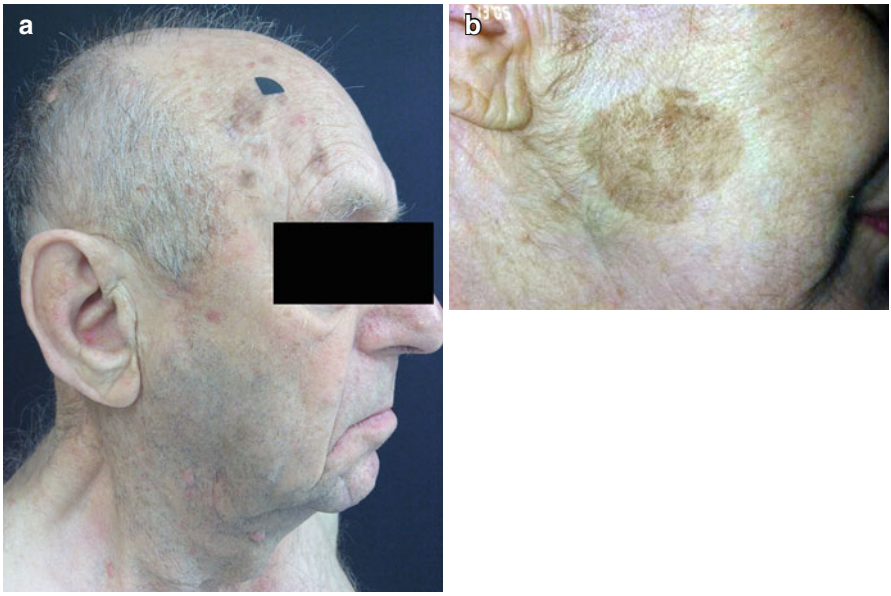

Fig. 3.4 Clinical example of (**a**) solar lentigo and (**b**) seborrheic keratosis

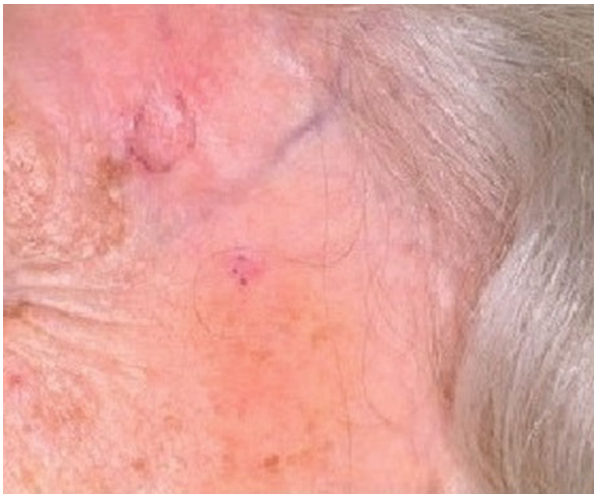

Fig. 3.5 Amelanotic lentigo maligna melanoma

public about those lesions that may call for further evaluation. While this mnemonic can be used in evaluating lesions of LM/LMM, simply failing to notice which lesion to evaluate contributes to the delay in diagnosis. Most lesions of LM/LMM occur on the face and are plainly in view. Many have been followed for years by physicians and patients. The often larger size and longer duration before diagnosis speaks to their slow, stealthy growth, asymptomatic nature and camouflaged appearance

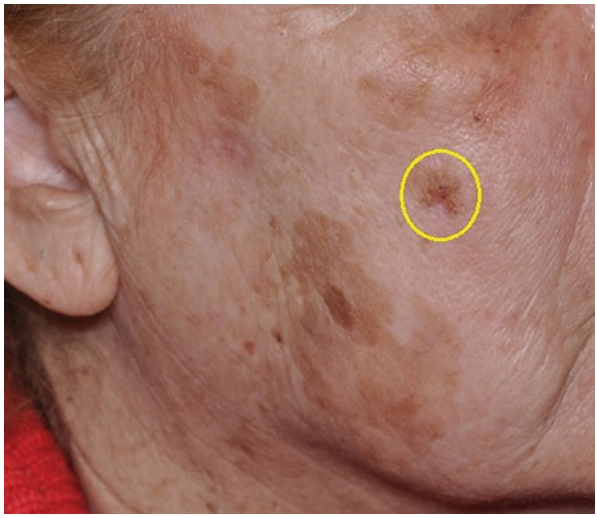

Fig. 3.6 Biopsy proven lentigo maligna on the cheek (*circled*) surrounded by sun damaged skin

against a background of photo damage (Fig. 3.6). These characteristics contribute to delay in diagnosis and highlight the need for the practitioner to maintain a high level of vigilance and suspicion, to sometimes step back and evaluate the patient's skin globally and to notice pattern rather than individual lesion as stressed by the ABCDE mnemonic.

Deciding Whether and How to Biopsy

As above, LMs are slowly growing and often asymptomatic. They typically occur in patients who may have decreased vision and therefore identification of suspicious lesions often relies on the physician's experience and level of suspicion. Clinicians seeing elderly fair skinned patients must remain vigilant and must carry a high index of suspicion and a low threshold for biopsy. A dermatoscope and/or a Wood's lamp may aid the clinician in the decision to biopsy but given the degree of clinical overlap, definitive diagnosis often relies on histopathologic examination.

Wood's Lamp

The Wood's lamp consists of a mercury vapor light source with a filter, which emits wavelengths from 320 to 450 nm, with peak emission at 365 nm. Epidermal melanin absorbs the shorter wavelengths emitted from the Wood's lamp, making superficially pigmented lesions appear darker than the surrounding normal epidermis (Fig. 3.7a). Superficially pigmented lesions can be more easily visualized and

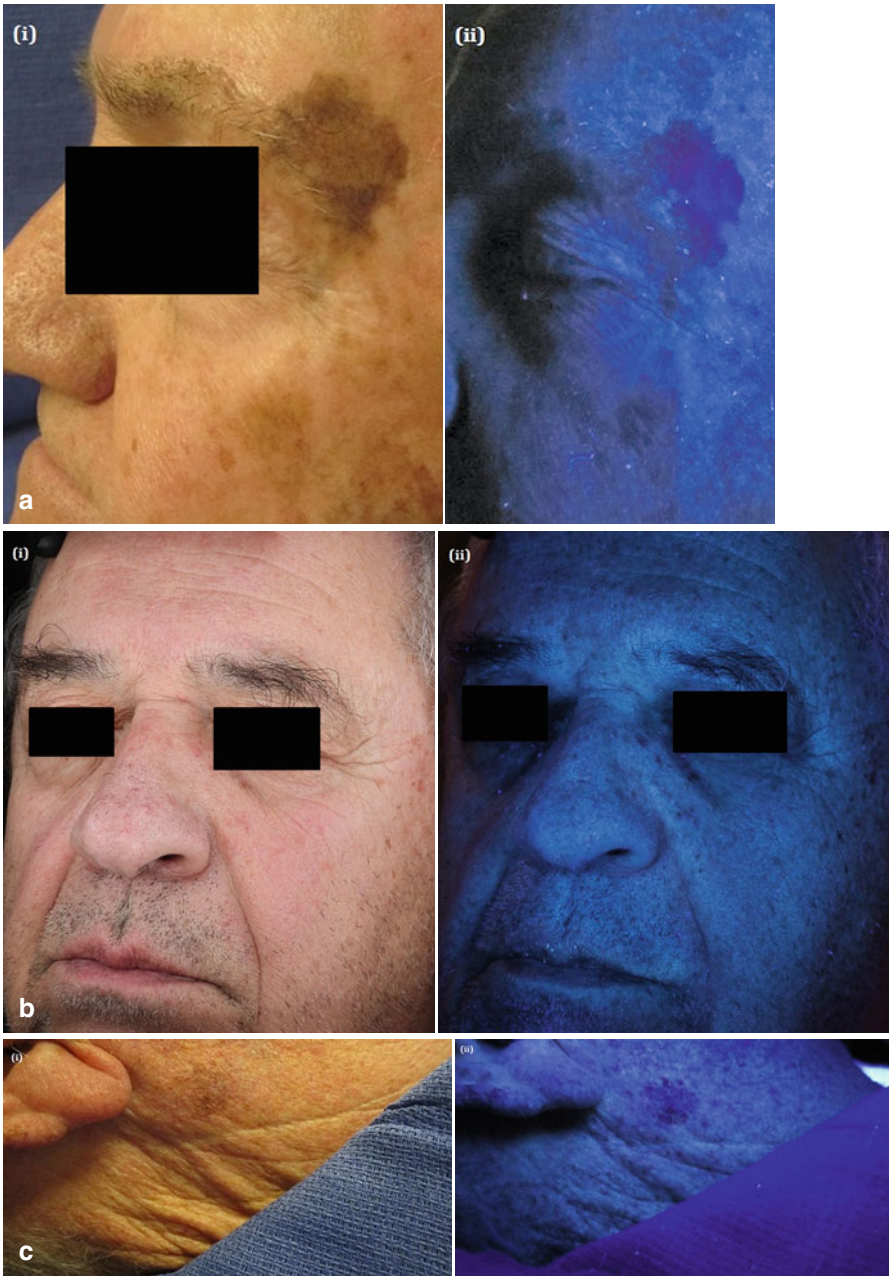

Fig. 3.7 (**a**) (i) Pigmented lesion on lateral brow (ii) Wood's lamp accentuating pigmentation. (**b**) (i) Patient with extensive photodamage (ii) Wood's lamp highlighting multiple benign pigmented lesions. (**c**) (i) Pigmented lesion below right ear (ii) Wood's lamp helping to estimate lesion size

outlined with the Wood's lamp. However, a clinician must recognize that dermal melanin is not accentuated by the Wood's light and may lead to false reassurance regarding a deeper atypical melanocytic lesion, such as a metastatic melanoma deposit or primary dermal melanoma [7]. Many benign melanocytic lesions are highlighted by the Wood's lamp including ephelides, lentigines, and nevi, and in the setting of diffuse photodamage this sometimes limits its utility as a diagnostic tool (Fig. 3.7b). For these reasons and in the authors' experience, the Wood's lamp may be more useful in helping the clinician estimate the size of lesions of LM with subclinical disease (i.e. lesion that may not be apparent to the naked eye) rather than in diagnosis (Fig. 3.7c).

Biopsy Techniques

After deciding to biopsy an atypical pigmented lesion, the clinician must decide both the *method* of biopsy such as shave, punch or ellipse and the *intent* of the biopsy—incisional or excisional. Incisional biopsies sample only part of the lesion while excisional biopsies sample the entire lesion. Which technique and approach is best depends on factors such as the size of the lesion (shave or punch can be excisional for small lesions but incisional for larger lesions), location of the lesion, patient and physician preference and clinical operations. It is widely understood that the depth of invasion is vitally important in the prognosis and treatment of primary melanoma. Shave biopsy poses greater risk of transecting melanoma at its base than punch biopsy however, deep or "scoop" shave or saucerized removal can help avoid this [8]. Punch biopsy can reduce the risk of transecting melanoma at its base but depth is more difficult to control in areas of thin skin. The literature supports that ultimately, melanoma can be sampled appropriately by both shave and punch biopsy. One study showed that shave biopsies were accurate and reliable in 97 % of their patient cohort, demonstrating the effectiveness of this tool in addition to full thickness excisional biopsies [9]. Similar to the punch biopsy, elliptical excision reduces the risk of transecting melanoma but is more reliant on clinician skill for optimal cosmesis. Since elliptical excision can result in a longer linear scar, patient preference and clinical operations may limit their use for routine biopsies.

When considering *intent* of the biopsy (that is whether to perform an incisional or excisional biopsy), the practitioner must understand that melanoma and in particular those of the LM/LMM type can vary in depth throughout the lesion and that the deepest area is not always the darkest or most elevated area. Any incisional biopsy that leaves remaining lesion is subject to sampling error.

In 1996, Somach et al. studied lesions that had an incisional biopsy with greater than 50 % of the clinical lesion remaining. They found that 40 % of the lesions demonstrated a more aggressive histology than originally seen on incisional biopsy [10]. Similarly Karimipour et al. showed that if 50 % or more of the original clinical lesion remained after incisional biopsy, the melanoma was upstaged 21 % of the time on subsequent excision [11]. Furthermore, Agarwal-Antal et al. reported that 16 % of LM contains invasive melanoma [12]. In a more recent paper by Gardner

et al., they noted that 24 patients (4%) of 624 patients with MIS on the head and neck were upstaged to invasive melanoma after surgical resection [13]. While the absolute percentage of cases upstaged on excision varied in these reports, these papers highlight that incisional biopsies for LM can contain areas of invasion i.e. the depth varies within these lesions and that an incisional biopsy can lead to underestimation of the depth of the lesion due to sampling error.

Sampling Error

Thus, to minimize the possibility of sampling error, excisional biopsy has long been held as the gold standard for diagnosing melanoma. The reader should recognize however that any step towards decreasing the risk of sampling error decreases the likelihood of a clinically significant error. For example, two punch biopsies or a deep shave (saucerization) from a large macule are better than one. Likewise, a larger incisional biopsy is better than two small punch biopsies and finally an excisional biopsy with narrow margins is most ideal (Fig. 3.8). As more of the lesion is

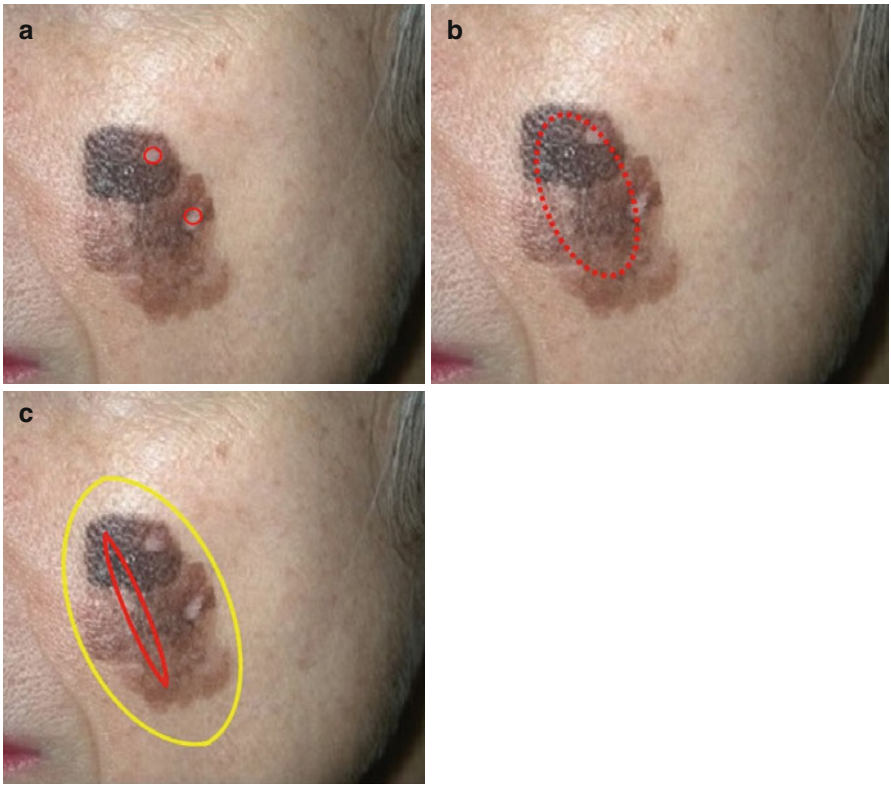

Fig. 3.8 Biopsy techniques: (**a**) Punch biopsy, (**b**) deep shave or saucerized biopsy, (**c**) incisional biopsy (*red*) vs. excisional biopsy (*yellow*)

sampled, it is less likely to have sampling error. When the entire lesion is evaluated, sampling error is minimized. However, excisional biopsy may not always be feasible in a very large lesion as illustrated in Fig. 3.8. For larger lesions initially biopsied by shave or punch, the authors recommend subsequent excisional biopsy or at least larger incisional biopsy for so called "microstaging" to reduce the risk of sampling error. It cannot be overstated that lesions of LM can vary in depth and that the deepest portion of lesion is often not predictable clinically. Excisional biopsies should be performed with narrow margins, minimal undermining, and simple primary closure, to avoid disrupting dermal lymphatics; particularly in LM, a broad shave to sample a larger area may be considered [14, 15].

Sampling error can also lead to missing the diagnosis of LM/LMM altogether. Note that LM can be difficult to differentiate from background melanocytic hyperplasia and atypia caused by chronic photodamage. When the clinician suspects LM/LMM but an incisional biopsy is reported by pathology as benign, re-biopsy must be considered if the clinician's suspicion remains high. Correlation between the clinical picture and histopathologic diagnosis is vital. Dermatopathologists skilled at evaluating melanocytic lesions are likewise critical to the diagnosis and treatment of LM/LMM. Despite an initially benign biopsy result, practitioners must maintain a high level of suspicion when faced with a larger pigmented lesion in sun-damaged skin.

Conclusion

The clinical diagnosis of LM/LMM requires that the practitioner remain vigilant and maintain both a high index of suspicion and a low threshold for biopsy of what are often subtle, asymptomatic, slowly growing lesions in the setting of chronic photodamage.

Realizing the critical importance to prognosis and treatment the Breslow thickness represents, the practitioner must understand the concepts of variations in depth within a lesion and sampling error. With these in mind, when LM/LMM is diagnosed on incisional biopsy and significant lesion remains, consideration should be given to excisional biopsy—"microstaging" or at least additional biopsies to minimize the impact of sampling error. Clinical-pathological correlation and experienced dermatopathologists are essential to the diagnosis and treatment of LM/LMM.

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Chapter 4
Role of Dermoscopy

Maria L. Marino, Cristina Carrera, Michael A. Marchetti, and Ashfaq A. Marghoob

Introduction

Lentigo maligna/lentigo maligna melanoma (LM/LMM) usually presents as an isolated pigmented macule or patch on chronically sun damaged skin. In its early stages its clinical presentation overlaps with solar lentigo, flat seborrheic keratosis (SK), pigmented actinic keratosis (AK), and lichen planus-like keratosis (LPLK), presenting a diagnostic challenge. As a result, LMM is often not recognized and diagnosis is delayed [1]. While Wood's lamp examination can help to accentuate lesion pigmentation for border detection, it cannot reliably help in differentiating LM/LMM from its benign mimickers [1]. Fortunately, ancillary non-invasive tools such as dermoscopy and reflectance confocal microscopy (RCM) can improve our diagnostic accuracy for LM/LMM as well as for solar lentigo, flat SK, pigmented AK, and LPLK. Although RCM is quite useful for the diagnosis of LM/LMM, dermoscopy remains the primary imaging instrument used to help identify lesions with the highest likelihood of being LM/LMM. Besides helping in the identification of LM/LMM, dermoscopy can improve LM/LMM margin delineation and detect potential recurrence after definitive treatment. Finally, when examining LM/LMM lesions with skip areas or clinically discontinuous foci, dermoscopy can aid in biopsy site identification [1, 2].

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_4

Dermoscopy Technique

The dermatoscope is a non-invasive handheld tool that provides illuminated magnification and changes the refractive index of light entering the skin surface. This allows the observer to see subsurface skin structures that are otherwise not visible to the naked eye [3]. Meta-analyses have demonstrated that dermoscopy improves clinicians' diagnostic accuracy compared to clinical evaluation alone [4–6]. The light source used in dermoscopy can be non-polarized or polarized. Using non-polarized light requires a liquid interface (gel, alcohol or water) between the skin and glass lens of the dermatoscope. Directly contacting the wet skin with the dermatoscope helps eliminate air spaces, reducing light reflection off the surface layer of the skin. This in turn permits more light to penetrate into the skin allowing for the observation of subsurface structures [7]. In contrast, polarized dermoscopy permits visualization of deeper skin structures without the need of a liquid interface or direct skin contact. Polarized and non-polarized dermoscopy provide complementary information for the diagnosis of LM/LMM. Superficial dermoscopic structures such as blue-white veil due to orthokeratosis, milia-like cysts, and granularity are usually more conspicuous with non-polarized dermoscopy. In contrast, deeper structures such as blood vessels and tumor stroma (i.e., shiny white structures) are most conspicuous, or only visualized, with polarized dermoscopy.

Anatomic Considerations of Lentigo Maligna Melanoma

Lentigo maligna/lentigo maligna melanoma usually presents on the head and neck but can also develop on the skin of the trunk or extremities that has received high cumulative lifetime ultraviolet radiation (UVR) exposure. Both the anatomical location and the degree of UVR damage impacts the dermoscopic features present in these lesions [6]. Facial skin is characterized by having attenuated rete ridges in addition to numerous terminal hair follicles and sweat gland ostia [2, 8]. Since the rete ridges are not prominent on facial skin, network structures and streaks are rarely seen. However, the presence of pigment in the epidermis together with the high concentration of adnexal/follicular openings present on facial skin creates a pseudo-network appearance. In addition, gray dots/granules and other pigment structures create the so-called annular granular pattern (Fig. 4.1) when they are organized around follicular openings. While the pseudo-network pattern is found in almost any pigmented lesion on the face, the annular-granular pattern is more commonly associated with LM/LMM [9].

UVR damaged skin of the torso and extremities differs from facial skin in that it usually has some preserved rete ridges and significantly fewer adnexal openings [10]. Thus, LM/LMM on non-facial sun damaged skin often reveals focal islands of network without an annular granular pattern.

One dermoscopic feature commonly seen in LMM, irrespective of anatomical location, is the presence of angulated lines. These angulated lines can coalesce to

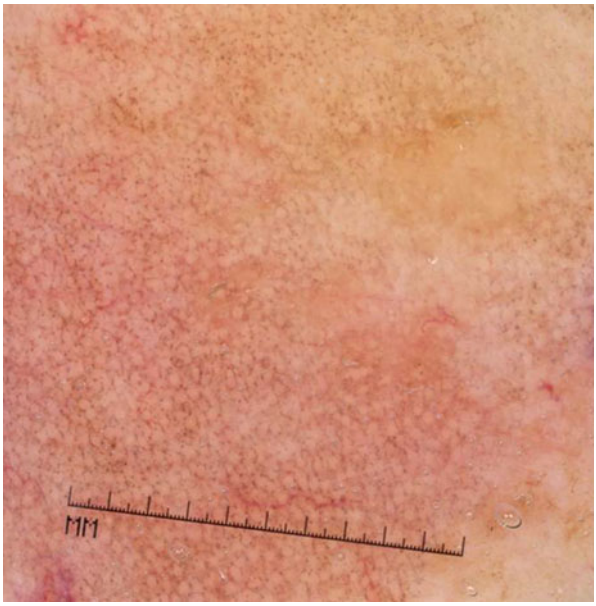

Fig. 4.1 Dermoscopy image of lentigo maligna melanoma on the cheek displaying an annular-granular pattern composed of *gray* and *brown dots* asymmetrically distributed around follicular openings

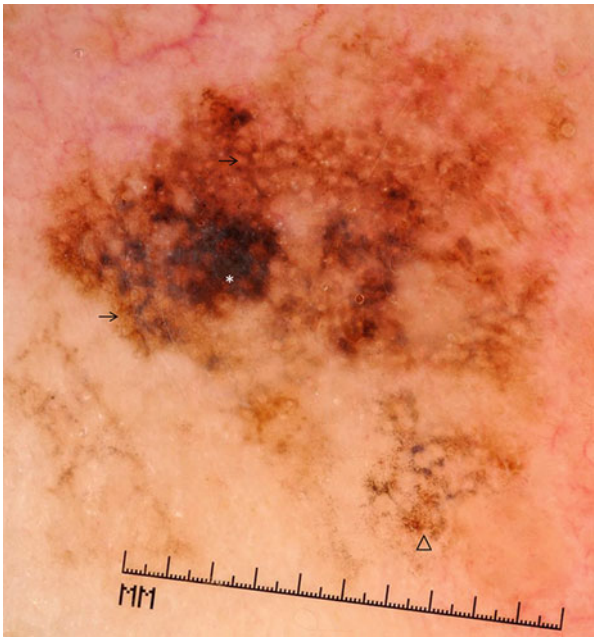

Fig. 4.2 Dermoscopy image of lentigo maligna melanoma on the cheek. Note *angulated lines* (*arrows*) leading to formation of rhomboidal structures, regression/granularity (*triangle*), and central blotch (*white asterisk*) with obliterated follicular openings

create zigzag lines and polygons. On facial skin the most common polygons formed are rhomboidal structures (Fig. 4.2). In contrast, on non-facial sun damaged skin the polygons tend to be larger than those on facial skin and can take on polygonal shapes other than rhomboids (Fig. 4.3) [1, 10].

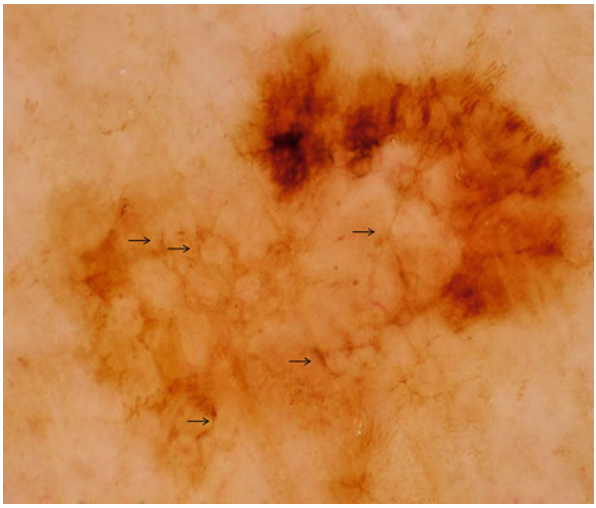

Fig. 4.3 Dermoscopy image of lentigo maligna melanoma on the shoulder. Note *numerous angulated lines* (*arrows*) that form polygonal structures including rhomboids

Dermoscopic Features of LM/LMM

The classic LM/LMM dermoscopic specific structures include:

- Asymmetric distribution of pigment, often with grayish hues, surrounding follicular openings (Fig. 4.3). This corresponds on histopathology to the presence of atypical melanocytes in the epidermis that are surrounding and/or descending into the hair follicles [8]. In addition, concentric pigmented circles surrounding follicular openings may be present. This feature is called the isobar structure or the circle-within-a-circle structure (Figs. 4.4, 4.5, and 4.6) [1].

- Grey dots/granules surrounding follicular openings. Gray dots/granules correspond on histopathology to melanophages in the upper dermis. Rarely one can also see streaks, which correspond to confluent junctional melanocytes [2, 11].

- Annular-granular pattern created when both gray dots/granules surrounding follicular openings and asymmetric pigmented follicular openings are present [2, 8]. At times the dots can be larger, corresponding to nests of melanocytes, and then these structures are called globules.

- Rhomboidal structures are formed when angulated lines coalesce into zigzag lines and polygons. The histopathology correlation of angulated lines consists of confluent junctional atypical melanocytes together with underlying melanophages in the papillary dermis [2, 12].

Shiffner et al showed that the presence of asymmetrically pigmented follicular openings, gray dots, gray globules, or rhomboidal structures located anywhere within a lesion has a sensitivity of 89 % and a specificity of 96 % for LMM [2]. Pralong et al found that at least one of these structures is present in 87 % of LMMs [13]. The presence of gray color appears to be a useful clue to the diagnosis of LMM

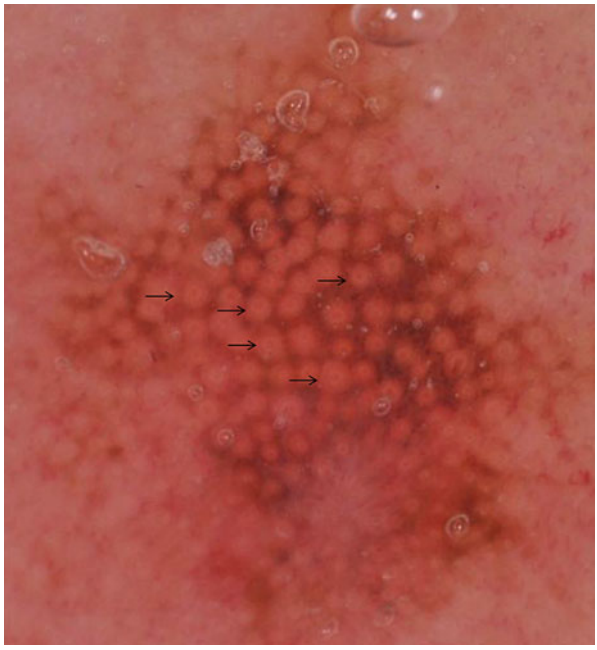

Fig. 4.4 Dermoscopy image of lentigo maligna melanoma on the earlobe showing pseudonetwork pattern and numerous *circle-within-a-circles* (*arrows*)

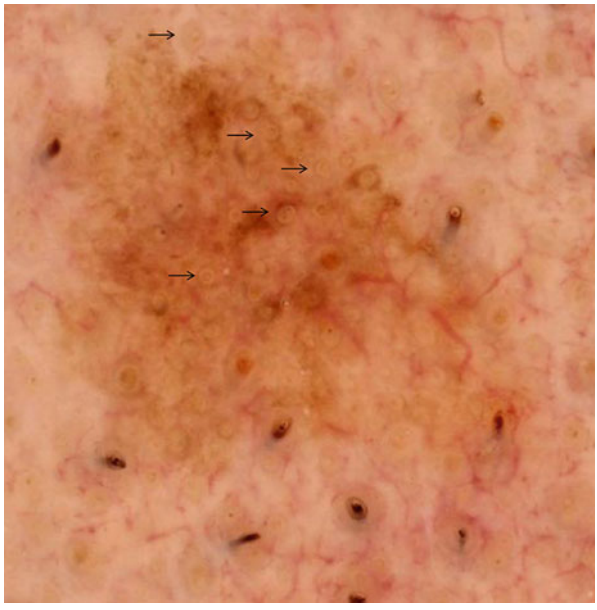

Fig. 4.5 Dermoscopy image of lentigo maligna melanoma on the cheek with many *circle-within-a-circles* (*arrows*)

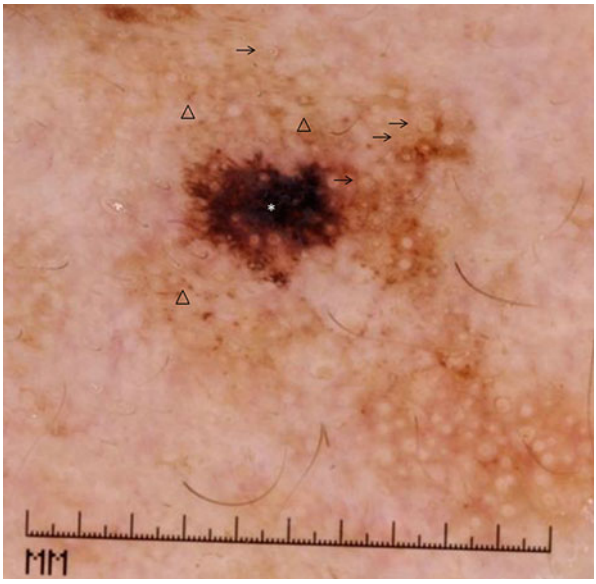

Fig. 4.6 Dermoscopy image of lentigo maligna melanoma on the cheek with asymmetrically pigmented follicular openings with granularity (*triangles*), *circle-within-a-circles* (*arrows*), and central blotch with obliteration of follicular openings and presence of *blue-white veil* (*asterisk*)

[14]. In a series of 201 LMMs, gray color was present in 88.6 % of cases [15]. Tschandl et al further reported that any gray structures, such as dots, circles, or lines, were present in 95.8 % of LMM lesions with a relative risk of 8.9 (95 % CI: 1.2–64.7) [16]. While gray color is possible in pigmented actinic keratosis and LPLK, this color is rare in solar lentigo and flat seborrheic keratosis.

Less prevalent dermoscopic features associated with LM/LMM include the isobar structure or the "circle-within-a-circle", identified in 5 % and 25.4 % of cases in 2 separate series [15, 16]. More recently described features include red rhomboidal structures, increased lesional vascular network density, and target-like pattern [13]. Red rhomboidal structures are created by a diamond or rhomboid-shaped vascular pattern occurring between hair follicles, and were reported to be present in 40 % of cases [13]. An increased density of the vascular network within the lesion compared to the peripheral skin was found in 58 % of cases [13]. A target-like pattern, defined as a dark dot in the center of the dark circle of a hyper-pigmented hair follicle, has been found in 19.4 % and 41 % of cases [13, 15]. Finally, the perception of the degree of pigment present within a lesion is a clue to the diagnosis of LM/LMM. In 25 % of LM/LMM the pigment appears darker and more variegated with different shades of brown and gray when viewed with dermoscopy compared to naked-eye examination [13].

It is plausible that certain LM/LMM-specific features are related to the type/thickness of the melanoma, the anatomical location of the tumor, or to patient-specific phenotypic factors. For example, Tiodorovic-Zivkovic et al showed that rhomboidal structures are more frequently seen in LMM located on the upper part of the face ($p = 0.028$), whereas asymmetric follicular openings were more common in LMM located on the lower part of the face ($p = 0.036$) [15]. Table 4.1 summarizes frequency and diagnostic accuracy of dermoscopic features of LMM.

Table 4.1 Frequency and measures of diagnostic accuracy of dermoscopic features described for lentigo maligna melanoma

Authors	Dermoscopic Feature	Prevalence n, (%)	Sensitivity (%)	Specificity (%)
Schiffner et al. [2]	Asymmetric follicular openings	25/37 (68)	67.6	88
	Rhomboidal structures	18/37 (49)	48.6	100
	Asymmetrically pigmented follicular openings, Rhomboidal structures, Gray globules, Gray dots	34/37 (93)	89	96
Pralong et al. [13]	Rhomboidal structures	86/125 (69)	68.8	
	Pigmented follicular openings	64/125 (51)	51.2	
	Annular-granular pattern	53/125 (42)	42.4	
	Obliterated hair follicles	16/125 (13)	12.8	
	Circles and semicircles	59/125 (47)	47.2	
	Circle-within-a-circle	6/125 (5)	4.8	
	Target like pattern	51/125 (41)	40.8	
	Red rhomboidal structures	50/125 (40)	40.8	
Tschandl et al. [16]	Any gray structure	23/24 (96)	95.8	30.6
	Gray dots, clods, circles or lines	13/24 (54)	54.2	83.3
	Circle-within-a-circle	1/24 (4)	4.2	98.1
	Rhomboidal structures	4/24 (17)	16.7	91.7
Tiodorovic-Zivkovic et al. [15]	Gray color	178/201 (89)	88.5	
	Asymmetric follicular openings	89/201 (44)	44.3	
	Annular Granular pattern	55/201 (27)	27.4	
	Circle-within-a-circle	51/201 (25)	25.4	
	Rhomboidal structures	36/201 (18)	17.9	
	Obliterated hair follicles	25/201 (12)	12.4	
	Target like pattern	39/201 (19)	19.4	
	Red rhomboidal structures	4/201 (2)	2	
Jaimes et al.[a] [10]	Patchy peripheral pigmented islands	28/76 (37)	36.8	
	Angulated lines pattern	23/76 (30)	30.3	
	Tan structureless and granularity pattern	9/76 (12)	11.8	
	No pattern	17/76 (22)	22.4	

[a]Extra-facial lentigo maligna melanoma

Progression Model of LMM

Stolz et al. proposed a progression model for LM/LMM based on dermoscopic findings (Fig. 4.7) [2]. While there are no prospective studies documenting the actual changes developing in longitudinally followed LM/LMM, cross-sectional observations do lend support for the proposed progression model. It is hypothesized that the mutated stem cell leading to LM/LMM resides within the hair follicle and this may help explain the folliculo-centric pathology findings in early LM [17]. These early proliferating malignant cells may favor the environment in and around the hair

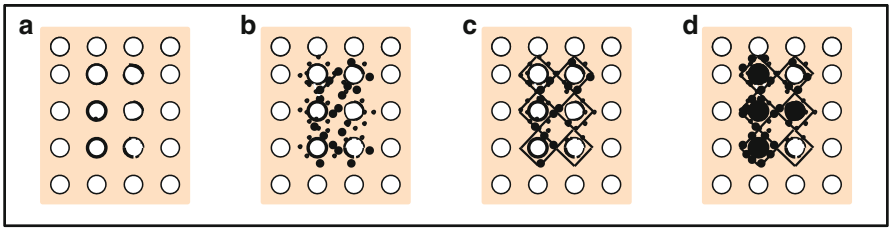

Fig. 4.7 Stolz's "progression model of lentigo maligna". (**a**) Asymmetric follicular openings; (**b**) Annular-granular pattern; (**c**) Rhomboidal structures; (**d**) Obliterated follicular openings

follicles and thus preferentially proliferate in this location. Dermoscopic findings favor this hypothesis since the earliest dermoscopic findings in LMM are the annular-granular pattern with asymmetrically pigmented follicular openings, perifollicular granularity, and circles-within-circles [1, 2, 8, 11]. As the melanoma progresses, the malignant cells proliferate within the inter-follicular epidermis leading to the dermoscopic observation of angulated lines forming zigzag structures. As the LMM continues to grow, the lines become more prominent and coalesce to form polygonal structures. Eventually the pigment becomes more confluent resulting in the formation of blotches. Within these blotches one can initially observe preserved adnexal openings; however, as the melanoma progresses the adnexal openings are obliterated resulting in solid black to blue-white blotches or structureless areas, which appear to correlate with the vertical growth phase of LMM [1, 2]. Once the melanoma invades the dermis, other dermoscopic features emerge including white scar-like depigmentation, shiny white structures, blue-whitish veil, milky-red areas, or atypical vessels. Rarely, desmoplastic melanoma is found in association with LMM. The desmoplastic component is associated with palpable firmness. While the desmoplastic melanoma can be pigmented and present as a bluish subcutaneous firm papule in association with LMM, they usually present as an amelanotic focal firm palpable area with atypical vessels in association with a LMM [18].

LM/LMM on Non-facial Skin

Extra-facial LM/LMM can be difficult to detect on skin harboring many solar lentigines. In addition, an early LMM is challenging to differentiate from a solar lentigo by naked-eye examination [19]. However, dermoscopy can reveal clues to the diagnosis of LM/LMM on non-facial skin. Jaimes et al analyzed 183 melanomas located on sun-damaged non-facial skin, of which 76 were LMM subtype. The most common dermoscopic structures present were granularity (126/186, 67.7 %), angulated lines (82/186, 44.1 %), and atypical dots (68/186, 36.6 %) [10], similar to previously published studies [20]. The authors determined that the most common patterns in LMM were the patchy peripheral pigmented island pattern (28/76, 36.8 %) followed by patterns composed of angulated lines (23/76, 30.3 %) or tan structureless areas with granularity (9/76, 11.8 %) (Figs. 4.3 and 4.8) [10].

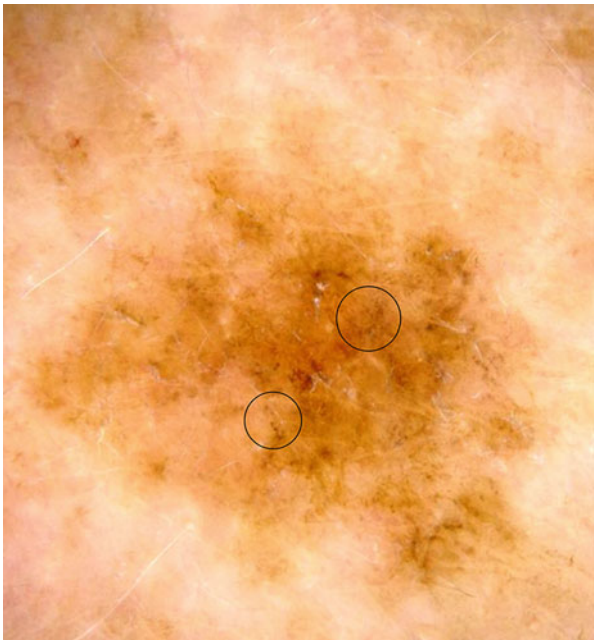

Fig. 4.8 Dermoscopy image of subtle lentigo maligna melanoma on the shoulder showing tan structureless pattern and fine *grayish granularity* (*circles*)

Dermoscopic Differential Diagnosis

The differential diagnosis for LM/LMM includes SL, SK, pigmented AK, and LPLK (Table 4.2). Differentiating a SL and flat SK from early LMM is challenging with naked-eye examination alone. Dermoscopy findings such as the presence of yellowish pigment, milia-like cysts, fingerprint like areas (Fig. 4.9), and/or moth-eaten borders in a lesion that lacks any of the LM/LMM specific structures listed in Table 4.2 is suggestive of a benign lesion [2, 9]. Some SL/flat SK reveals asymmetrically pigmented follicular openings; however, the pigment in these lesions is usually light brown in color with minimal variability in its hues. In contrast, the peri-follicular pigmentation in LM/LMM manifests with increased variability in brown hues, often with gray pigment present [1, 2]. Since LM/LMM is located on sun-damaged skin, collision tumors between LM/LMM and lentigo or flat SK are possible. Thus, any lesion on sun damaged skin revealing any LM/LMM specific structures, irrespective of how small the focus, within an otherwise benign appearing background pattern of a SK or SL should be biopsied or monitored closely.

A pigmented AK shares clinical and dermoscopic features with LM/LMM. On examination, pigmented AK has a rough texture on palpation whereas LMM has a smooth texture. Pigmented AK often contains gray dots, globules, scalloped borders and/or angulated lines and can manifest an annular-granular pattern [25, 27, 28]. Akay et al found the presence of gray pseudo-network and annular-granular pattern in 36 % and 39 % of PAK, respectively [28]. While angulated lines are seen in PAK, the presence of rhomboidal structures is associated with LM/LMM [28]. Additionally, Nascimento et al described the inner gray halo, defined as an homoge-

Table 4.2 Clinical and dermoscopic features of benign simulators of lentigo maligna melanoma

Lesion	Clinical features	Dermoscopic findings
Flat seborrheic keratosis/ solar lentigo [1, 21–23]	Patch or thin plaque, tan colored, sometimes with subtle verrucous surface	Sharp demarcation Moth-eaten border Milia-like cysts Comedo-like openings Yellow opaque areas Light brown fingerprint-like structures
Pigmented lichen planus-like keratosis [16, 24]	Macule or papule Most frequently located on sun exposed areas on trunk and upper limbs	Typical pseudonetwork Granular pigmentation (coarse or fine, gray to blue) Dots or lines pattern May have remnants of flat seborrheic keratosis or solar lentigo
Pigmented actinic keratosis [1, 25, 26]	Rough tan to brown macule	Superficial brown pseudonetwork Keratin plugs Inner gray halo

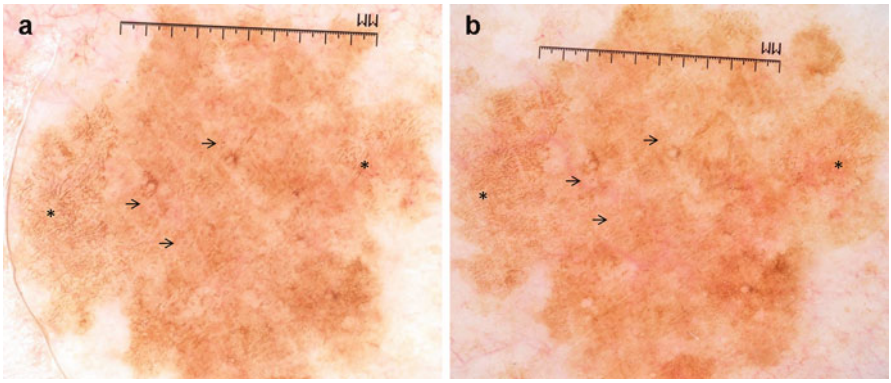

Fig. 4.9 Solar lentigo on the chest followed with sequential digital dermoscopic imaging over 4 years (Panels **a** and **b**). Note symmetrical follicular openings (*arrows*) and fingerprint-like pattern (*asterisks*). There is an absence of lentigo maligna melanoma specific features, such as *gray color*

neous beige or gray halo around the follicular openings, as a useful feature in diagnosing pigmented AK as it was found in 94.1 % (53/58) of pigmented AKs but in only 23.8 % (5/21) of LMM cases [26].

Regarding LPLK, it is important to underscore that it is often impossible to differentiate LPLK from LMM with dermoscopy. However, there are some clues that may help distinguish LPLK from LMM. While both can reveal gray granularity, the granularity in LPLK tends to be coarser and distributed more uniformly as compared to the granularity seen in LM/LMM. Furthermore, since LPLK represents the involution of SK/SL it is possible to see granularity as well as remnants of SK or SL in these lesions [16, 24].

Management of LM/LMM

Dermoscopy helps in the management of LM/LMM [29]. While use of a Wood's lamp can help delineate the borders of LM/LMM, dermoscopy is superior to Wood's lamp examination for this purpose [30, 31]. In addition, although surgical excision remains the standard of care for treating LM/LMM, unique situations sometimes arise that require the use of non-invasive or ablative therapies for LM/LMM. In such scenarios, dermoscopy can assist in monitoring therapy and post treatment follow up to detect disease recurrence [32]. Recently, Guitera et al, reported the dermoscopy finding of "dust-like dots" as a clue for treatment failure in cases of LMM treated with imiquimod or radiotherapy [33].

Conclusion

Use of dermoscopy not only aids the detection of LM/LMM, but also biopsy site selection, margin assessment, and post-treatment monitoring.

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Chapter 5
Pathologic Diagnosis

Maija Kiuru and Klaus J. Busam

Introduction

Current Nomenclature

Lentigo maligna melanoma (LMM) is one of the four clinicopathologic subtypes of invasive melanoma along with superficial spreading, nodular, and acral lentiginous melanoma [1–3]. Characteristically, it occurs on chronically sun-exposed skin of the elderly and shows an increased density of predominantly basilar melanocytes initially with little pagetoid growth [1, 4]. When the melanoma is not invasive and confined to the epidermis (in situ), it is called lentigo maligna (LM) or melanoma in situ, lentigo maligna type. Contrary to the frequent misconception that LM is a premalignant lesion, LM is in fact a fully developed melanoma in situ. When the melanoma is invasive, it is called lentigo maligna melanoma (LMM) [5, 6]. In this article, lentigo maligna (LM) and lentigo maligna melanoma (LMM) will describe the in situ and invasive melanoma, respectively.

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_5

History: Hutchinson's Melanotic Freckle and Circumscribed Precancerous Melanosis of Dubreuilh

LM/LMM was first described clinically by Hutchinson [7–9] dating back to late nineteenth century. He reported freckles on the skin of elderly that slowly enlarge and become black and eventually ulcerate. He assumed the process was infective in nature and called these lesions "infective senile freckles". His work gave later rise to the terminology Hutchinson's melanotic freckle. Dubreuilh reported a series of patients with similar findings and named the condition "lentigo malin des viellards" ("malignant lentigo of the elderly") and "la melanose circonsite precancereuse" [10], giving rise to the term circumscribed precancerous melanosis of Dubreuilh [11]. Described since by many other authors using a variety of names including "praecanceroese melanose", "malignant mole", "junction nevus: nevocarcinoma" (reviewed in [11, 12]), and finally "lentigo maligna" [13].

Histologic Diagnosis

Obtaining a Biopsy Specimen

Given the characteristic large size and the exposed anatomic location of LM/LMM, obtaining a biopsy specimen can be challenging. If the suspicious lesion is small, an excisional biopsy either by a punch excision, a shave removal, or an elliptical excision, is recommended [14]. If the lesion is too large to be completely removed, a representative biopsy or biopsies of the darkest, most palpable, or otherwise clinically/dermoscopically most suspicious portion is recommended [5, 15]. The clinical history provided to the pathologist should include, at a minimum, the clinical size of the lesion [14, 16].

Histologic Features

The classic microscopic picture of a LM is characterized by an increased density of predominantly solitary units of melanocytes along the dermal-epidermal junction and focally above it, typically associated with solar elastosis [1, 4] (Figs. 5.1, 5.2, and 5.3). While junctional nests and pagetoid spread are usually only a minor component, some lesions of LM feature nests and/or pagetoid spread prominently.

The first clue to the diagnosis of LM is an increased density of junctional melanocytes [1, 4], typically associated with a solar lentigo-like background, i.e. hyperpigmentation of basilar keratinocytes. The neoplastic melanocytes may be cytologically bland. Not uncommonly, however, there is some nuclear atypia [1] (Figs. 5.1 and 5.3), ranging from slight nuclear enlargement to two or three times

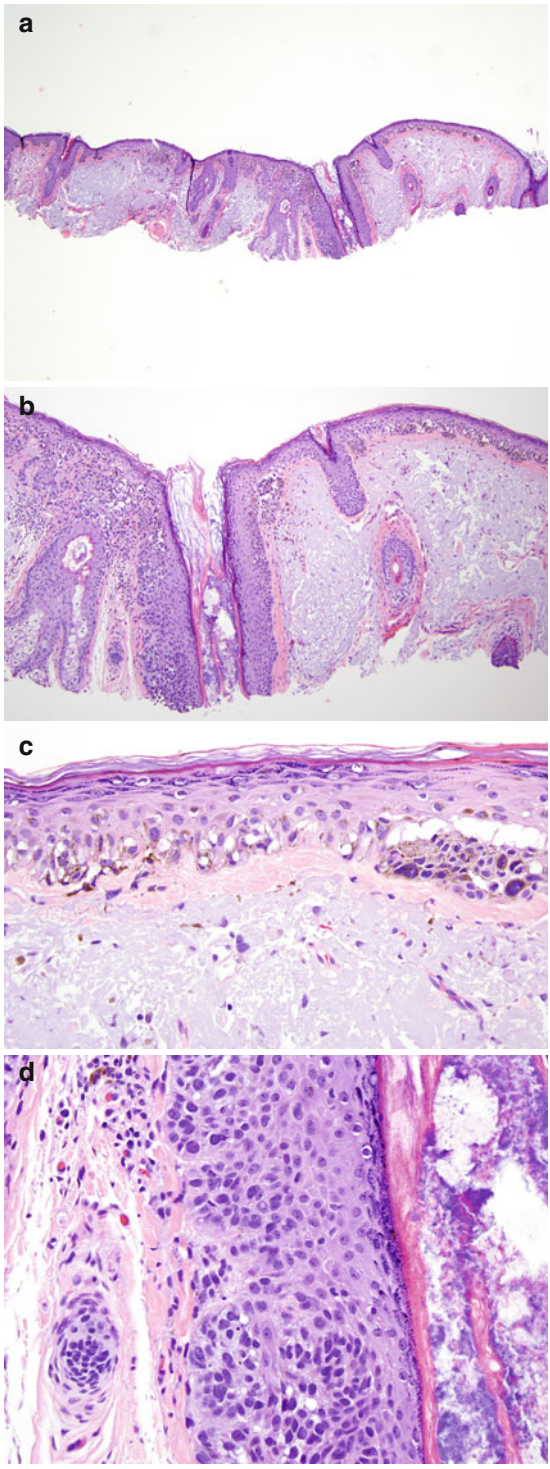

Fig. 5.1 Lentigo maligna. Severe solar elastosis with increased density of junctional melanocytes (**a**), asymmetric nests (**a–c**), adnexal involvement (**a, b, d**), and cytologic atypia of melanocytes (**c, d**)

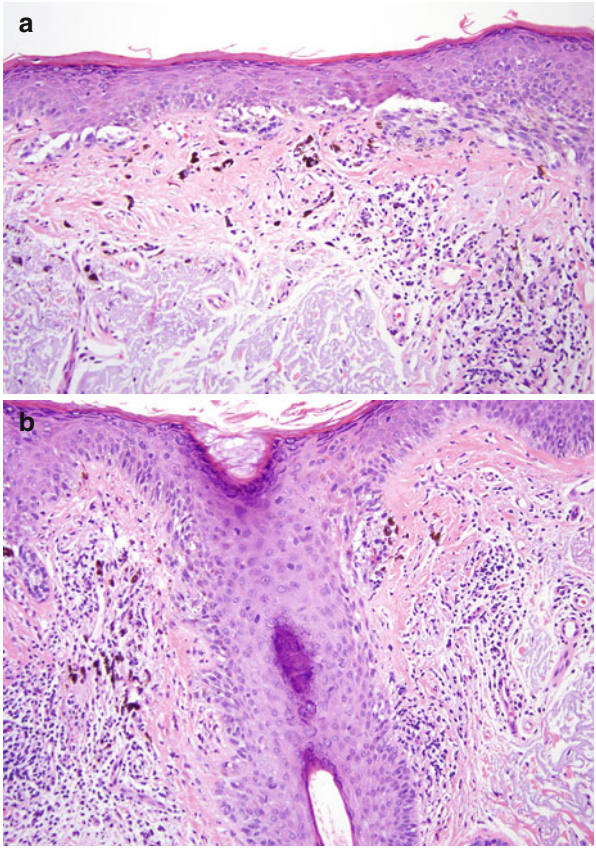

Fig. 5.2 Lentigo maligna. Severe solar elastosis with irregular nests (**a, b**) also involving the adnexal epithelium (**b**), and dermal inflammatory infiltrates with melanophages (**a, b**)

the size of a normal melanocyte. Nuclear enlargement is often associated with hyperchromasia [1].

The density of junctional melanocytes varies. While in early lesions solitary units of melanocytes may be separated from each other by a few keratinocytes, in more developed lesions, melanocytes form strips or files and become confluent [1, 4], i.e. form junctional aggregates without interspaced keratinocytes. A conspicuous cytoplasmic fixation retraction artifact producing a clear halo may be present. Neoplastic melanocytes commonly extend into adnexal structures [15] (Figs. 5.1, 5.2, and 5.3). Adnexal involvement is most often first seen in the infundibular portion of the follicle. However, melanocytes may extend deeper to the level of the sebaceous gland and inferior portion of the follicle [4]. This may occasionally cause challenges in assessing dermal invasion and tumor thickness. Junctional tumor growth may lead to the formation of junctional nests. Melanocytes may also be found in the spinous layer [1].

The epidermis of LM is often atrophic with flattening of the rete ridges [12, 17] (Fig. 5.3). The dermis often contains a patchy or band-like lymphocytic infiltrate with melanophages (Fig. 5.2). Some authors suggest that the presence of melanophages is a helpful clue against reactive melanocytic hyperplasia of chronically sun-damaged skin [4]. However, this does not apply when one considers a lichenoid

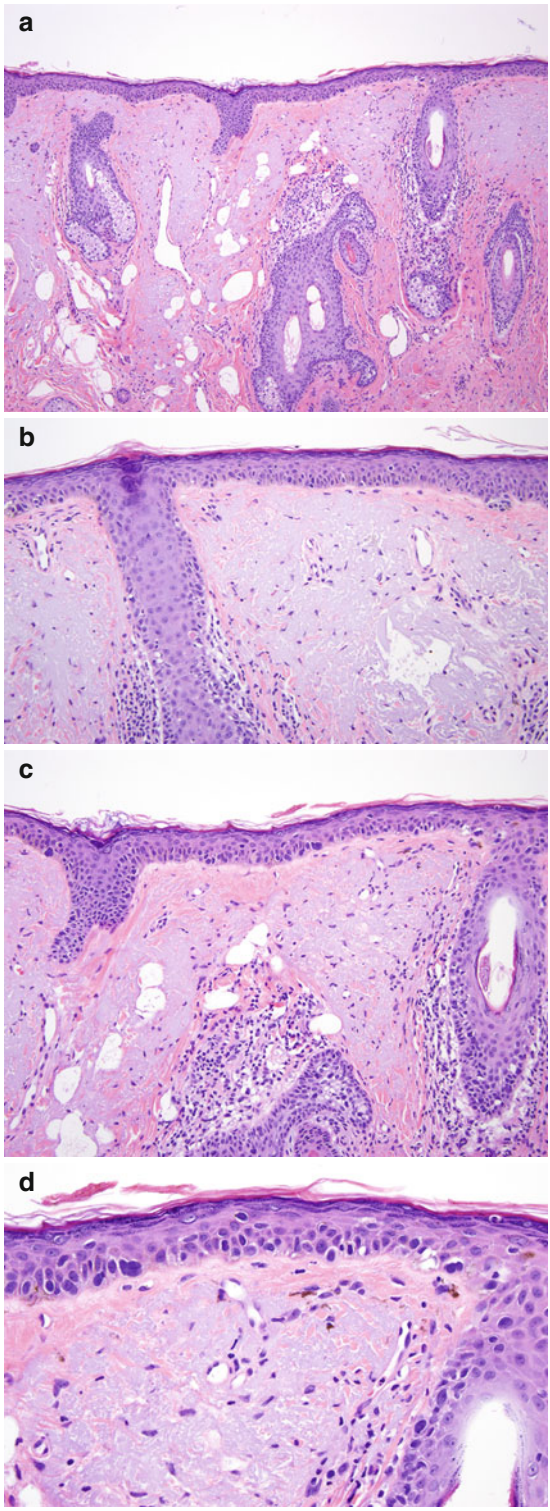

Fig. 5.3 Lentigo maligna. Severe solar elastosis with increase in mostly solitary units of melanocytes in the epidermis and adnexal epithelium (**a, c, d**), with asymmetric nests of small melanocytes (**b**), some multinucleated melanocytes (**c, d**), and pagetoid growth of single melanocytes (**c, d**)

keratosis in the differential diagnosis, since melanophages are commonly seen in this benign condition, which may also be associated with a reactive melanocyte hyperplasia.

In more developed lesions of LM, the nuclear atypia of melanocytes may become more prominent characterized by an angulated or somewhat spindled shaped nucleus [1]. The nuclear chromatin pattern is typically dark (hyperchromatic) [1]. Some of the melanocytes are multinucleated with prominent dendritic processes, a phenomenon, which has been called "starburst giant cell" [18]. The greater the number of nuclei within a multinucleated giant cell, the more likely it is associated with LM [18]. However, the starburst giant cell is not specific for LM, but can also be seen in benign melanocytic nevi, including junctional nevi [19]. Additionally, some melanocytes, possibly already in initial stages of LM, show dendritic appearance, with thick dendrites reaching the upper spinous layer [4, 11].

Associated invasive melanoma may have many different appearances from amelanotic (common) to pigmented (uncommon), epithelioid, fusiform or mixed cell type [20]. A minor degree of stromal fibrosis is often a clue to early superficial invasion. Superficial invasion is often limited to a few isolated tumor cells or small cell aggregates in the papillary dermis. If they are cytologically bland and form nests, they may be difficult to distinguish from a small nevus remnant. Subtle invasive melanoma may at times only be located around follicular structures. Invasive melanoma is readily recognizable, if the tumor cells are pleomorphic, mitotically active and form a mass. Vertical growth phase melanoma is defined as cohesive nests, nodules or plaques larger than those within the epidermis and consisting of atypical tumor cells cytologically different from those in the radial growth phase. In lentigo maligna melanoma, the vertical growth phase often shows spindle cell morphology. Invasive tumors associated with LM may or may not display stromal desmoplasia and perineural invasion [20]. If desmoplasia is prominent, the tumor is designated "desmoplastic". Up to two thirds of desmoplastic melanomas are associated with LM [21–23]. Neurotropism is rare in small superficial tumors, but not uncommon in more deeply invasive LMM [4]. While it is most often seen in association with fusiform cells, epithelioid melanoma may also be neurotropic.

Although the epidermis is typically atrophic, LM may also contain areas with elongated rather than attenuated rete ridges. This may be in some cases due to LM coinciding with a pigmented actinic keratosis, solar lentigo, or seborrheic keratosis [24]. Some authors describe these lesions as simulating a dysplastic nevus or a lentiginous nevus. Based on one study, dysplastic nevus–like areas, defined as having elongated and/or fused rete ridges and prominent medium to large nests of pleomorphic melanocytes with little or no pagetoid upward migration, predominated in as much as 43 % of LM/LMM [25]. Some authors have suggested a term lentiginous melanoma for lesions with features of LM but with preservation of rete ridges and absence of prominent solar elastosis [26]. It is important to recognize these variants, especially if examining a partial biopsy to avoid a pitfall of erroneous diagnosis of a dysplastic nevus or a lentiginous nevus.

Ancillary Diagnostic Test

Immunohistochemistry

Immunohistochemical stains for melanocyte antigens may facilitate a more accurate assessment of melanocyte density and growth pattern. This is specifically useful if a dense inflammatory infiltrate is present, pseudonests are suspected, or if a distinction between LM and reactive melanocyte hyperplasia due to chronic sun damage or prior surgery is difficult [27]. A pseudonest or a pseudomelanocytic nest is an aggregate of cells and cell fragments, including keratinocytes and inflammatory cells, and occasional melanocytes, that may mimic a melanocytic proliferation. The histologic evaluation of surgical margins, where the utility of immunohistochemical markers may be particularly useful in certain instances, is covered elsewhere in the textbook.

Melanocyte antigens include S100 (anti-S100 antibody), SOX10 (anti-SOX10 antibody), gp100 (HMB-45 antibody), Melan-A or MART1 (anti-Melan-A, anti-MART1, or A103 antibodies), microphthlamia transcription factor (MITF) (anti-MITF antibody), tyrosinase (anti-tyrosinase), and nerve growth factor receptor (NGFR) (anti-NGFR antibody) [28]. Of these, S100 protein, SOX10, and NGFR are particularly helpful for the detection of desmoplastic melanoma [29], but they are the least "specific" markers, because the respective antigen is also expressed by a number of non-melanocytic cells [28]. Caution is necessary when calibrating immunohistochemical stains. Tyrosinase and Melan-A/MART1 are sensitive markers for melanocytes, however, in many laboratories the suboptimal use of immunohistochemical markers with cytoplasmic stains may overestimate the density of melanocytes [27, 30, 31]. The use of nuclear markers (MITF or SOX10) avoids that pitfall, but comes at the expense of potential "false-positive" interpretations of non-melanocytic dermal cells, which may be positive for MITF and SOX10. Due to limited sensitivity the use of HMB-45 may result in underestimation of intraepidermal melanocyte density [32, 33].

At present, there are no markers to discriminate between benign and malignant melanocytes. Recently, some have suggested that the differential localization of soluble adenylate cyclase (sAC) in LM versus benign melanocytes may be a useful diagnostic adjunct for the diagnosis of LM [34]. However, we have not found this marker to be reliable or useful (KJB, 2015, personal observations). Normal sun-damaged melanocytes may show nuclear expression of sAC. In our experience the vast majority of cases of lentigo maligna can and should reliably be diagnosed by examining one or a few H&E-stained sections. The routine use of immunohistochemical markers is unnecessary, and may at times lead to overdiagnosis.

Immunohistochemical markers, however, may help identify a dermal invasive component, such as a subtle desmoplastic melanoma, and help distinguish invasive melanoma from a histologic simulant, such as in the scenario of LM colliding with an atypical fibroxanthoma. Immunohistochemical stains may also on occasion help

distinguish a nevus remnant from a nevoid invasive melanoma. If, for example, a nevoid dermal population is immunoreactive for BRAFV600E while the associated lentigo maligna melanoma in situ is BRAF-negative, one can reasonably conclude that the nevoid population is unrelated to the lentigo maligna and unlikely to represent an invasive LMM. While *BRAF* V600E mutations would be very unlikely in a LMM [35, 36], some tumors carry an *NRAS* mutation. An immunohistochemical stain for NRASQ61R can help document the presence of such a mutation for treatment purposes.

Molecular Tests

The diagnosis of LM/LMM is usually made by histopathologic examination. Molecular tests may be considered for rare invasive tumors with microscopically ambiguous or controversial features and/or to determine eligibility for targeted therapies for metastatic melanoma. Currently, the molecular tests used for diagnosis include cytogenetic methods, such as fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH) [37] and possibly gene expression profiling [38, 39]. Mutation analysis is indicated to guide targeted therapy of metastatic melanoma, especially to determine the presence or absence of *BRAF* (*B-Raf Proto-Oncogene, Serine/Threonine Kinase*) V600 codon mutations [40, 41]. Prognostic gene expression panels have also been proposed, but are associated with methodological shortcomings and have not yet been validated [38, 39, 42].

Differential Diagnosis

Melanocytic Hyperplasia of Sun-Damaged Skin

The number and size of melanocytes can be slightly increased in benign chronically sun-damaged skin [43]. The melanocytes should, however, be regularly distributed along the basal layer at an equal distance from one another [4] (Fig. 5.4). Extension to the infundibulum of the hair follicle may be seen, but the increase in melanocytes should not involve the inferior part of the hair follicle. Nests are not present and starburst giant cells are rare.

The average number of melanocytes of non-lesional skin from the head/neck skin is approximately 9–10 melanocytes per 0.5 mm on H&E (hematoxylin & eosin)—stained sections and 12–15 per 0.5 mm using Melan-A/MART1 immunohistochemistry [44–47]. Continuous melanocytes, atypical melanocytes, and follicular extension can occasionally be seen in the sun-damaged skin surrounding

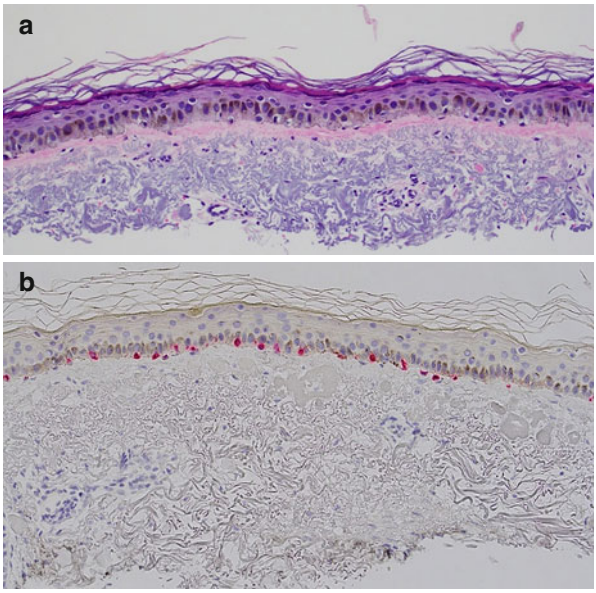

Fig. 5.4 Solar lentigo with melanocytic hyperplasia. (**a**) Basal layer hyperpigmentation with a slight increase in the density of cytologically bland melanocytes. (**b**) An immunostain for melan-A documents a slight increase in the density of junctional melanocytes

melanoma or non-melanoma skin cancer [46]. In one study, one third of the non-lesional skin specimens showed areas with moderate confluence with 3–6 adjacent melanocytes based on MART1 immunohistochemical staining [44]. Melan-A/MART1 may lead to overestimation of the density of melanocytes, especially when the immunohistochemical methods are suboptimal [33]. Nuclear staining (MITF, SOX10) allows a better distinction between a keratinocyte and a melanocyte and may therefore be the preferred method for measuring melanocyte density within the epidermis. The most helpful features suggestive of LM other than an increased number of solitary units of melanocytes include nests of melanocytes, especially unevenly placed nests, irregular distribution of melanocytes, including deep extension of melanocytes along the adnexal epithelial structures, irregular distribution of melanin pigment, presence of melanocytes above the junction, and atypical nuclei [47].

Solar Lentigo

Solar lentigo may be difficult to distinguish from early LM, especially if there is a background of solar melanocyte hyperplasia (melanocytic hyperplasia of chronically sun-damaged skin). In general, solar lentigo shows normal to only slightly increased melanocyte density. The mean melanocyte count in solar lentigines is significantly lower than in fully evolved melanoma in situ, 27 versus 112 per 1 mm,

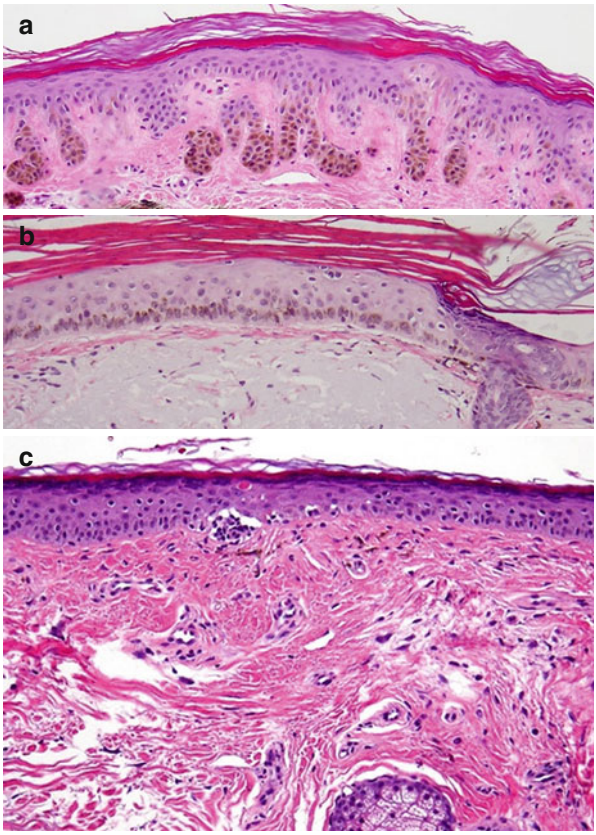

Fig. 5.5 Differential diagnosis of Lentigo maligna: (**a**) Solar lentigo, (**b**) Pigmented actinic keratosis, (**c**) Lichenoid Keratosis

respectively [33]. Additionally, confluence of melanocytes, nests of melanocytes, growth along the deeper portions of adnexal structures, and pagetoid melanocytes are absent in solar lentigines [48] (Fig. 5.5a). Melanocyte atypia can be seen if superimposed melanocytic hyperplasia of chronically sun-damaged skin is present. Rete ridges are typically normal or elongated, although focal effacement may be present. Knowledge of the clinical size and complexity of the lesion is imperative for correct pathologic diagnosis.

Pigmented Actinic Keratosis

In addition to characteristics features of actinic keratosis, including basilar keratinocytic atypia, alternating ortho- and parakeratosis, and solar elastosis, pigmented actinic keratosis shows an increased melanin pigment deposition in keratinocytes [48] (Fig. 5.5b). Sometimes melanophages are present. Notably, melanocytic

hyperplasia of sun-exposed skin may also coincide with a pigmented actinic keratosis.

Lichen Planus-Like Keratosis

Lichen planus-like keratosis or lichenoid keratosis often contains pseudonests, characterized by aggregates of keratinocytes, macrophages and lymphocytes as well as occasional melanocytes and their fragments [49]. Immunohistochemical stains may be necessary to distinguish inflammatory or mixed inflammatory and epithelial pseudo-melanocyte nests from true melanocytic nests, especially small junctional micronests (Fig. 5.5c).

Pigmented Squamous Cell Carcinoma In Situ

Clinically and at times histopathologically, pigmented squamous cell carcinoma in situ with "bowenoid" or "pagetoid" intraepidermal growth of atypical keratinocytes may be confused with melanoma in situ. If careful histopathologic examination for epithelial features (close apposition of cells, intercellular bridges, cytoplasmic granules) does not solve the diagnostic dilemma, immunohistochemical stains for epithelial and melanocyte markers should.

Junctional Melanocytic Nevus

LM with junctional nests can be easily mistaken for a junctional nevus, especially in partial biopsies or if attention is not paid to the clinical history, including the anatomic location and the patient's age. A junctional nevus, especially a dysplastic nevus, on the face of an elderly person with sun damage is unlikely, and should raise concern of LM. As the rete ridges are not necessarily attenuated in LM, elongated rete ridges do not exclude LM [25]. Clinical correlation is very helpful. A larger or new and changing lesion in an elderly individual is more likely a LM than a junctional nevus. However, one should consider a junctional nevus in a younger or middle-aged patient, especially, if the lesion has been present for some time and there are other facial nevi. Caution is necessary with small shave biopsies to avoid overcalls of melanoma: a traumatized nevus may on an initial shave biopsy display architectural disorder within the epidermis (e.g. solitary units of melanocytes in the spinous cell layer) that overlaps with melanoma in situ. If the findings are not unequivocal, it is best to acknowledge this in the report and proceed with a small incisional or excisional biopsy for definitive diagnosis instead of immediate plans for a wide excision (Fig. 5.6).

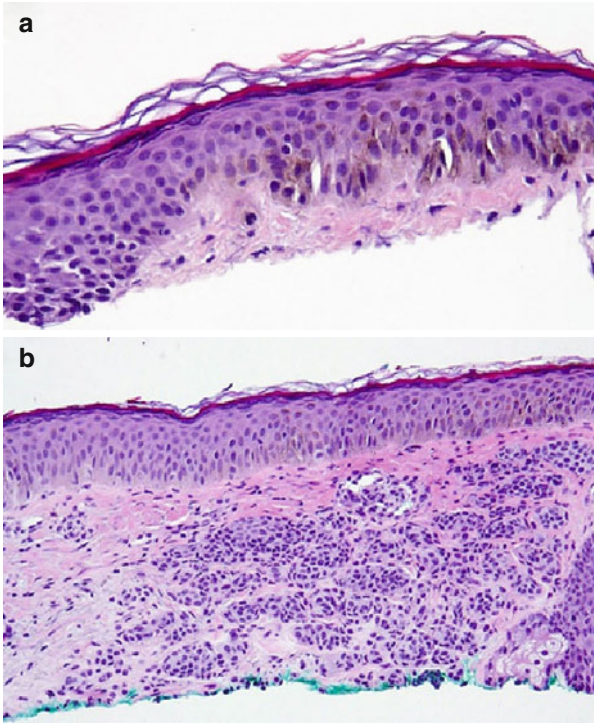

Fig. 5.6 Nevus vs. melanoma (**a**) Initial shave biopsy shows an atypical intraepidermal melanocytic proliferation; (**b**) With the benefit of an excisional biopsy, the findings on the initial shave are most in keeping with the surface of a traumatized nevus

Future Considerations

In the new era of precision medicine and targeted therapies, the traditional classification of melanoma based on clinical and histologic features is being replaced by molecular classification that also guides targeted therapy. Due to the effects of chronic UV radiation, LM/LMM is typically associated with a high mutational burden. It is interesting to note, that the most common targetable mutation in melanoma, *BRAF* V600E (*B-Raf Proto-Oncogene, Serine/Threonine Kinase*), is not typically found in melanomas occurring on chronically sun-exposed skin such as LM/LMM [35, 36]. Other mutations, such as those in *RQCD1* (*Required for Cell Differentiation1 Homolog*) gene were recently reported in LM/LMM [50]. Finally, desmoplastic melanomas, of which some are associated with LM in situ component, harbor mutations in *NF1* (*neurofibromatosis 1*) mutations [51, 52] or mutations of the NF-kB inhibitor ε pathway, including promoter mutations of *NFKBIE* (*Nuclear Factor Of Kappa Light Polypeptide Gene Enhancer In B-Cells Inhibitor, Epsilon*) [51].

Summary

- LM is characterized histologically by an increased density of solitary units of melanocytes along the dermal-epidermal junction and along the adnexal epithelium of severely sun-damaged skin with limited pagetoid growth.

- Prominent junctional nests and pagetoid growth of single melanocytes are later events typically preceding invasion into the dermis.
- Immunohistochemical stains, such as nuclear marker MITF or SOX10, may be a helpful diagnostic adjunct in evaluating the density and growth pattern of melanocytes.
- The differential diagnosis between early LM and melanocytic hyperplasia of sun-damaged skin, solar lentigo, pigmented actinic keratosis, pigmented squamous cell carcinoma in situ, junctional nevus, or lichen planus-like keratosis can be challenging.
- Melanomas occurring on chronically sun-exposed skin, including LM/LMM show a high mutational load and characteristic genomic signature different from melanomas of intermittently sun-exposed skin.

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Part III
Surgical Management

Chapter 6
Staged Excision Techniques

Kira Mayo, Timothy M. Johnson, and Kelly L. Harms

Introduction

Lentigo maligna (LM) and lentigo maligna melanoma (LMM), particularly on the head and neck, are associated with variable subclinical extension. This often makes complete excision challenging, with a potentially higher risk of local recurrence when using standard surgical excision methods with bread-loaf histologic margin control [1–7]. The goal of all excision methods is prevention of local recurrence due to residual disease at a margin. Numerous studies have demonstrated that margins of 0.5–1.0 cm may be inadequate in a number of cases for complete excision of LM and LMM primarily on the head and neck, with a reported recurrence rate of LM after standard surgical excision as high as 6–20 % [3–13]. Of note, the report of 20 % utilized 2 mm margins [7]. Standard surgical excision may be executed successfully in properly selected cases, especially off the head and neck, with low recurrence rates if performed with appropriate clinical margins in conjunction with expert dermatopathologist margin interpretation.

More comprehensive margin-controlled surgical techniques such as staged excision with paraffin-embedded permanent sections are often indicated for the treatment of LM and LMM subtypes due to the association of poorly defined clinical margins, unpredictable subclinical extension, and frequent occurrence on the head and neck where tissue sparing is desired. Staged excision most often involves the use of paraffin-embedded permanent sections rather than frozen sections for the histological evaluation of surgical margins, which remains the "gold standard" for margin assessment for melanocytic lesions [14]. Margin interpretation may occur over days between each excision and the final reconstruction, hence the terminology "staged."

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_6

Several subtle variations of staged excision techniques have been described, all aiming to optimize more comprehensive margin control prior to reconstruction, all separating the duties between surgeon and dermatopathologist. These include the "square" procedure and associated variations, the "spaghetti technique" and associated variations, slow Mohs, staged excision with radial vertical sections, and mapped serial excision techniques [4, 10–13, 15–33]. No side-by-side comparisons within a cohort between these various staged excision techniques are reported.

Prior to a staged excision technique, the majority of the clinically apparent lesion is often excised to ensure that a more extensive and deeper subclinical lesion does not exist. Microstaging in this manner optimizes the definitive treatment approach and maintains the option of consideration for sentinel lymph node biopsy if indicated. This may be particularly relevant on the head and neck with ambiguous lymphatic drainage patterns. Importantly, identification of unexpected invasive melanoma is highly variable with reports ranging from 5 to 52% [10–13, 15–17, 22–25, 27, 28]. Notably, invasive desmoplastic melanoma most commonly occurs within the LM pattern and may be clinically silent beneath a macular lesion.

General overlapping commonalities exist between most staged excision techniques. Following local anesthesia in an office-based setting, the clinical margin of the biopsy scar/tumor is outlined. In some cases a Wood's lamp may help delineate subclinical tumor; however, care to appreciate background photodamage and benign pigmented and nonpigmented lesions is necessary to prevent margin overestimation. A surgical margin, most commonly 0.5 cm (LM) or 1.0 cm (LMM) is drawn; narrower margins may be utilized for tissue sparing in critical anatomic areas. Each stage is excised to the subcutaneous tissue, deep to adnexal structures where present. Following excision, a map is drawn to maintain proper orientation of the tissue. The tissue is delivered to the histopathology lab where is it inked, often with surgeon and laboratory personnel working together to ensure proper orientation and processing. All of these techniques require a close collaborative relationship with a dermatopathologist with expertise in interpretation of melanoma. Margin interpretation results typically occur over one to several days. The process repeats itself until all peripheral margins are free at which time the final reconstruction is performed. The deep margins are assessed at variable staged excision time points depending on the technique. The depth of the final excision should always be deep to adnexa at a minimum, typically to muscle fascia at a maximum, with the definitive depth depending on the lesion diagnosis. Herein, we describe five main staged excision techniques with subtle variations of each, as well as advantages, disadvantages, and reported recurrence rates.

Staged Excision Techniques

Square Procedure and Associated Variations

Two variations of the square procedure exist: the 2-bladed square procedure and the full square procedure [18, 19]. The 2-bladed square procedure is most commonly utilized in anticipation of a definitive reconstructive sutured repair

following confirmation of disease free peripheral margins. The full square procedure is most commonly utilized in anticipation of granulation or a delayed skin graft and may also be utilized in one stage in conjunction with a straightforward layered closure.

For the 2-bladed square procedure the surgical margin is drawn with relatively straight lines and sharp-angled corners creating a geometric shape (i.e. square, rectangle, diamond, octagon, etc.) around the lesion (Figs. 6.1 and 6.2). Using a 2-bladed scalpel or a #15-blade freehand, a 2–3 mm wide strip of tissue is excised vertically (perpendicular to the skin surface) along the surgical margin, the outer incision corresponding to the surgical margin. One corner of the geometrically shaped strip is tagged with a suture for orientation. The resulting narrow "picture frame" excised portion is sutured with a running nonabsorbable suture, leaving no open wounds on the patient. The central island remains intact while the peripheral margins are assessed. The specimen is delivered to pathology, inked, pinned to polystyrene foam to prevent rolling of the edges, and fixed in formalin. The specimen is paraffin embedded and en face vertical sections containing 100 % of the peripheral margins are processed. Relatively straight lines facilitate en face tissue processing for total (100 %) peripheral margin evaluation and sharp-angled corners facilitate precise orientation. Following histologic review by the dermatopathologist, any area(s) of

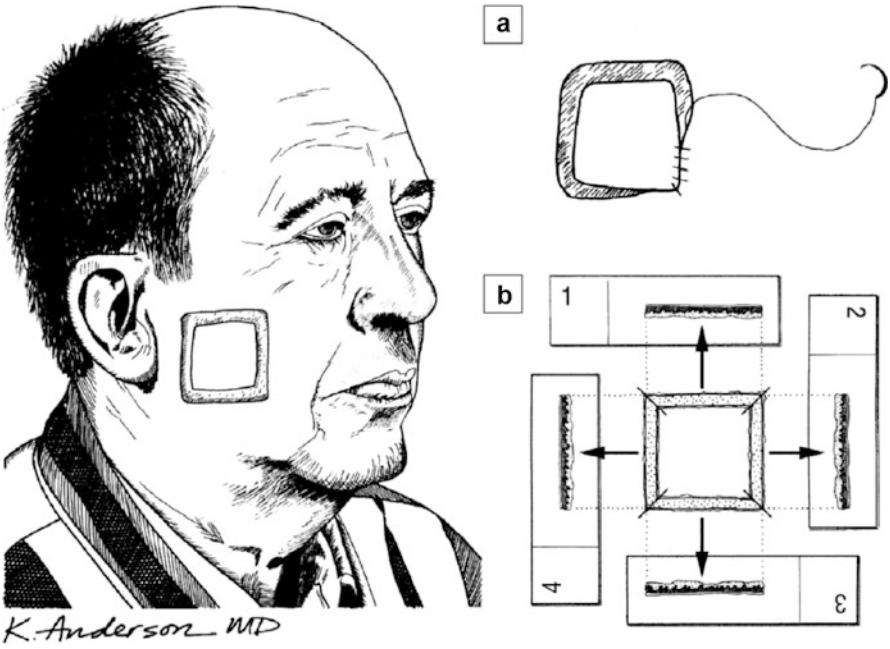

Fig. 6.1 The 2-bladed square technique, (**a**) The purpose of the initial stage(s) is to define the lesion perimeter. The peripheral wound is sutured, (**b**) Tissue is processed to examine 100 % of the peripheral margins. After the peripheral margins are clear, the central island(s) is excised and the wound is reconstructed (Reproduced with permission from Arch Facial Plast Surg. 2001. 3(3):202–6. Copyright (2001) American Medical Association. All rights reserved [19])

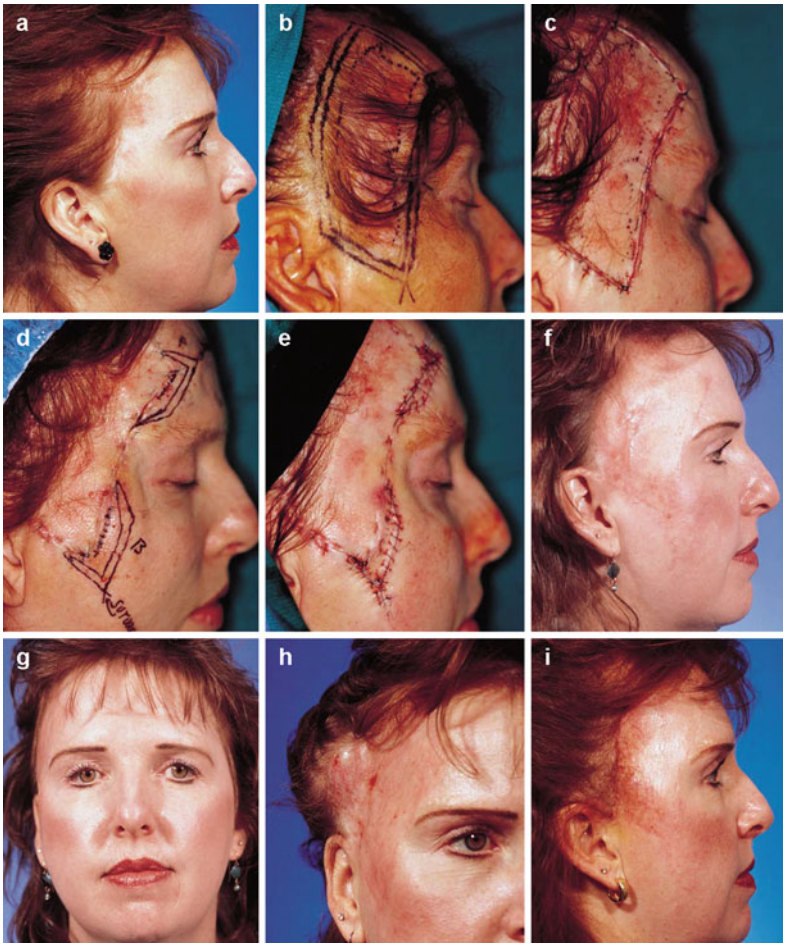

Fig. 6.2 The 2-bladed square technique, (**a**) Locally recurrent amelanotic melanoma in situ located on the scalp, forehead, temple, and cheek of a 46-year-old patient who had been treated at least 7 times over 13 years. Treatments included multiple excisions (with slight atypical junctional melanocytic hyperplasia to the margins), cryotherapy, laser, and chemical peel, (**b**) Planned square excision with 1.0- to 1.5-cm margins. The *central dotted line* outlines the *faint-pink* lesion. The peripheral 2-lined *rectangle outlines* the peripheral lines of excision. A 2-bladed scalpel with 4.0-mm spacers is used for the procedure, (**c**) The tissue containing 100 % of the peripheral margin is excised and tagged with a suture for orientation. The specimen is paraffin embedded, and routine vertical sections containing 100 % of the peripheral margins are processed. The excision strip wound is sutured, (**d**) Two areas of positivity were identified (*black dots*). A thin strip of tissue containing 100 % of the peripheral margins was excised in a geometric fashion, with 1.0-cm margins around the areas of positivity, and again sent for processing, (**e**) The peripheral strip wound has been sutured. All peripheral margins were interpreted as negative for lesional atypical junctional melanocytic hyperplasia. The central islands of tissue were excised and sent to the pathology laboratory. The defect was repaired using bilateral supraclavicular full-thickness skin grafts, (**f** and **g**) Two-month postoperative result, (**h**) A tissue expander has been placed in preparation for scalp advancement to enhance the final cosmetic result and to recreate the natural hairline, (**i**) One-week postoperative removal of tissue expander and scalp advancement. No recurrence identified after 10 years (Reproduced with permission from Arch Facial Plast Surg. 2001. 3(3):202–6. Copyright (2001) American Medical Association. All rights reserved [19])

positivity is again excised, most often with about 0.5 cm margins precisely around the area(s) of positivity with straight lines and sharp-angled corners. This process is repeated until the entire peripheral margin is interpreted as free of disease. The central island is then excised deep to and below adnexal structures and sent for serial bread-loaf sectioning to assess for any residual invasive disease and confirm free deep margins. Reconstruction is performed at the time of excision of the central island, most commonly by the dermatologic, oculoplastic or facial plastic/plastic surgeon.

For the full square procedure, the entire lesion, including the 0.5 or 1 cm margin, is excised during the first stage. Once delivered to pathology, the peripheral margins are shaved again like a picture frame. All peripheral margins are processed and evaluated in the same manner as the 2-bladed square technique, while the center of the specimen is vertically serial sectioned. This method allows the pathologist to see the lesion from the center to the trailing edge, which may facilitate interpretation of the peripheral margin and help differentiate the malignant trailing edge from benign melanocytic up regulation often seen with chronic photodamage. This method may also be utilized for microstaging if significant clinical lesion remains, or in one stage combined with layered primary closure for lesions at lower suspicion for extensive subclinical extension.

The perimeter technique is similar to the 2-bladed square procedure [17]. Polygonal perimeter excisions and geometric staged excisions are variations of the full square procedure [16, 20]. The geometric staged excision differs from the full square only by use of a unique ink color at each peripheral margin specimen epidermal edge, and use of immunohistochemistry from the reported institution [20]. The use of immunohistochemistry with Melan A increased in the reporting institution over time from initially rare to standard for every case. No confirmed benefit of routine staining with immunohistochemistry of permanent sections exists. However, the dermatopathologists in this institution noted potential utility in assessment of melanocytic density at specimen margins in some cases. The need for immunohistochemistry for staged excision is the exception, not the rule.

Spaghetti Technique and Associated Variations

The “spaghetti” technique is almost identical to the 2-bladed square procedure [24]. It differs by the use of curved lines and rounded edges instead of straight lines and sharp-angled corners. Curved lines facilitate some tissue preservation (Figs. 6.3 and 6.4) [10, 13, 24, 28, 29]. Rounded edges may result in minimal loss of precision of margin associated anatomic location. The curved tissue specimens are pliable and can be pinned straight for perimeter en face sectioning, making the potential of false positive peripheral margins due to cutting deeper into the block with rounded instead of straight edges negligible.

A 2–3 mm wide strip of tissue is excised perpendicular to the skin like the outer ring of a dartboard, with the outer edge of the strip corresponding to the surgical margin. The central island containing the tumor is left intact and the marginal strip

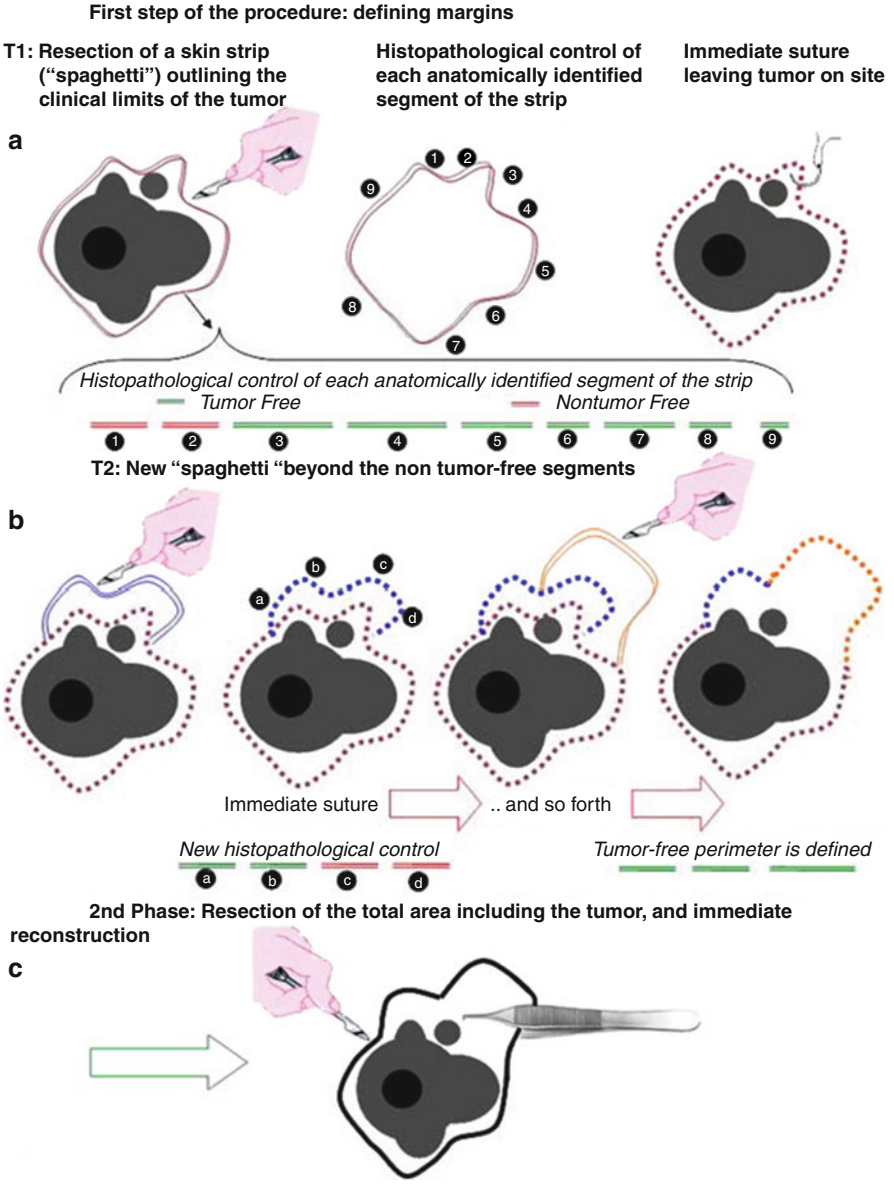

Fig. 6.3 "Spaghetti" technique, (**a**) A strip of skin along the surgical margin is resected, and is then divided into appropriately sized segments. The excised portion is sutured, leaving the central island intact, (**b**) Positive margins are identified and the process is repeated, (**c**) Once all margins are clear, the entire area, including the central island, is resected and the defect is reconstructed (Reprinted from J Am Acad Dermatol, Vol 64, Gaudy-Marqueste C, Perchenet AS, Tasei AM, Madjlessi N, Magalon G, Richard MA, et al., The "spaghetti technique": an alternative to Mohs surgery or staged surgery for problematic lentiginous melanoma (lentigo maligna and acral lentiginous melanoma). p. 113–8. Copyright 2011, with permission from Elsevier [24])

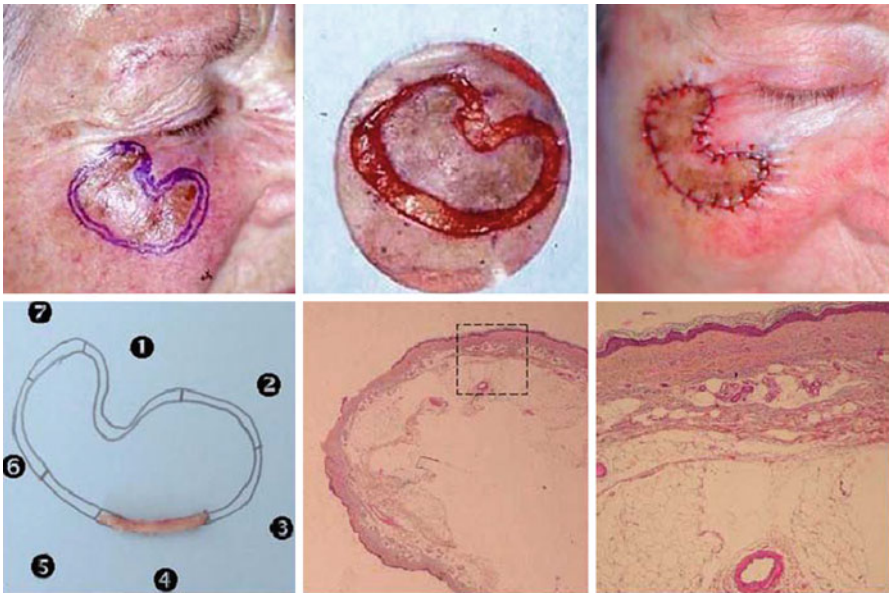

Fig. 6.4 "Spaghetti" technique. Outlining limits of a lentiginous melanoma: Resection of the spaghetti, division into anatomically defined segments, suture of the defect (*upper panel*). Macroscopic appearance of the spaghetti segment together with histologic sections (*lower panel*) (Reprinted from J Am Acad Dermatol, Vol 64, Gaudy-Marqueste C, Perchenet AS, Tasei AM, Madjlessi N, Magalon G, Richard MA, et al., The "spaghetti technique": an alternative to Mohs surgery or staged surgery for problematic lentiginous melanoma (lentigo maligna and acral lentiginous melanoma). p. 113–8. Copyright 2011, with permission from Elsevier [24])

is sutured; the patient is left with no open wounds. The excised specimen is divided into appropriately sized segments, and a map is created for precise anatomic orientation. Each tissue specimen is stretched and pinned to convert a round specimen to a straight line specimen, processed with permanent vertical sections en-face for total peripheral margin control, and examined by a dermatopathologist. If areas of positivity are noted, the patient returns for subsequent procedures until all margins are free of disease. With each procedure a 2–3 mm wide strip of skin is excised around the positive margins, typically with up to 0.5 cm margins. After all peripheral margins are free of disease; the central island(s) is excised and processed with vertical serial sections. Definitive reconstruction is performed in this final stage.

Several variations have been described including a similar technique excising the entire lesion in the first stage identical to a full square, but with curved lines and rounded edges identical to the spaghetti method (Fig. 6.5) [13]. Another described this method with use of routine S100 and Melan A immunohistochemistry stains and digital pictures to facilitate orientation in cases with multiple stages [29].

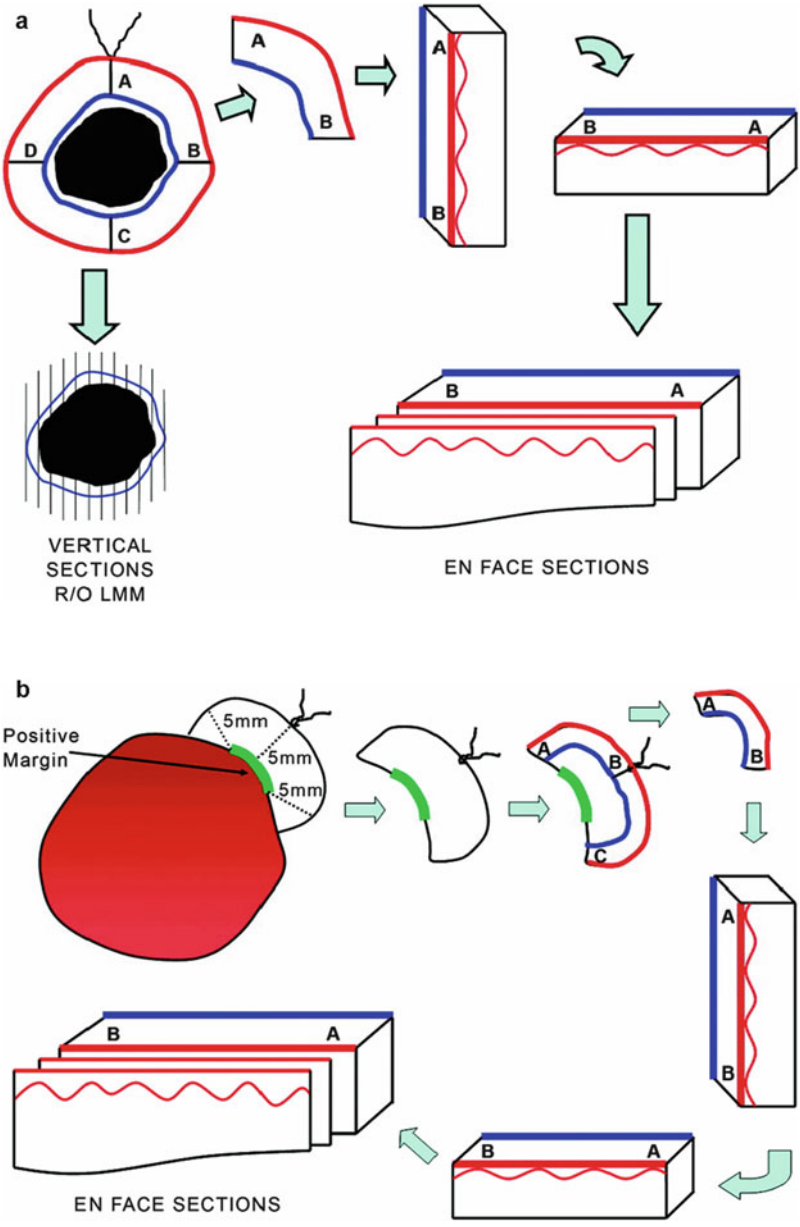

Fig. 6.5 Variation of spaghetti and full square method with first stage excision of entire lesion with *curved edges*, (**a**) Representative diagram of the first stage of the staged excision procedure. The specimen is subjected to gross examination according to protocol and the margins are evaluated by en face sectioning, (**b**) Representative diagram of the second stage (re-excision) of the staged excision procedure. An additional 5-mm margin is taken from around the positive area, and the tissue is again subjected to gross examination according to protocol and the margins are evaluated by en face sectioning (Reprinted from Bosbous MW, Dzwierzynski WW, Neuburg M. Staged excision of lentigo maligna and lentigo maligna melanoma: a 10-year experience. Plast Reconstr Surg. 2009 Dec;124(6):1947–55. Reproduced with permission from Wolters Kluwer Health [13])

Slow Mohs

A modified staged surgery "slow Mohs" technique for LM treatment was first described in 1990 [30]. The technique as originally described involves excising the biopsy scar/tumor using the standard Mohs technique with a 45-degree inward bevel. The specimen is placed in formalin, divided, inked, mapped for orientation, processed for permanent sections cut horizontally in a standard Mohs fashion, and examined by a dermatopathologist. An added level of training, understanding, and expertise by the histotechnician is necessary to process the tissue with the deep and epidermal margin in the same horizontal plane. Additional expertise in interpretation of horizontal sections by the dermatopathologist is also required. One stage is performed per day with final reconstruction of the wound following clear margins.

Several variations have been reported since slow Mohs was first described [31–33]. One technique variation begins with the standard Mohs technique using frozen sections until all margins are interpreted as free of disease by the Mohs surgeon [31]. Another standard Mohs stage with a 1–3 mm margin is then performed and sent for permanent sections per slow Mohs above. The tissue is processed horizontally with the deep and epidermal margin within the same plane per the standard Mohs technique. If positive margins are noted by the dermatopathologist, another stage is performed excising tissue from the area of positivity with tissue processed with permanent sections as above. The process is repeated until all margins are interpreted free of disease resulting in a granulating wound, which may be repaired.

Another technique variation using permanent section margin processing for histologic evaluation was described [32]. Identical to the standard Mohs technique, a 45-degree inward bevel is used to excise the scar/tumor with a surgical margin. A 3–5 mm peripheral strip of tissue is dissected from the edges of the specimen and divided according to the map and corresponding skin scores placed during standard Mohs technique. The peripheral margin specimens are inked, mapped and processed in pathology for en face horizontal sections. The peripheral margin process is similar to spaghetti method previously described but with horizontal instead of vertical sectioning. The central specimen is serial sectioned vertically. If positive margins are noted, subsequent stages are performed until margins are free, at which time reconstruction of a granulating wound can be performed. Another similar technique using total circumferential margin control with both horizontal and vertical sections was reported [33].

Staged Excision with Radial Vertical Sections and Variations

A complex staged excision technique utilizing permanent vertical sectioning was described in 2008 [10]. The clinical lesion is excised using a standard vertical incision perpendicular to the skin surface. The peripheral margin is excised and divided into four quadrants and mapping is performed with orientation to the face of a clock

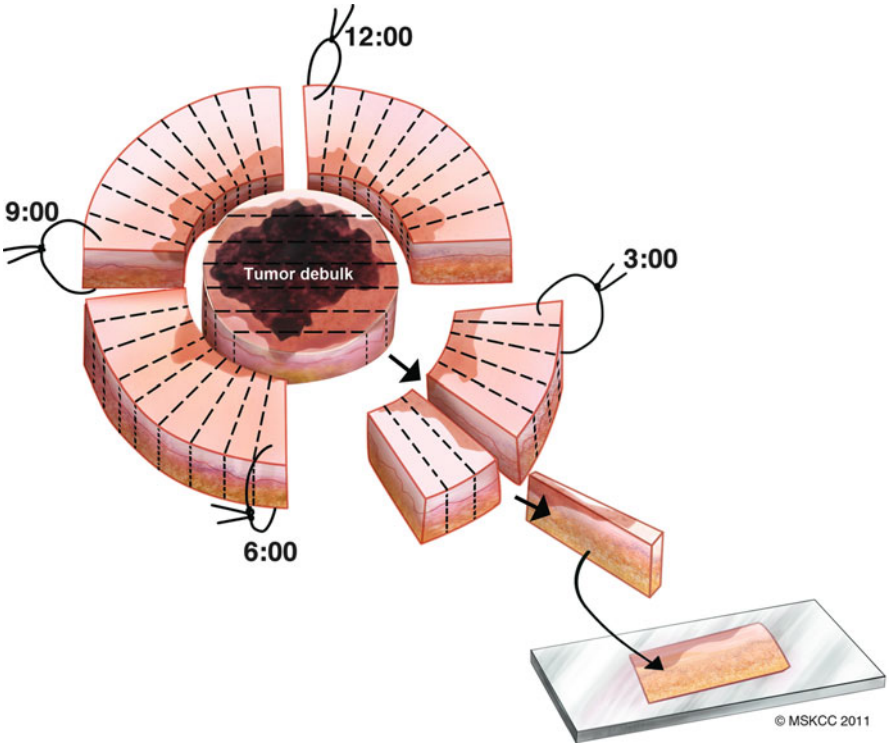

Fig. 6.6 Staged excision rush permanent section technique. Illustration shows tumor debulking and margins excised and evaluated with vertical sections with complete preservation of tissue orientation (Reprinted from McGuire LK, Disa JJ, Lee EH, Busam KJ, Nehal KS. Melanoma of the lentigo maligna subtype: diagnostic challenges and current treatment paradigms. Plast Reconstr Surg. 2012 Feb;129(2):288e–99e. Reproduced with permission from Wolters Kluwer Health [27])

(Fig. 6.6). A suture is placed at the 12, 3, 6 and 9 o'clock positions of each specimen, which is placed individually in corresponding formalin bottles. These 5 bottles are sent to pathology, along with a line drawing. The central debulk tissue is serially sectioned vertically at 2 mm intervals. The outer quadrants, the true surgical margin, are inked and vertically serially sectioned (not en face) at 2 mm intervals in a clockwise orientation. The permanent sections are evaluated by an experienced dermatopathologist. If positive margins are identified, or if tumor is noted within 2 mm of the peripheral margin in any section, a second stage with a 0.2–0.5 cm margin is obtained at 24 h. The specimen is processed as above with serial vertical sections and the process repeats until clear margins are obtained, at which point the patient returns and the granulating wound is reconstructed. A variation of this technique is reported where the central tumor is not debulked or separated from the true margin [12]. Instead, the lesion and the margin are excised en bloc, the specimen is mapped with orientation to the face of a clock. The specimen is placed in formalin and sent to pathology. The specimen is then bisected or divided into quadrants, which are then radially sectioned at 1 mm intervals [12].

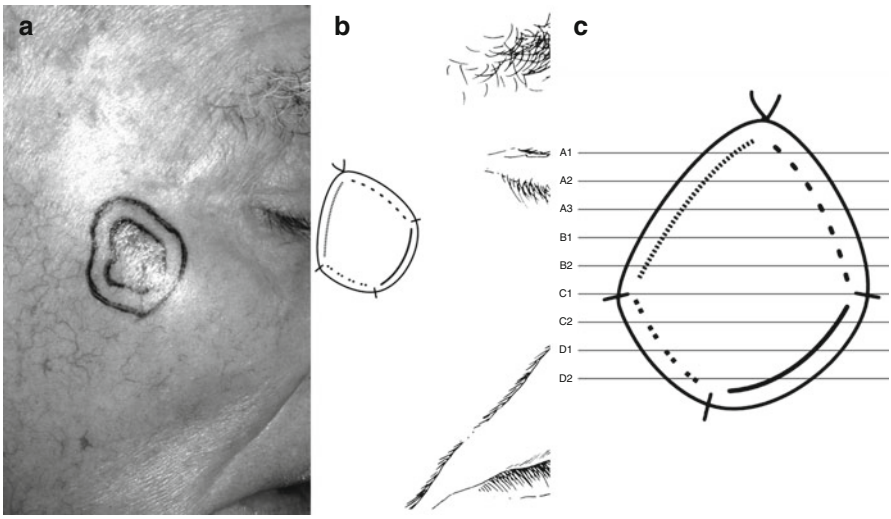

Fig. 6.7 Mapped serial excision (**a**) Lentigo maligna on the right cheek outlined with 5-mm margins, (**b**) Tissue map showing a suture at the 11-o'clock position; nicks at the 3-, 6-, 8-, and 11-o'clock positions; and *blue* (*dashes*), *red* (*solid line*), *black* (*double dots*), and *yellow* (*broken line*) dyes, (**c**) Diagram showing the number and location of tissue blocks (Reproduced with permission from Arch Dermatol. 2004. 140 (9):1087–92. Copyright (2004) American Medical Association. All rights reserved. [11])

Mapped Serial Excision

The mapped serial excision technique, first reported in 1998, simply involves more extensive serial sectioning (Fig. 6.7) [4, 11, 22, 23]. The specimen is excised in a typical fashion, tagged with a suture(s) for general orientation, mapped, inked, placed in formalin, and sent to pathology for permanent sectioning. The specimen is processed over 24 h with vertical bread loaf serial sections at 1–2 mm instead of standard 3–4 mm intervals. If positive margins are noted by the dermatopathologist, another excision typically with up to a 0.5 cm margin is performed at the area(s) of positivity with tissue processed again as above. The process continues daily until all margins are free of disease, at which time the granulating wound is repaired.

Advantages and Disadvantages of Staged Excision Techniques

The staged excision techniques with their associated variations described above are all linked by the advantage of formalin-fixed permanent section margin interpretation, which remains the "gold standard" for diagnosis and margin interpretation of melanocytic lesions [14]. All apply a more comprehensive assessment of margins compared to standard serial sectioning, without routine immunohistochemistry. Staged excision techniques are associated with relatively high local control rates (Table 6.1). Each differs with respect to nuances primarily in tissue handling and

Table 6.1 Local recurrence rates for staged excision techniques

Technique	Reference/Year	Follow-up duration: mean: months (range months) [years]	Local recurrence rate/lesions (percentage)
Square procedure and associated variations	Johnson et al. [18]	Not reported "1–3 years after first patient"	0/35 (0 %)
	Anderson et al. [19]	Not reported "less than 5 years"	1/150 (0.67 %)
	Agarwal-Antal et al. [16]	Not reported "4 years after first patient"	0/92 (0 %)
	Mahoney et al. [17]	mean: 4.7 months (range 1–13.4) [0.4 years]	0/11 (0 %)
	Jejurikar et al. [15]	mean: 31.8 months (range 16–46) [2.7 years]	0/51 (0 %)
	Demirci et al. [21]	mean: 49 months (range 9–112) [4.1 years]	1/40 (2.5 %)
	Abdelmalek et al. [20]	mean: 32.3 months (range 2–96) [2.7 years]	4/239 (1.7 %)
Spaghetti technique and associated variations	Moller et al. [28]	mean: 14 months (range 1–36) [1.2 years]	0/49 (0 %)
	Bosbous et al. [13]	mean: 27 months (range 0–122) [2.25 years]	1/59 (1.7 %)
	Gaudy-Marqueste et al. [24]	mean: 25.4 months (range 0–72) [2.1 years]	1/21 (4.7 %)
	De Vries et al. [29]	mean: 60 months (range not reported) [5 years]	4/100 (4 %)
Slow Mohs	Dahwan, et al. [30]	Single original case report [1 year]	0/1 (0 %)
	Cohen et al. [31]	mean: 57 months (range 15–106) [4.8 years]	1/45 (2.2 %)
	Clayton et al. [32]	mean: 22 months (range not reported) [1.8 years]	1/106 (0.9 %)
	Lee et al. [33]	mean: 42 months (range 12–89) [3.5 years]	3/31 (9.7 %)
Staged excision with radial vertical sections	Bub et al. [12]	mean: 57 months (range 9–139) [4.8 years]	3/62 (4.8 %)
	Connolly et al. [34]	mean: 60 months (range up to 144) [5 years]	4/100 (4 %)
Mapped serial excision	Hill et al. [23]	mean: 25 months (range 10–48) [2.1]	1/66 (1.5 %)
	Huilgol et al. 2004 [11]	mean: 38 months (range 5–100) [3.2 years]	4/161 (2.5 %)
	Walling et al. 2007 [4]	mean: 95 months (range 6–240) [7.9 years]	3/41 (7.3 %)
	Malhotra et al. 2013 [22]	mean: 32 months (range 1–100) [2.7 years]	4/141 (2.8 %)

processing. The advantage of all of these techniques is realized most for lesions characterized by unpredictable subclinical extension and locations where tissue sparing is warranted. The main disadvantage is only one stage can typically be processed per day, increasing the time and associated inconvenience for tumor removal and delay in reconstruction. Also several methods described require closure of a granulating wound. This is advantageous for a delayed skin graft to minimize contour deformities. However, excision or repair of a granulating wound with a flap or layered closure may be more difficult than a fresh wound due to fibrosis and increased vascularity noted in a granulating wound. The 2-bladed square and spaghetti techniques with their associated variations offer the advantage of reconstruction of a fresh wound rather than a granulating wound.

Conclusion

Most melanomas on the trunk and extremities can be managed effectively with standard excision and tissue processing approaches. However, LM and LMM on the head and neck in the background of chronic photodamage is more challenging to manage effectively. The histopathological differentiation between benign melanocytic up regulation due to photodamage or a benign process versus malignant trailing edge of melanoma in the background of chronic photodamage requires tremendous competence and experience. At most major melanoma centers, the dermatopathologist is often most skilled in this interpretation with the use of permanent sections. This may, or may not be the case in all programs or all private practice offices. Utilizing the strength of each multidisciplinary component optimizes the treatment approach with the ultimate goal of tumor clearance first, reconstruction second. No "best" treatment for LM/LMM currently exists due to a lack of high quality overall evidence [3]. The "best" method depends on the strengths and weaknesses of each program, team and office, whichever results in the highest cure, best outcome, and most favorable cost-effectiveness.

Success with all staged excision techniques requires a multidisciplinary team with expertise. Close communication, collaboration, clinical-pathological correlation, and consistency in histopathology interpretation are critical. The advantages of tissue sparing, local control and cure outweigh the disadvantages of time and cost in a subset of melanomas associated with subclinical extension and high local recurrence rates when utilizing standard excision approaches.

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Chapter 7
Mohs Surgery for Lentigo Maligna Melanoma

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Introduction

Optimal surgery for lentigo maligna melanoma (LMM) includes three conditions: (1) accurate staging of the primary melanoma prior to reconstruction; (2) excision with clear microscopic margins; and, (3) reconstruction in tumor-free skin. Accurate staging of the primary melanoma prior to reconstruction is important because it determines the width of conventional excision margins and indications for sentinel lymph node biopsy. Excision with clear microscopic surgical margins is essential to reduce local recurrences of LMM and additional procedures for incompletely excised tumor. Reconstruction in tumor-free skin increases the likelihood that patients will have an optimal functional and aesthetic outcome.

Multiple challenges make it difficult to meet these conditions in LMM if conventional surgery is used. This chapter will review how Mohs micrographic surgery (MMS) can address these challenges and meet the conditions for optimal surgery for LMM. MMS is defined by three essential characteristics: (1) excision of the skin cancer; (2) immediate microscopic frozen section examination of 100 % of the peripheral and deep excision margin by the Mohs surgeon; and (3) mapping of the excision specimens to maintain precise orientation relative to the patient.

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_7

History of Mohs Micrographic Surgery

The name MMS honors the late Dr. Frederic E. Mohs, a surgeon who pioneered the technique at the University of Wisconsin beginning in the 1930s [1, 2]. Initially, the technique was called "chemosurgery," because a zinc chloride paste was used to fix the skin cancer and surrounding tissue *in vivo*. By the 1970s, the fresh tissue technique with microscopic frozen sections had gained favor, because it increased the speed of the surgery and allowed same day reconstruction. Mohs surgeons now use the fresh tissue technique.

In 1997, Zitelli et al. reported 5-year rates of local recurrence, metastases, and survival of 553 melanoma patients treated with the fresh-tissue technique and hematoxylin and eosin stains. Defined as tumor in or adjacent to the scar of the procedure, local recurrence occurred in only 0.5 % of *in situ* (1/184) and invasive (2/369) melanomas. Compared to historical controls treated with conventional excision, rates of metastasis and survival were equal or better for tumors of all thicknesses [3].

Despite these favorable results, interpretation of hematoxylin and eosin-stained frozen sections remained controversial for reliable evaluation of melanoma. Whereas some authors have claimed that interpretation is unreliable [4–6], others have shown that interpretation of high quality hematoxylin and eosin frozen sections can be reliable [7, 8]. It is fair to conclude that interpretation of melanoma margins on hematoxylin and eosin-stained frozen sections is challenging, especially when a dense inflammatory infiltrate is present, when the melanocyte density is low, and when the melanoma arises heavily sun-damaged skin with keratinocytic atypia.

The reliability of frozen section pathology for melanoma margins has increased with the addition of frozen section immunohistochemistry. In 1998, Griego and Zitelli first reported successful treatment of a multiply recurrent acral melanoma using MMS with frozen section HMB-45 immunohistochemical stains [9]. Subsequent case series comparing different immunostains for MMS of melanomas demonstrated MART-1 staining to be superior to HMB-45 and S100 [10–13]. After the introduction of rapid frozen section immunohistochemical stains, MMS for melanoma was more accessible and reliable. Between 2003 and 2008, utilization of MMS for invasive melanoma and melanoma in situ increased by 60 % [14]. Of all melanomas captured by the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, 3.5 % (6872) were excised by MMS between 2003 and 2008 [14]. Numerous investigators have reported high local cure rates for melanoma treated by MMS supplemented by frozen section immunostains [15–19].

The Process of Mohs Micrographic Surgery for Melanoma

MMS allows immediate microscopic examination of the entire surgical margin with frozen sections, and pathology is interpreted by the Mohs surgeon, rather than a separate pathologist. The visible tumor is excised with a margin of clinically normal skin. Hash marks are made on the skin surface to maintain orientation relative to the

patient. The surgeon grossly sections the excision specimen into pieces that will fit on a microscopic slide. The free cut edges of all grossly sectioned specimens are inked, and a surgical map is drawn to represent the method of gross sectioning and inking. The tissue is frozen, rather than formalin-fixed, and microscopic frozen sections are cut from 100 % of the complete peripheral and deep margins.

For melanoma, the tissue sections are stained with both hematoxylin and eosin and a melanocytic immunohistochemical stain, such as MART-1 or MITF. The Mohs surgeon evaluates the pathology. If tumor is detected at the margin, the Mohs surgeon indicates the precise location of residual cancer on the specimen map. Targeted excision, or a second "stage," is performed around the residual tumor. Again, the free cut edges of the specimen are inked, a map of the specimen is created, and the frozen sections of the entire peripheral and deep margin of the specimen are examined by the Mohs surgeon. The process continues until clear margins are achieved. The average turnaround time for each stage is 1–2 h. Reconstruction is performed only after confirming clear margin status.

Tumor Debulking for Melanoma Pathologic Staging

An excisional biopsy with a rim of normal tissue is the ideal method to biopsy a lesion suspicious for melanoma but this method is impractical if the lesion is large or located in a cosmetically or functionally sensitive location. Thus residual melanoma is frequently present in the initial Mohs excision specimen as the diagnostic biopsy may not remove the entire tumor with a margin of normal skin as commonly occurs in large facial LMM. Microscopic examination of the residual melanoma may reveal a more advanced tumor stage in 5–22 % of cases [10, 17, 20–26]. Accurate melanoma staging is necessary to counsel patients about prognosis, direct staging workup, determine surveillance intervals, and determine adjuvant treatment if necessary. Therefore the central tumor debulking excision should never be discarded during Mohs surgery. It is appropriate and necessary to send melanoma debulking specimens for formalin-fixed paraffin embedded sections [20].

Immunohistochemical Stains for Melanoma

Melanocytic immunohistochemical stains have greatly improved MMS for melanoma. While accurate interpretation of hematoxylin and eosin frozen sections of melanoma may be possible [7], accurate interpretation of single atypical melanocytes on hematoxylin and eosin-stained frozen sections is challenging [5]. MMS *without* immunohistochemical stains carries approximately a 5 % risk of leaving behind melanoma [27], compared to less than a 1 % risk after MMS *with* immunostains [16, 17]. Frozen sections with immunohistochemical stains are more reliable to identify melanocytes and interpret melanoma margins [13].

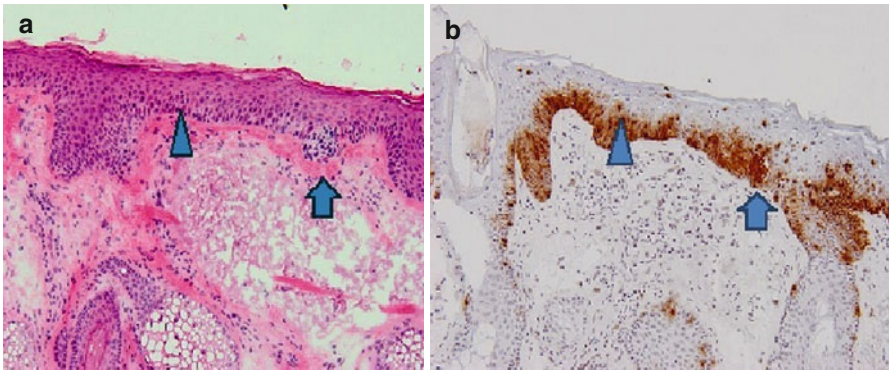

Fig. 7.1 Immunohistochemical stains for melanocytes during Mohs surgery. (**a**) Hematoxylin and eosin-stained frozen section of melanoma in situ (magnification, 20×) with a large nest of melanocytes (*blue arrow*). The hyperchromatic *dark blue* nuclei of pagetoid melanocytes (*blue triangle*) are challenging to discern. (**b**) MART-1 frozen section immunostain of the same specimen (magnification, 20×). The nest of melanocytes is clearly visible (*blue arrow*) as well as many more pagetoid melanocytes (*blue triangle*)

MART-1 is the preferred immunohistochemical stain to identify melanocytes at the frozen section melanoma margins, due to its high sensitivity (Fig. 7.1) [11]. MART-1 immunohistochemistry is reliable and accurate in frozen sections as in formalin-fixed paraffin-embedded sections [12, 13]. Melanoma cohorts treated with MMS supplemented with MART-1 immunostains have low local recurrence rates [16, 17]. High quality MART-1 frozen sections can be produced in one hour or less [28, 29].

MART-1 staining has some disadvantages. Prominent staining of the cytoplasm in the dendrites of melanocytes may lead to false positive interpretation of MART-1 immunostains, and some authors prefer the crisp nuclear staining pattern with microphthalmia transcription factor (MITF) [30, 31]. MART-1 does not stain pure desmoplastic melanoma, therefore supplemental staining with S-100 or SOX-10 may be necessary [32]. Even after interpretation of margins with high quality immunostains, evaluation of hematoxylin and eosin stains is still necessary to assess keratinocyte atypia, assess cytology of melanocytes, identify desmoplastic melanoma, and evaluate incidental lesions, such as nevi and keratinocytic cancers.

Highly Skilled Mohs Lab Necessary for Melanoma

In the year 2000, only 12 % (13/108) of laboratories run by members of the American College of Mohs Surgery reported the use of frozen section immunostains, possibly due to cost, added time, and lack of training [33]. The current percentage of Mohs laboratories using immunohistochemistry is uncertain. Production and interpretation of high quality melanocytic immunostains requires expertise from both the

histotechnologist and the Mohs surgeon. In order to produce 2–4 μm thick tissue sections without artifact or distortion, histotechnicians require excellent training, abundant experience, and high quality equipment [28]. Mohs surgeons must gain adequate training to interpret the margins of melanoma. The Mohs laboratory must have careful protocols in place for quality control, and the Mohs surgeon must be prepared to invest the time and resources necessary to treat melanoma patients.

Local Recurrence After Mohs Surgery

MMS allows for clear microscopic margins with 100 % microscopic evaluation of the peripheral and deep margin, allowing for immediate detection and removal of microscopic melanoma that is not clinically visible. Evidence also demonstrates that partial margin assessment with conventional breadloafed pathology sections

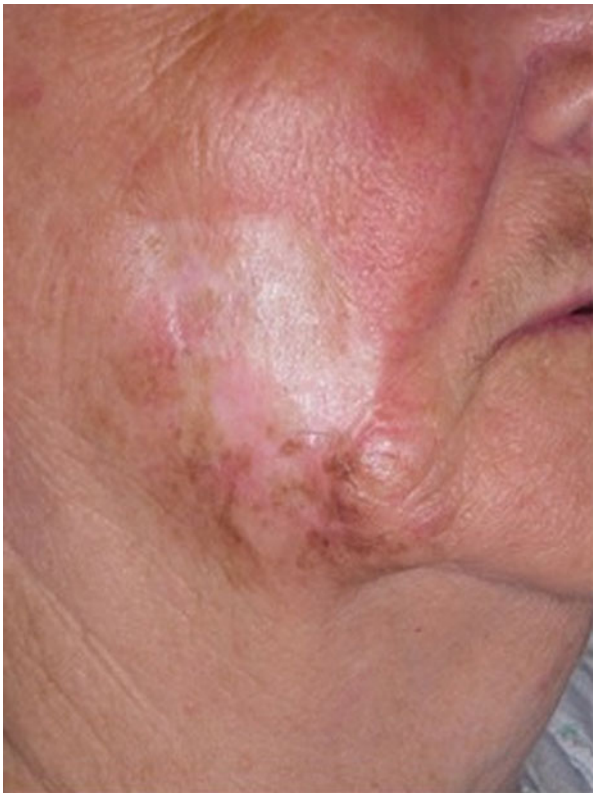

Fig. 7.2 Local recurrence after incomplete excision. Patient with local recurrence of melanoma after conventional wide local excision with purportedly "clear" microscopic margins and repair with a full-thickness skin graft; melanoma recurred along the margins of the graft

Table 7.1 Melanoma local recurrence rates after Mohs surgery

Mohs without immunostains		
Reference	Local recurrence rate (%)	Followup mean months {Range}
Walling et al. [34]	33 (6/18)	117.5 {61–157}
Hou et al. [35]	1.9 (3/154)	94.8
Zitelli et al. [3]	0.5 (3/553)	60
Bienert et al. [8]	0 (0/92)	33 {8–72}
Temple and Arlette [36]	0 (0/202)	29.8 {0.25–114.6}
Mohs with immunostains		
Newman et al. [18]	1.1 (5/460)	34
Bhardwaj et al. [19]	0.5 (1/200)	38.4 {6–58}
Bricca et al. [15]	0.3 (1/331)	58 {0–238.8}
Kunishige et al. [16]	0.3 (3/1120)	56.4 {0.24–282}
Etzkorn et al. [17]	0.3 (2/597)	33.6
Zalla et al. [10]	0 (0/68)	16 {1–32}

increases the risk for false negative margins and local recurrence (Fig. 7.2). By examining the entire surgical margin under the microscope, MMS eliminates the potential for sampling error and decreases local recurrence rates. The low local recurrence rates support the effectiveness of MMS supplemented by immunostains to achieve clear microscopic margins [3, 8, 15–19, 34–36]. However, interpretation of these studies must be taken in context of the variable follow up times and heterogeneous cohorts (Table 7.1).

Indications for MMS

LMM with subclinical spread benefits from MMS to detect and remove microscopic tumor not visible by clinical examination. Melanomas that require reconstruction with a flap or a graft also benefit from MMS or other margin-controlled techniques to confirm clear microscopic margins prior to reconstruction. A consensus panel representing the American Academy of Dermatology, the American College of Mohs Surgery, the American Society for Dermatologic Surgery, and the American Society for Mohs Surgery deemed MMS to be appropriate for the following clinical scenarios: (1) primary lentigo maligna (LM) and MIS, non-LM type, located on the head and neck, acral sites, genitalia, and pretibial leg; (2) locally recurrent LM and MIS, non-LM type, in any anatomic location [37] (Table 7.2). Although consensus guidelines do not yet include invasive melanoma, the likelihood for subclinical spread and reconstruction with a flap or graft does not differ between melanoma in situ and invasive melanoma. Compared to melanomas on the trunk and proximal extremities, melanomas located on the head and neck, genitalia and distal extremities are nearly twice as likely to have subclinical spread and 10 times more likely to require reconstruction with a flap or a graft. Compared to primary melanomas, locally recurrent melanomas are nearly twice as likely to have subclinical spread or to require reconstruction with a flap or graft [38].

Table 7.2 Indications for Mohs micrographic surgery of melanoma

Tumor location on head and neck, distal extremities, or anogenital area
Clinical margins are indistinct as tumor arises in aged or heavily sun-damaged skin
Large tumor size
Requirement for reconstruction with a tissue-rearranging flap or large graft
Tumor has recurred after previous treatment with either excision or destruction

Table 7.3 Comparison of melanoma excision and specimen processing and margin evaluation techniques

	Conventional wide local excision	Staged excision variations with paraffin sections	Mohs micrographic surgery
Who excises the tumor?	Surgeon	Surgeon	Mohs surgeon
Who examines the margin under the microscope?	Dermatopathologist	Dermatopathologist	Mohs surgeon
How is tissue processed?	Formalin-fixed paraffin-embedded sections	Formalin-fixed paraffin-embedded sections	Frozen tissue sections
Typical delay between excision and microscopic margin evaluation	2–5 days	1–3 days	1–2 h
Percentage of surgical margin examined under the microscopic	<1 % (insert reference)	Up to 100 %, depending on method	100 %
Ability to perform same day microscopic margin assessment and reconstruction	No	No	Yes

Advantages of Mohs Surgery

Optimal surgery for melanoma includes three conditions: (1) accurate staging of the primary melanoma prior to reconstruction; (2) excision with clear microscopic surgical margins; and, (3) reconstruction in tumor-free skin. Conventional wide excisional surgery with breadloaf sectioning is not able to meet these conditions for certain melanoma subtypes, especially LMM on the face. To appreciate the relative advantages of MMS for melanoma, one must first understand the different methods of specimen processing and margin evaluation. Table 7.3 summarizes key differences between conventional wide local excision, staged excision techniques with formalin-fixed paraffin-embedded sections, and MMS.

Detecting Melanoma Upstaging Prior to Reconstruction

Since complete sampling of many LMM is not always practical prior to MMS, the Mohs surgeon may detect upstaging of melanoma prior to reconstruction. MMS combines breadloaf sectioning of the tumor debulking with excision and complete

microscopic margin evaluation and mapping [17]. If a patient subsequently upstages to candidacy for sentinel lymph node biopsy (SLNB), the Mohs surgeon may delay reconstruction to maximize the likelihood of an accurate SLNB as shown in Fig. 7.3.

Breslow depth of melanoma may be measured using frozen section examination [39]. In a cohort of 614 patients treated with MMS that combined breadloaf frozen sectioning of the central debulking excision with complete peripheral and deep microscopic margin evaluation, 1.3 % (8/614) of the melanomas upstaged to can-

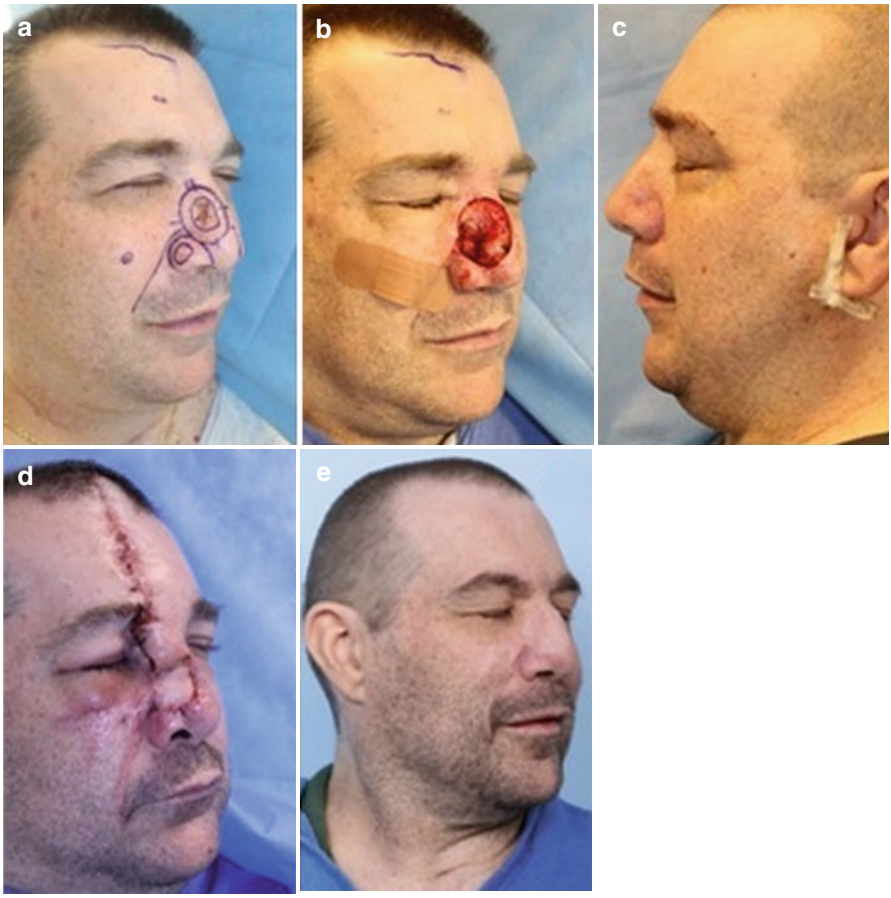

Fig. 7.3 Melanoma upstaging and sentinel lymph node biopsy prior to reconstruction. (**a**) 49 year old male with melanoma (partial biopsy showed melanoma 0.22 mm, no mitoses, no ulceration) of the right nasal sidewall. The *outer circle* on the nasal sidewall shows the 7 mm margin excised with the first stage of Mohs surgery (Biopsies marked of an incidental squamous cell carcinoma in situ of the right ala and a melanoma in situ of the right premaxillary cheek). (**b**) Defect after obtaining clear margins with Mohs surgery. Frozen section breadloaf sections of the debulking excision revealed melanoma invasive to a depth of 0.95 mm. Reconstruction was delayed for sentinel lymph node biopsy. (**c**) Bandage on preauricular cheek covers incision from sentinel lymph node biopsy. Two lymph nodes from the left parotid gland showed no evidence of metastasis. (**d**) After sentinel lymph node biopsy, patient returned for reconstruction under local anesthesia with a paramedian forehead flap. (**e**) Normal appearance was restored

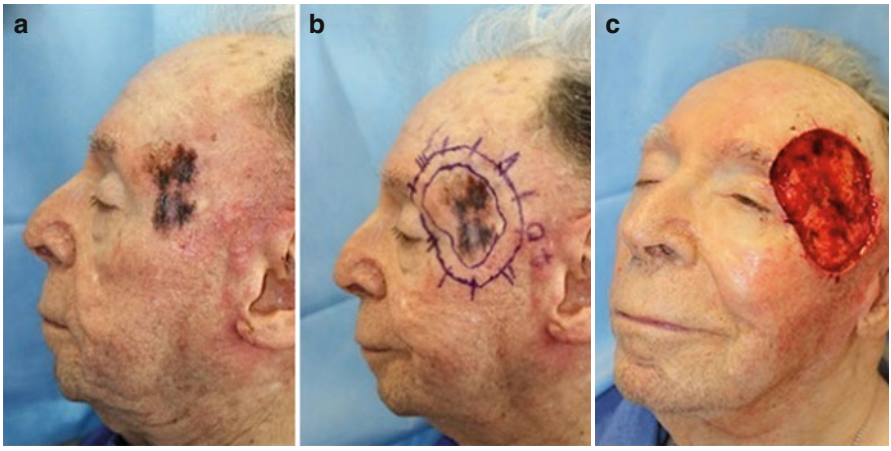

Fig. 7.4 Partially biopsied melanoma with unsuspected invasion and melanoma upstaging. (**a**) Partially biopsied melanoma (Breslow depth 0.65 mm, 2 mitosec/mm^2, no ulceration); patient declined sentinel lymph node biopsy. (**b**) Mohs micrographic surgery with 1 cm margin cleared margins. Tumor debulking revealed focal unsuspected invasion to a Breslow depth of 2.3 mm; upstaged from stage IB to IIA (T3aN0M0). (**c**) Sentinel lymph node biopsy offered prior to reconstruction of defect

didacy for SLNB after evaluation of the breadloafed debulking specimen [17]. In 7 of 8 of these cases, a discussion about SLNB ensued prior to reconstruction, and the patient elected to delay reconstruction and undergo SLNB in three cases. While the role of SLNB for melanoma remains controversial, especially after an excision, it is recommended for staging of patients with melanomas of T1b or greater [40] as illustrated in Fig. 7.4. Although further study is needed, SLNB is considered more accurate prior to tissue rearrangement from reconstructive surgery.

Mohs Excision with Clear Histologic Margins Prior to Reconstrution

Just as partial biopsies of melanoma may yield unreliable tumor staging, partial sampling of surgical margins may result in false negative microscopic margins [41]. The method of tissue processing determines the amount of the surgical margin available for microscopic assessment [42]. Breadloaf sectioning, which remains the most common method to process tissue after conventional excision of melanoma, typically examines <1 % of the microscopic surgical margin. The risk for false negative margins increases as the number of breadloaf sections decreases [43]. Local recurrence rates remain high for subsets of melanoma such as LMM, even after excision with purportedly clear margins. For example, approximately 10 % (range 2.8–28 %) of melanomas on the head and neck recur locally after conventional excision of melanomas on the head and neck [17]. Figure 7.5 illustrates a LMM with indistinct clinical margins with persistent melanoma at surgical margins after 7 prior conventional excisions.

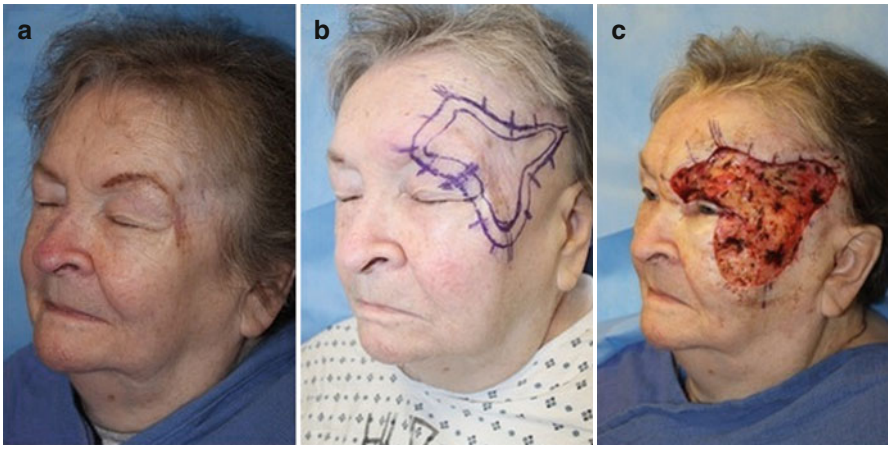

Fig. 7.5 Melanoma with histologically positive margins after conventional excisions. (**a**) Patient with melanoma in situ of left lateral canthus and brow with positive surgical margins despite 7 prior conventional wide local excisions over 2 years. (**b**) Concentric outlines represent clinically visible tumor and surgical margin for the first stage of Mohs micrographic surgery. Microscopic examination revealed melanoma in situ present in the entire outlined area. Additional Mohs stages necessary to remove subclinical melanoma extending along medial brow and zygoma; final surgical defect larger than initially excision margin

Immediate Reconstruction After Clear Mohs Histologic Margins

MMS provides real-time evaluation of the entire surgical margin and allows immediate reconstruction in a tumor-free field. Reconstruction is done only after confirming clear microscopic margins. Approximately 50% of patients undergoing Mohs surgery for facial melanoma require reconstruction with a flap or a graft [38]. Especially when complex reconstruction is required, patients benefit from the convenience of same day excision, margin assessment, and reconstruction (Fig. 7.6).

Mohs Surgery for Lentigo Maligna Melanoma: Controversies

Some have also argued that melanocytes are not readily visible on frozen sections. However, the advent of frozen section melanocytic immunostains has made this criticism less valid. Whereas accurate interpretation of hematoxylin and eosin stained melanoma frozen sections is controversial [4–8], Mohs surgery experts argue interpretation of MART-1 immunostains of melanoma is accurate and equally effective as formalin-fixed paraffin embedded immunostains. Interpretation of MART-1 staining was shown to be equally accurate on frozen and permanent sections [12, 13]. Low local recurrence rates after MMS with MART-1 frozen sections

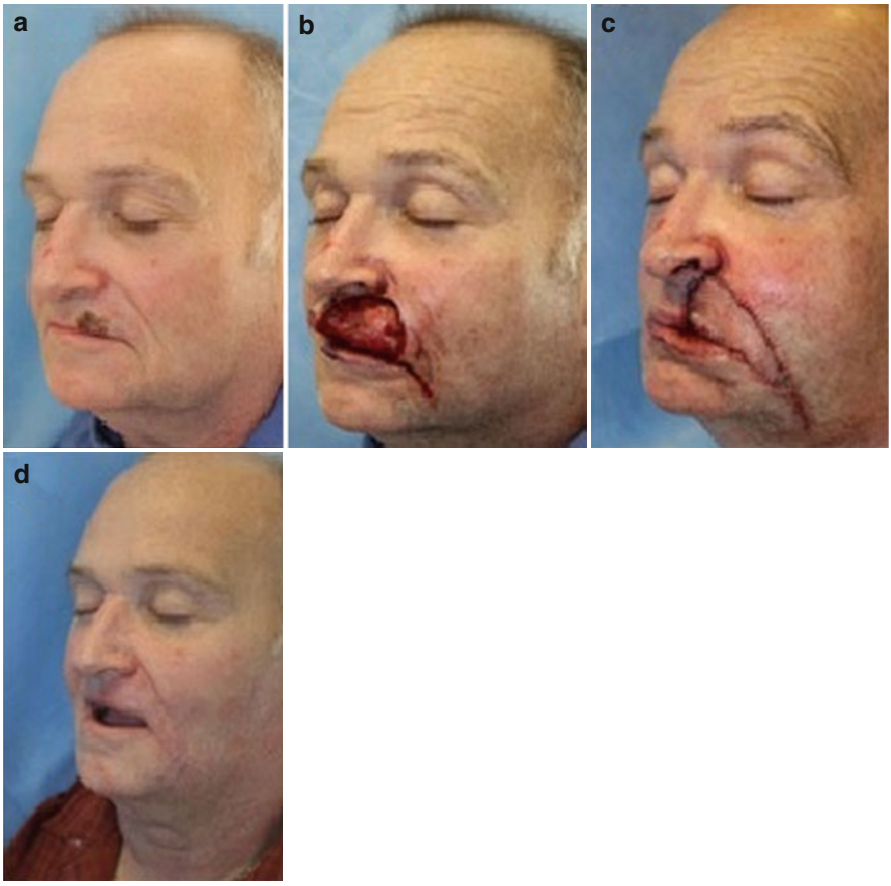

Fig. 7.6 Mohs micrographic surgery allows same day reconstruction in a tumor-free field. (**a**) Patient with a melanoma in situ of the left upper lip. (**b**) Surgical defect with clear margins following Mohs surgery. (**c**) Immediate reconstruction with a V-Y advancement flap under local anesthesia. (**d**) Normal appearance and function of lip and mouth restored

support that melanoma can be interpreted accurately on frozen sections in those with proper training and extensive experience [15–17].

Importance of Establishing a Standard Definition for a "Positive Margin" of Melanoma

Interpretation of melanoma margins is challenging, because there is no consensus on the criteria for a positive margin. When analyzing margins for lentigo maligna and lentigo maligna melanoma, expert pathologists agree whether the margin is positive or negative only approximately 50 % of the time [44]. Since many melanomas, especially those on the head and neck, present in sun-damaged skin that makes

margin interpretation difficult, the Mohs surgeon must have a deep understanding of melanocyte distribution patterns in sun-damaged skin.

In 2006, Hendi et al. published a study to explore the characteristics of normal melanocytes stained by MART-1 in long-standing sun-exposed skin [45]. One-hundred and forty nine patients undergoing Mohs surgery for basal and squamous cell carcinomas of the face and neck were randomly selected as subjects in the study. The group measured the mean number of melanocytes per high power field and confluence of adjacent melanocytes to determine the level of normal melanocyte hyperplasia in sun-exposed skin. They reported an average of 15–20 melanocytes per high-power field in sun-exposed skin. Confluence of up to 9 adjacent melanocytes and extension along hair follicles are also normal in sun-exposed skin. Nesting and pagetoid spread were not observed in normal sun-exposed skin.

Barlow et al. also published a study to clarify the density and distribution patterns of melanocytes adjacent to skin cancers [46]. One hundred and eighty patients were enrolled, with nearly 59 % of cancers being located on the face and neck. They report an overall melanocyte density of 7.97 melanocytes per millimeter of epidermis with a broad variation between individual cases. Findings of melanocytic hyperplasia and contiguous melanocytes can be normal in skin bordering melanomatous and non-melanomatous skin cancers. Therefore, findings of increased melanocyte density, moderate confluence, and presence of melanocytes along follicular epithelium are not enough to make the diagnosis of melanoma in sun-exposed skin.

Features for a positive margin include nesting of ≥3 melanocytes, confluence of ≥10 melanocytes in direct contact with the basement membrane, pagetoid spread of melanocytes at or above the level of the mid epidermis in the presence of increased melanocyte density, confluent extension of melanocytes deep to the follicular infundibulum, and severe melanocytic atypia, defined by large atypical nuclei and/or significant pleomorphism.

Challenges for Widespread Use of Mohs Surgery for Melanoma

Although MMS with immunostains has resulted in low rates of local recurrence for melanomas treated at numerous centers [3, 15, 17–19, 47], the technique is not widely available. Further utilization will require standardization of competency training for histotechnologists and Mohs surgeons, development of metrics for high quality histopathology, reduction in variations of the technique, and monitoring of results. To ensure responsible use of healthcare resources, guidelines for appropriate use of MMS for melanoma must be developed. The dermatology community must integrate with melanoma specialists from other disciplines and educate the medical community about the role of MMS for melanoma. Lack of standardization and non-adherence to guidelines may result in unnecessary variation and suboptimal outcomes for melanoma patients [48].

Conclusion

MMS allows surgeons to meet the three conditions for optimal local surgery of challenging large melanomas with indistinct clinical margins especially in the head and neck region. The specialized technique allows accurate staging of the primary melanoma prior to reconstruction; maximizes the likelihood of excision with clear microscopic margins; and allows immediate reconstruction in tumor-free skin. The advent of frozen section immunostains has greatly improved interpretation of frozen section melanoma margins.

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Chapter 8
Histologic Processing and Evaluation of Surgical Excision Specimens

Cerrene N. Giordano, Karen L. Connolly, Klaus J. Busam, and Kishwer S. Nehal

Introduction

Lentigo maligna (LM) is a subtype of melanoma in situ, defined by a predominant lentiginous growth pattern of melanocytes as solitary units at the dermoepidermal junction, typically occurring on chronically sun-damaged skin. If an invasive component is present, the terminology lentigo maligna melanoma (LMM) is used. These tumors commonly present with ill-defined borders and the potential for significant subclinical extension, thereby complicating treatment. This is particularly cumbersome in anatomically sensitive regions such as the head and neck where maximum tissue preservation is desired. Multiple treatment modalities have been described [1–7], however, surgical excision remains the standard of care, with lower local recurrence rates, the ability to detect unsuspected invasion, and achieve clear histologic margins [8, 9].

Unique to this subtype of melanoma, excision with standard surgical margins (5 mm for LM and 10 mm for thin LMM) has proven ineffective, with less than 50 % of cases achieving adequate clearance using these guidelines [5, 8–17]. Additionally, the total margin size appears to correlate with the initial lesion diameter, with lesions larger than 2 cm requiring larger surgical margins to achieve clearance compared to their smaller counterparts [8]. Margin-controlled surgical techniques, such as staged excision with rush paraffin-embedded permanent sections or Mohs micrographic surgery (MMS), have largely replaced standard margin excision as the new standard of care, achieving low recurrence rates of 0.5–5 % [13,

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_8

14, 16, 18–22] compared to the traditional excision method with local recurrence rates of 8–20 % [3, 5, 23]. Each margin-controlled method displays a slight variation in surgical technique and histologic processing, yet maintains the ultimate goal of clear peripheral and deep margin verification prior to reconstruction to minimize persistent or recurrent disease.

Histologic evaluation of margins following surgical extirpation of LM/LMM can be challenging and requires consideration of several key points. This chapter will address breadloaf versus en face versus radial specimen sectioning, advantages and disadvantages of frozen versus permanent sections, and the role of immunohistochemical staining. In addition, issues of an acceptable histopathologic margin of clearance and pitfalls of follicular involvement and skip areas will be reviewed. Various controversies unique to the surgical clearance of LM will also be addressed.

Standard Breadloaf

Technique

Most conventional melanoma excisions on the trunk and extremities utilize the "breadloaf" histologic technique for tissue processing (Fig. 8.1a) [24, 25]. In general, the lesion of concern is excised with standard margins in an elliptical fashion,

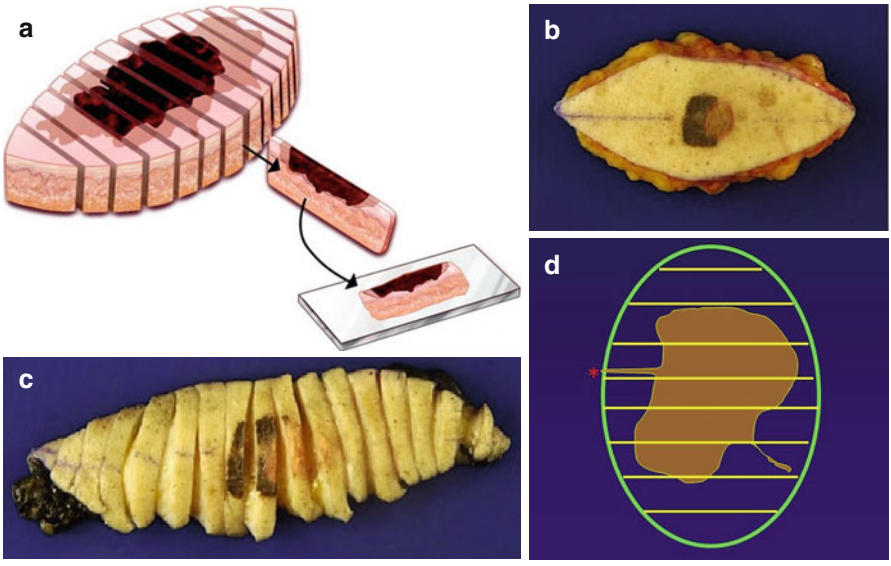


Fig. 8.1 Breadloaf technique. (**a**) Standard excision processed with breadloaf technique (Image ©2016, Memorial Sloan Kettering Cancer Center. Used with permission). (**b**) Melanoma excised with standard margin as an ellipse. (**c**) Melanoma specimen processed with breadloaf technique. (**d**) Sampling error: *red asterisk* shows missed tumor at peripheral margin with breadloaf technique (Image by Kishwer S. Nehal)

and the tissue is sent in formalin fixation to the laboratory for processing (Fig. 8.1b). Multiple sections perpendicular to the long axis of the specimen are obtained with sampling occurring through the central portion of the grossly-defined tumor, cutting on average at 1–5 mm intervals, largely based on tumor type (Fig. 8.1c) [24, 26]. The tips of an ellipse are often processed separately and inking of the specimen is laboratory-dependent [27]. Another name for this process is step sectioning, in contrast to true serial sectioning, which involves the complete processing of the specimen in an unbroken sequence with theoretical 100 % specimen evaluation [26]. The latter technique would require hundreds to thousands of sections (assuming each section is only 4 or 5 micrometers thick), which is often impractical for even smaller specimens. The sections are fixed in paraffin-embedded blocks, microscope slides are created and stained with hematoxylin-eosin and sent to the dermatopathologist for microscopic review. The dermatopathology excision report states final pathologic features of the melanoma (pathologic staging) and histologic status of the surgical margins [27].

Advantages

The breadloaf technique has many advantages compared to other processing methods, highlighting its popularity for standard excisions [25]. Small skin specimens bode fairly well and are easy to interpret in this manner. More importantly, there is a clear distinction between central tumor and peripheral margin, with the ability to detect a narrow margin of clearance. This technique allows for better assessment of the field of damage, without the need for a "normal control" specimen for clarification.

Limitations

However, the breadloaf technique is not without limitations. More sections are often required for better examination of margins. The major limitation is lack of full margin assessment, with often less than 1 % of the total peripheral and deep margin microscopically examined. This can lead to the potential for missed tumor at margins between evaluated sections (Fig. 8.1d) [26]. In LM, this is particularly worrisome as some authors feel that the tumor extends in subclinical projections that may be easily missed in the discarded portions between sections [28, 29]. In one recent study, patients with LM were at a greater risk of persistent disease in wide local excisions compared to other subtypes of melanoma, despite a reported negative margin on excisional biopsy [30]. Immediate reconstruction of surgical defects with complex flaps or grafts without confirmation of clear surgical margins further complicates the situation as it is often difficult to pinpoint location of residual melanoma following tissue rearrangement. Thus excision with standard surgical margins is often ineffective in LM/LMM prompting the need for methods with more complete margin control [5, 8, 9, 11–17, 23].

Margin Controlled Excision Techniques

The focus on LM treatment has more recently shifted toward techniques with more meticulous margin evaluation, including en face and radial sectioning and processing with frozen or permanent sections. Each of these techniques has the advantage of more complete margin evaluation and low local recurrence rates of 0–5 % [31–37] compared to standard excision with local recurrence rates of 8.8–20 % [3, 5, 23]. Unique, distinguishing characteristics of each margin controlled technique will be reviewed.

Mohs Micrographic Surgery Using Frozen Sections

Technique

A modified en face sectioning with frozen sections is used in MMS [10, 14, 15, 18, 20–22, 31, 37] and offers the advantage of complete margin control. The MMS technique relies on two main principles in order to achieve success in tumor clearance: (1) contiguous tumor growth for microscopic mapping, and (2) accurate histologic assessment of tumor cells and differentiation from non-tumor cells on frozen sections [37]. MMS for melanoma involves clinically demarcating the central pigmented lesion with a margin of normal-appearing tissue. This central tumor debulking specimen is excised and sent for serial sectioning [14] with permanent histology for confirmation of tumor depth and staging information. An additional margin is excised to the subcutaneous plane and the complete peripheral and deep margins are processed according to the Mohs technique into frozen sections and evaluated by the Mohs surgeon [14] (Fig. 8.2). The Mohs surgeon microscopically maps residual tumor which guides subsequent Mohs excisions until a tumor-free plane is obtained.

Advantages

The MMS frozen-section technique offers several advantages over standard excision for LMM: (1) tumor with poorly defined clinical margins and unpredictable subclinical extension can be mapped with virtually 100 % margin control; (2) maximal preservation of normal tissue in the anatomically and cosmetically sensitive region of the head and neck, (3) immediate tissue processing and evaluation with same-day repair minimizing wound care and transportation burdens for the patient and (4) low local recurrence rates compared to standard excision [13, 14, 21, 37–42].

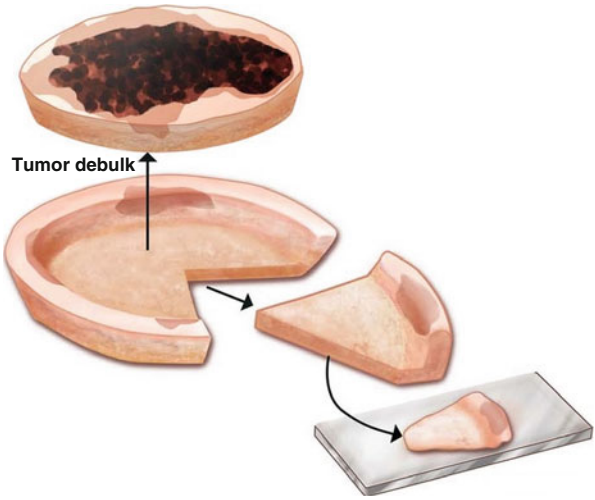


Fig. 8.2 Mohs micrographic surgery technique: tissue is processed with frozen sections for complete margin evaluation (Image ©2016, Memorial Sloan Kettering Cancer Center. Used with permission)

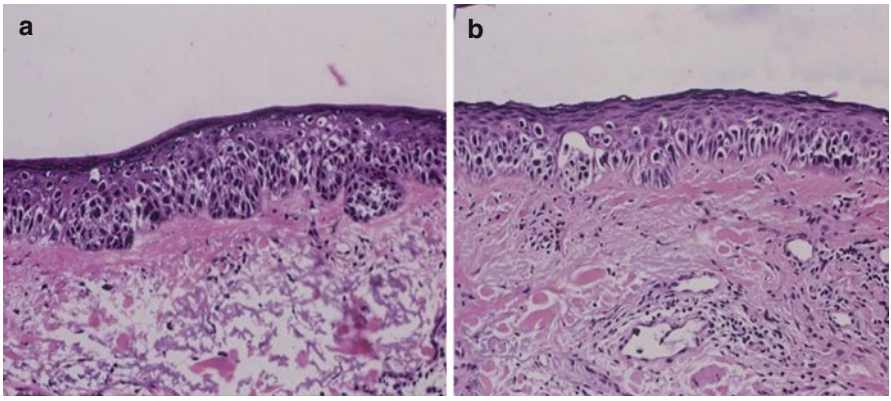


Fig. 8.3 Frozen vs. permanent section evaluation of lentigo maligna. (**a**) Frozen section (H&E). (**b**) Paraffin-embedded permanent section (H&E)

Limitations

Most criticism posed against MMS for melanoma involves the quality of frozen sections versus the gold-standard permanent paraffin-embedded sections . Processing high quality thin frozen sections for LM margin evaluation while avoiding tissue distortion and freeze artifact requires highly skilled histotechnicians [41]. Additionally, melanocytes on frozen sections lose their characteristic retraction halo seen on permanent sections, making identification more challenging (Fig. 8.3) [14, 37]. Other pitfalls on Mohs frozen sections include presence of inflammation obscuring tumor, severe keratinocytic atypia within epidermis, and identifying solitary isolated atypical melanocytes [14, 37, 41]. Single melanocyte spread is

particularly challenging to identify, as this often occurs in chronically sun damaged skin and distinction with frozen sections can be difficult [37].

From a quality assurance perspective, another disadvantage of MMS for melanoma margin assessment is the lack of a routine independent review of every case by another pathologist (as is routine for intraoperative frozen sections). While MMS may achieve negative margins with low recurrence rates there is lack of independent verification whether all the layers during a procedure that were taken were truly necessary (some may have been falsely read as positive leading to greater tissue defects than medically required).

One alternative to overcome the pitfalls of frozen section evaluation of LMM margins is to excise tissue with the Mohs technique but send the specimen for paraffin embedded en face sectioning. Another option is to excise an additional layer and send for permanent sections at the conclusion of MMS with final margin confirmation by a dermatopathologist [13, 18, 40]. Most studies using this method of checks and balances have found reasonable correlation between frozen and permanent sections [40, 42], however one small study demonstrated higher recurrence rates in frozen MMS sectioning (33 %) compared to rush permanent serial sectioning (7.3 %) in a follow-up period approaching a mean of 10 years [39]. To address challenges of interpreting LMM margins on Mohs frozen section with hematoxilyn & eosin (H&E) staining alone, melanocytic immunostains are commonly used as outlined in the Mohs Surgery chapter.

Staged Excision with Rush Permanent Sections with En Face Sectioning

Technique

En face sectioning of LMM margins can also be assessed with paraffin embedded rush permanent sections to ensure complete margin control while avoiding frozen section pitfalls and need for immunostains. The tumor is clinically demarcated and removed with a surrounding margin of normal appearing tissue ranging from 2 to 10 mm based on the anatomic location and depth of melanoma invasion identified on biopsy [9, 28, 38, 43, 44]. The central portion of the tumor is debulked and processed with serial sectioning or traditional breadloaf sectioning for identification of unsuspected invasion and determination of final Breslow depth for melanoma staging. The perimeter is then divided into smaller sections, often inked for orientation, and the outer-facing rim (true surgical margin) is mounted flat, serially sectioned vertically, and stained with hematoxylin and eosin for examination by a dermatopathologist. This allows for complete peripheral margin evaluation with precise

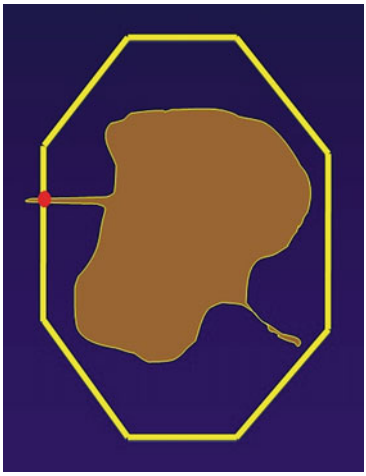


Fig. 8.4 Staged excision with en face permanent sections: *Red dot* shows tumor detected at peripheral margin (Image by Kishwer S. Nehal)

mapping of residual tumor (Fig. 8.4). Generally speaking a geometric, sharp angled border is easier to section vertically [32, 44], however despite the change in the shape of the strips, the contoured technique is not reported to have processing difficulties [34]. If a positive margin results, the process is repeated in the mapped area until tumor free margins are achieved. The exception is the square technique, which leaves the central tumor intact until the peripheral margins are clear [32]. The remaining central tumor is then removed and processed in the final steps.

Advantages

While technically tedious for histotechnicians, the en face technique allows for fewer sections to be examined by the dermatopathologist when compared to the traditional breadloaf method. Most importantly, full evaluation of margins allows for the removal of significantly smaller margins in successive steps until tumor-free margins are achieved, thereby minimizing the cosmetic defect while reducing the rates of local recurrence [9, 28]. One study directly compared the local recurrences rates of conventional excision versus en face sectioning with rush permanent sections and found a 0.7 % local recurrence rate in the en face group compared to 6.4 % with conventional excision [28]. Furthermore, these authors found a significant effect of en face sectioning on recurrence-free survival in patients with thinner LMM (less than or equal to 1 mm in depth). Another study showed no local recurrence using en face techniques, although duration of follow up was not specified [43].

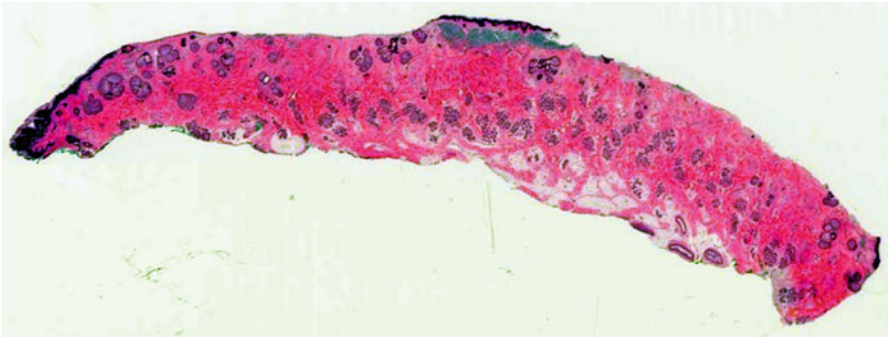


Fig. 8.5 Technical challenge with en face processing: incomplete epidermal margin

Limitations

The main disadvantages of the en face sectioning technique include inability to define the margin of tumor clearance, and difficulty in tracking out the subtle changes of the trailing edge of LM, with less precise distinction between lesion and background. Some have suggested taking a sample of "normal" yet equally sun-damaged skin to act as a control specimen. However this results in an additional wound/scar for the patient, which is not ideal [9, 45]. Additionally, sections tend to be large and tedious to process, with difficulty obtaining quality sections [25]. Formalin fixation may warp tissue, reduce tissue pliability, and pose a challenge to obtaining a complete en face peripheral margin (Fig. 8.5). However, one group proposed a variation to the traditional fixation technique to reduce this complication by gently fixing the tissue specimen between two glass slides to maintain the flat margin architecture during formalin processing [46]. Furthermore, en face sectioning relies entirely on a contiguous tumor growth pattern, and does not account for possible skip areas within the tumor itself, potentially complicating perfect margin control.

Staged Excision with Rush Permanent Sections with Radial Sectioning

Technique

Radial sectioning is an alternative method for processing LMM margins. Staged excision with rush paraffin-embedded permanent sections using radial sectioning offers the advantage of enhanced margin examination along with the ability to view the transition from tumor to background photodamaged skin (Fig. 8.6a) [8, 17]. The clinical pigmented lesion is demarcated with the use of a Wood's lamp, and a margin of normal-appearing skin is marked based on initial biopsy

characteristics (5 mm margin for melanoma in situ, 7 mm margin for melanoma in situ with regression or radial growth phase microinvasion, and 10 mm margins for invasive melanoma ≤1 mm in Breslow depth) (Fig. 8.6b). The central pigmented lesion or tumor debulking is excised to the deep subcutis and sent to pathology for serial vertical sections to determine final melanoma depth and pathologic staging. The peripheral margins are excised separately to the deep subcutis, divided into 4 quadrants, similar to the face of the clock (12–3, 3–6, 6–9, 9–12 o'clock with sutures to maintain orientation) placed in separate formalin containers (Fig. 8.6c), and sent for rush paraffin-embedded permanent sections. The peripheral margins are inked to identify the inner and the true outer surgical margin, sectioned radially at 1–2 mm intervals in clockwise orientation, and each section placed in a separate cassette (Fig. 8.6d) for processing. Tissue is stained with hematoxylin and eosin, and evaluated by a dermatopathologist and location of residual melanoma communicated to the surgeon. Further excisions are performed based on mapped location of residual LM until margins are histologically cleared. Clear margins are defined as a 3 mm distance between LM and the nearest side margin where anatomically feasible. Studies with 5 years of followup show a 5 % local recurrence rate [17, 47, 48].

Advantages

Advantages of the radial sectioning technique include the ability to evaluate tumor margins compared to central tumor and determine margin of clearance, unlike the en face technique. In this technique, the radial or centrifugal orientation of the specimen shows a clear transition between LM/LMM, atypical junctional hyperplasia, and normal histologic features. This enables detection of subtle changes in cellular density from the central melanoma to the periphery (Fig. 8.7a), which serves as a critical factor when distinguishing tumor-involved margin from chronically sun-damaged background changes. For this reason, immunostains and "normal" control biopsies are rarely needed for a definitive diagnosis/margin evaluation as there is an inherent control when examining the specimen in a radial fashion. The radial evaluation of LMM and its margins also allows the dermatopathologist to measure a margin of clearance (Fig. 8.7b). Our experience suggests that narrow margins of clearance can increase risk of local recurrence over time.

Limitations

Although serial vertical sections are more easily processed in a general pathology laboratory that may be unfamiliar with Mohs or en face section techniques, this technique does require more total slides to be examined by the dermatopathologist

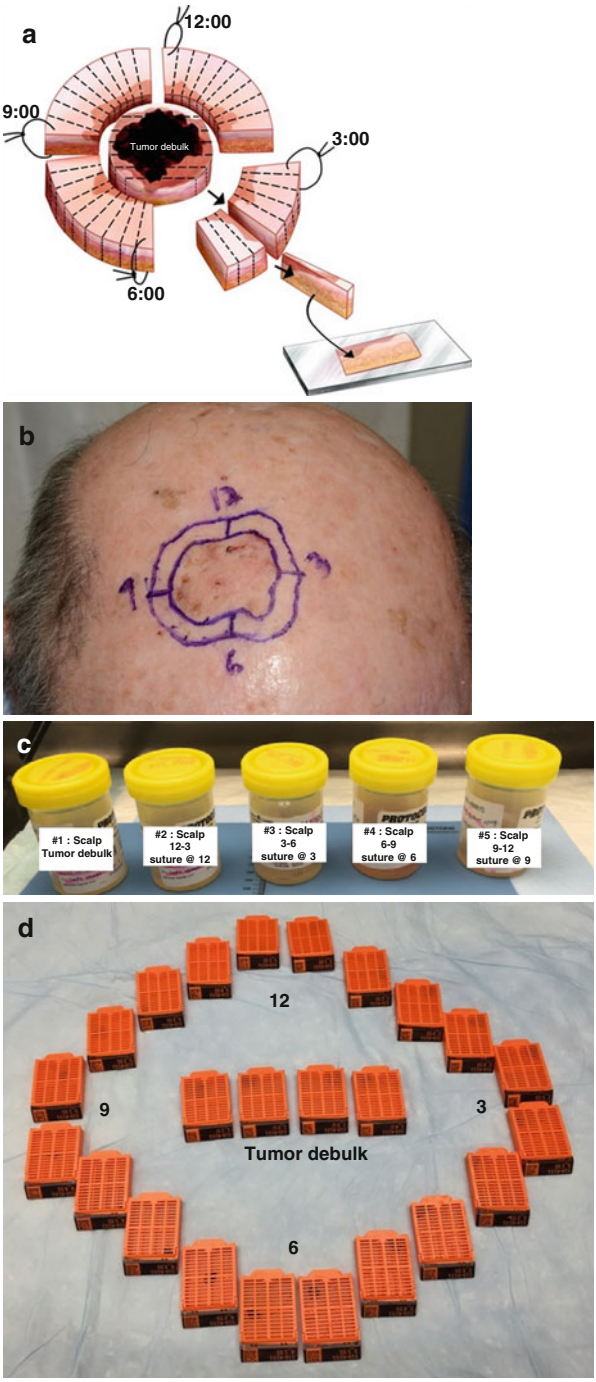


Fig. 8.6 Staged excision with radial sectioning technique. (**a**) Illustration shows tumor debulking and margins excised (Image ©2016, Memorial Sloan Kettering Cancer Center. Used with permission). (**b**) Melanoma in situ marked with 5 mm excision margin. (**c**) Tumor debulking and peripheral margins placed in separate formalin containers. (**d**) The divided tissue is placed into cassettes for processing and embedding with complete preservation of tissue orientation

which can be time consuming. In addition, this method cannot examine 100 % of the peripheral margin compared to the en face technique or MMS. However, it is unlikely that LM at a peripheral margin would be missed with this technique that examines multiple thin sections (2 mm) and uses a 3 mm safety margin of clearance (Fig. 8.7c). Reconstruction is not same-day, and the overall process may be time-consuming with 24-h tissue processing turn-around time between serial excisions. As with any technique, intimate coordination of care and frequent communication between oncologic surgeon, pathologist and plastic surgeon is essential.

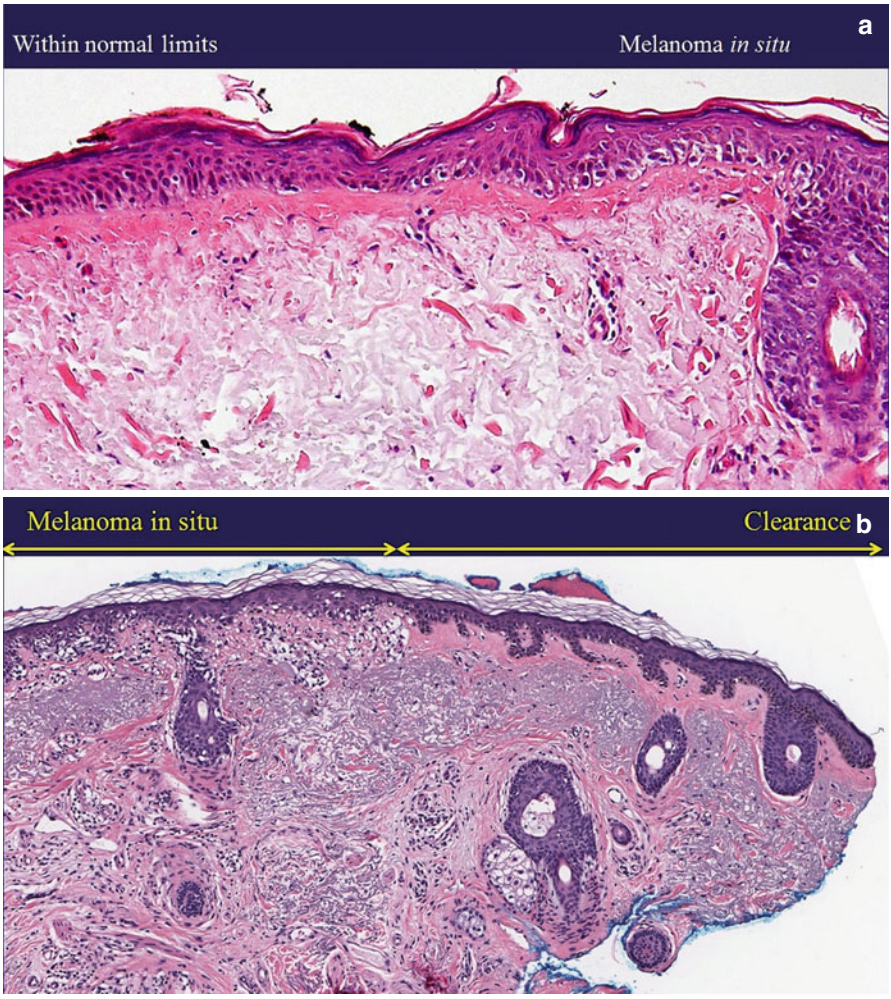
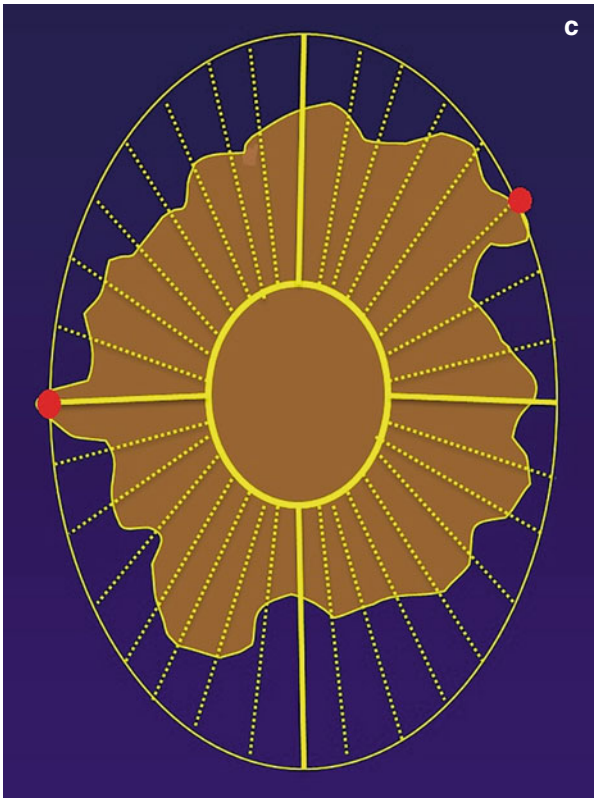


Fig. 8.7 Radial sectioning advantages. (**a**) Clear visualization of melanoma in situ centrally as it transitions to normal sun damaged skin at surgical margins peripherally (H&E). (**b**) A margin of clearance can be measured from the outer surgical margin inked in *blue* (H&E). (**c**) Tumor can still be detected at peripheral margins (*red dots*) (Image by Kishwer S. Nehal)

Fig. 8.7 (continued)



Immunohistochemistry

Immunohistochemistry (IHC) for melanocyte differentiation antigens may be used for the diagnosis of melanocytic neoplasms on both permanent and frozen sections. Markers to visualize intraepidermal melanocytes include MART-1/Melan-A, Sox10, Tyrosinase, Mel-5, and MITF (Fig. 8.8). S100 protein and HMB-45 are less suitable due to limitations in sensitivity (HMB-45, S100P) and specificity (S100P). Although rapid and efficient processing systems have been developed [49–51], they still require an additional 20–40 min on average per section [52]. Additionally, the process is highly technical and as previously stated, requires a skilled and experienced laboratory [1].

Melanoma recognized by T cell antigen 1 (Melan-A, MART-1) staining is more commonly used due to its high sensitivity and specificity [15, 53]. It is a cytoplasmic melanosome-associated glycoprotein that stains adult melanocytes, melanomas, and nevus cells [38, 54]. Microphthalmic transcription factor (MITF) and SOX10 are nuclear antigens, which is beneficial for analyzing heavily pigmented lesions [38, 55]. For the recognition of invasive desmoplastic melanoma, S100 protein Sox10 and NFGR are the best markers.

IHC is rarely necessary for a high quality formalin-fixed and paraffin-embedded hamtoxylin and eosin-stained section [8]. IHC may be needed, if the melanocytes are

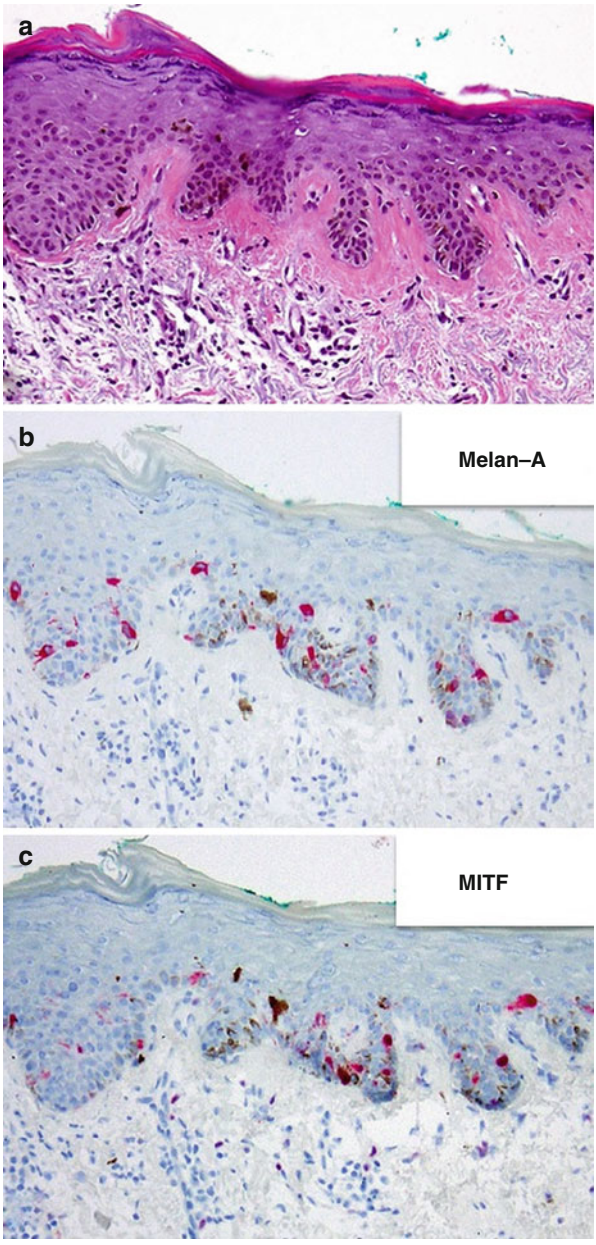


Fig. 8.8 Immunohistochemistry for melanocyte density. (**a**) H&E. (**b**) Melan—A. (**c**) MITF

difficult to see due to poor staining or when a dense inflammatory cell infiltrate obscurese the junctional melanocytes (Fig. 8.9). Frozen and en face sections more heavily rely on immunostains for assessing melanocyte density and growth patterns . Interestingly, in one survey from 2000, less than 15 % of MMS laboratories were using immunostains in LM [56]. However, with improved technologies and staining processes and more operator comfort with stains, it is uncertain if this figure is now higher.

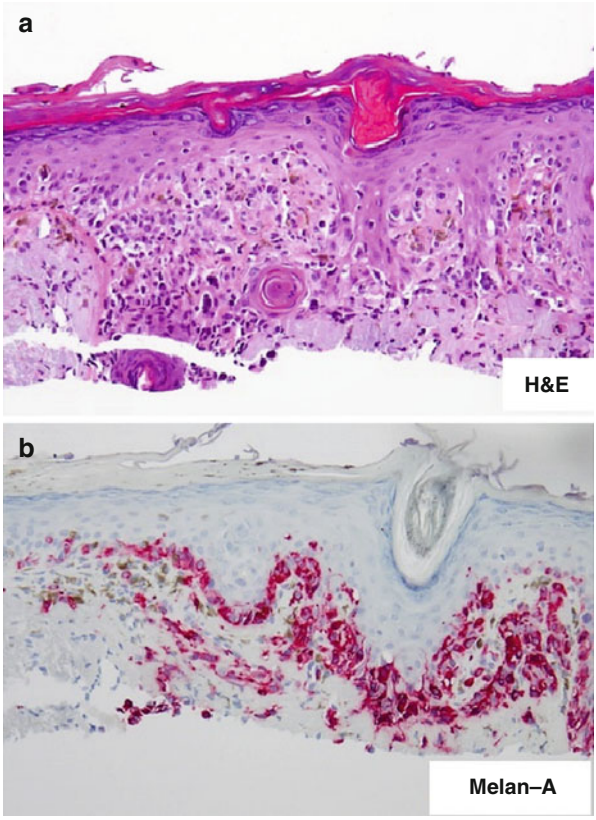


Fig. 8.9 Immunostains for Lentigo Maligna. (**a**) Inflammation can obscure a junctional melanocytic proliferation (H&E). (**b**) Melan-A highlights the melanocytic proliferation

Pathologic Staging and Lymph Node Management

Once the LM and LMM has been completely excised, pathologic staging can be completed according to American Joint Committee on Cancer [57] as with other subtypes of melanoma. The recommendations for management and workup of invasive melanoma are outlined in National Comprehensive Cancer Network clinical practice guidelines [58].

Tumor staging is determined by Breslow depth and presence or absence of ulceration and/or mitoses (57). In situ melanoma (LM) is stage Tis. T1 tumors have a thickness ≤ 1.0 mm, with T1a tumors showing no ulceration and mitosis $<1/mm^2$, and T1b tumors with ulceration or mitosis $\geq 1/mm^2$. T2 tumors have a thickness of 1.01–2.0 mm, with T2a tumors without, and T2b with ulceration. T3 tumors have a thickness of 2.01–4.0 mm, with T3a without, and T3b with ulceration. T4 tumors are >4.0 mm in thickness, with T4a without, and T4b with ulceration.

Nodal staging is determined as follows: NX patients are those in whom the regional lymph nodes cannot be assessed (57). N0 patients have no regional metastasis. N1a category refers to those with 1 node containing micrometastasis (found on sentinel lymph node biopsy or lymph node dissection), while N1b refers to 1

node containing macrometastasis (clinically detectable). N2 category refers to patients with 2–3 nodes classified by the following subcategories: a. micrometastasis, b. macrometastasis, or c. In transit met/satellite without metastatic nodes. N3 category includes those with 4 or more metastatic nodes, matted nodes, or in transit mets/satellites with metastatic nodes. Distant metastasis M categories are determined as follows: M0 is no detectable evidence of distant metastases; M1a includes metastases to the skin, subcutaneous tissue, or distant lymph nodes; M1b includes metastatic disease to the lung; M1c includes metastases to all other sites or distant metastases in combination with increased serum LDH levels.

Clinical staging for 0 through IIC depends on tumor stage alone, with N0 and M0 and categorization as follows: Stage 0 is Tis, Stage IA is T1a, Stage IB is T1b and T2a, Stage IIA is T2b and T3a, Stage IIB is T3b and T4a, and Stage IIC is T4b. Stage III includes any T stage and ≥N1 but M0, and Stage IV includes any T or N stage and M1.

Sentinel lymph node biopsy (SLNB) can be a useful prognostic tool in selected cases of LMM to detect subclinical metastases. At the author's institution, SLNB is discussed with patients according to NCCN guidelines by stage. Specifically, for those tumors with an intermediate depth of 1.0–4.0 mm, an SNLB is discussed and offered to patients for prognostic information, with consideration of the patient's overall health status. While there is not a firm consensus for utility of SLNB in those with a melanoma 0.76–1.0 mm thick, SLNB is discussed in select cases with high risk pathologic features. For those with melanomas ≤ 0.75 mm in thickness, while high risk features such as lymphovascular invasion are rare, SLNB may be discussed on an individual basis when they are seen.

The complex lymphatic drainage of the head and neck area has added to the discussion of the utility of SLNB, with some authors questioning the reliability of SLNB in this region; however, other authors have shown accuracy of SLNB of the head and neck region in predicting lymph node metastasis [59–61].

Diagnostic Pitfalls and Controversies

Various diagnostic pitfalls and controversies in the surgical treatment and histologic assessment of LM/LMM can be encountered. Pitfalls associated with follicular involvement, unsuspected invasion, skip areas and desmoplastic melanoma are described. These features pose unique challenges in the pathology assessment and overall treatment of LM and LMM.

Follicular Involvement

Follicular involvement in LM is fairly common and can manifest superficially along the follicular infundibulum but in some case can also extend deep into the follicle (Fig. 8.10). If the excision depth does not extend beyond the base of the follicle,

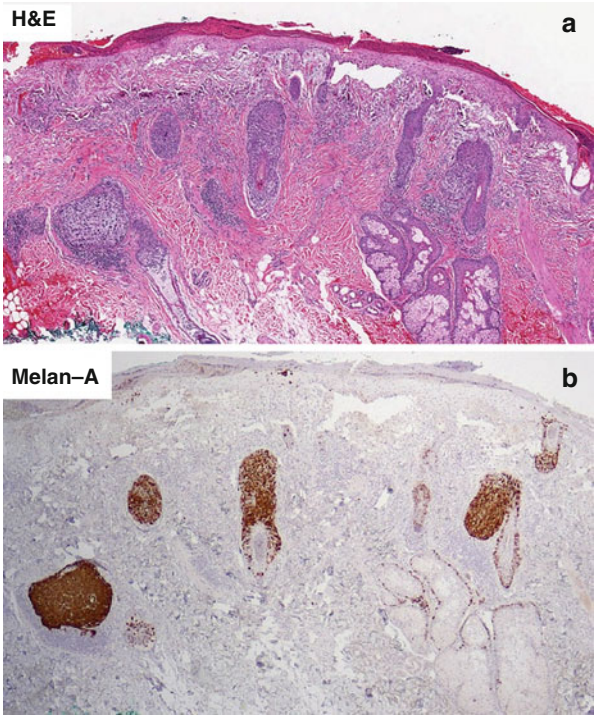


Fig. 8.10 Follicular involvement. (**a**) Lentigo maligna with extensive follicular involvement (H&E). (**b**) Highlighted with Melan-A

there is the potential for melanoma in situ to inadvertently remain at the deep margin within a transected follicle, and increase risk of persistence and recurrence. Infrequently, melanoma in situ originating from a follicle can also invade into the dermis forming a nodule making it difficult to assign a Breslow depth. The debate is whether to measure the melanoma depth from the granular layer or from the point in the follicle that the invasive melanoma likely originated from. In our experience transected follicles are more likely to occur in excisions on the helix or nose in an attempt to preserve normal tissue in anatomically sensitive locations.

Unsuspected Invasion

Unsuspected invasion or an underlying deeper melanoma component has been reported in 5–67 % of LM specimens [8, 16, 17], as subtotal biopsies are commonplace when these tumors are large or located on cosmetically sensitive areas [62]. The rate of unsuspected invasion decreases as a greater proportion of the pigmented lesion is sampled during the initial biopsy. The inability to preoperatively determine final depth of LMM can complicate overall management including margin control and potential need for sentinel lymph node biopsy. Fortunately, invasive LMM when noted on excision is often limited to the radial growth phase and does not change the prognosis significantly (Fig. 8.11) [8].

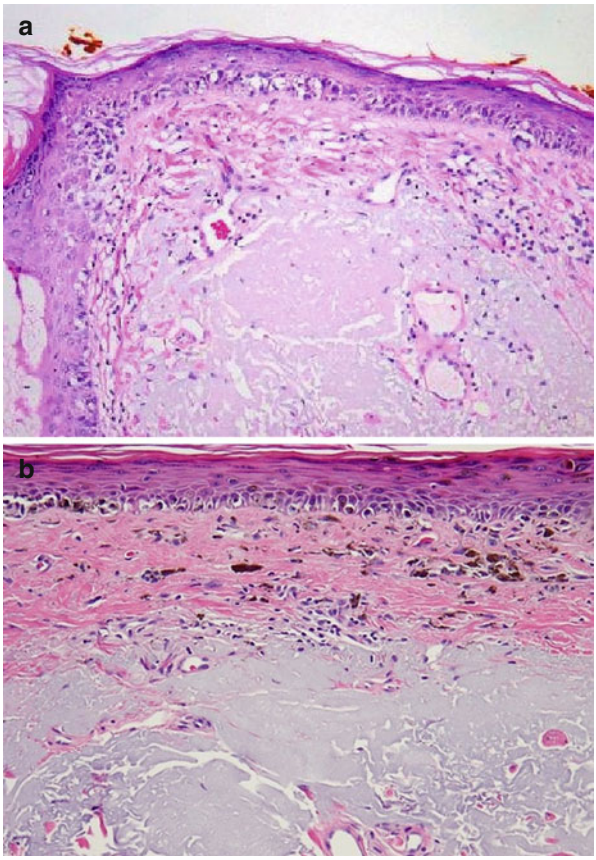


Fig. 8.11 Unsuspected invasion. (**a**) Initial biopsy—melanoma in situ with follicular involvement. (**b**) Melanoma in situ with microinvasion noted after complete excision

Skip Areas

LM tends to involve single cells predominating over nests, further complicating complete margin assessment [1] with potential for skip areas. One of the major disadvantages discussed with breadloafing and radial sectioning techniques are the lack of complete margin identification. Even with tightly controlled intervals between sectioning, there is a risk of tumor "skip areas" where subclinical extension will go unidentified in a section that was not microscopically examined. The MMS and en face sectioning techniques have the advantage of nearly 100 % margin identification, however they entirely rely on the existence of a contiguous tumor growth pattern in order for this technique to remain reliable. While LM classically demonstrates contiguous cell spread, there is a theoretical concern for skip areas even utilizing these complete margin-controlled techniques (Fig. 8.12). Complete serial sectioning of several 2 mm thick tissue blocks confirmed that there is little variation in margin clearance from the first section to the last section of the respective blocks (KJB, personal observation).

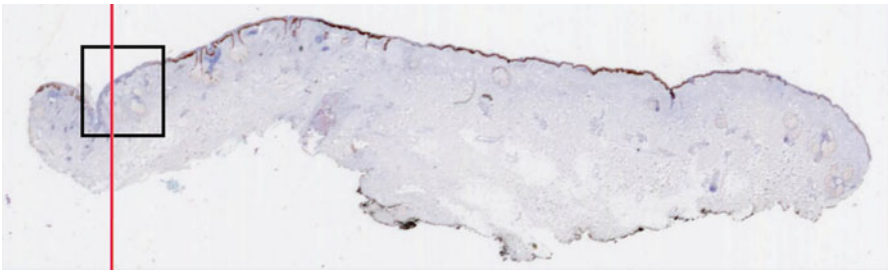


Fig. 8.12 Lentigo maligna has potential for skip areas (*black box*) which would not be detected with en face sectioning (*red line*)

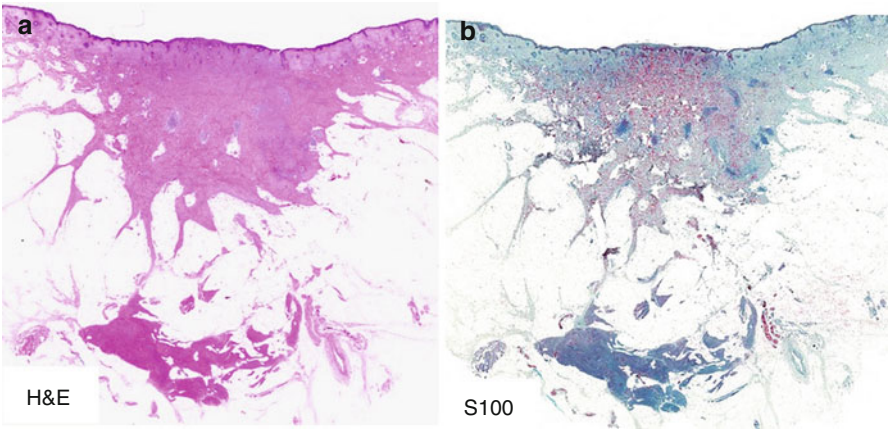


Fig. 8.13 Desmoplastic melanoma. (**a**) Spindle proliferation (H&E). (**b**) S100 staining demonstrates desmoplastic melanoma in the dermis

Desmoplastic Melanoma

Desmoplastic melanomas have been reported underlying LM which presents a problematic. Identification can be challenging on frozen sections and these spindled tumors do not reliably stain with cytoplasmic immunomarkers commonly used on frozen MMS techniques, such as Melan-A/MART-1 and HMB-45 [10, 37, 54]. Often if there is suspicion, permanent sections are sent for formalin fixation for confirmation of complete tumor removal where SOX10, S100, NGFR, or other more reliable nuclear markers are used (Fig. 8.13) [63].

Field Damage

One major controversy and complication in LM treatment involves the background cutaneous "field of damage," and the difficulty associated with accurately distinguishing single melanocyte spread found at the periphery of lentigo maligna from

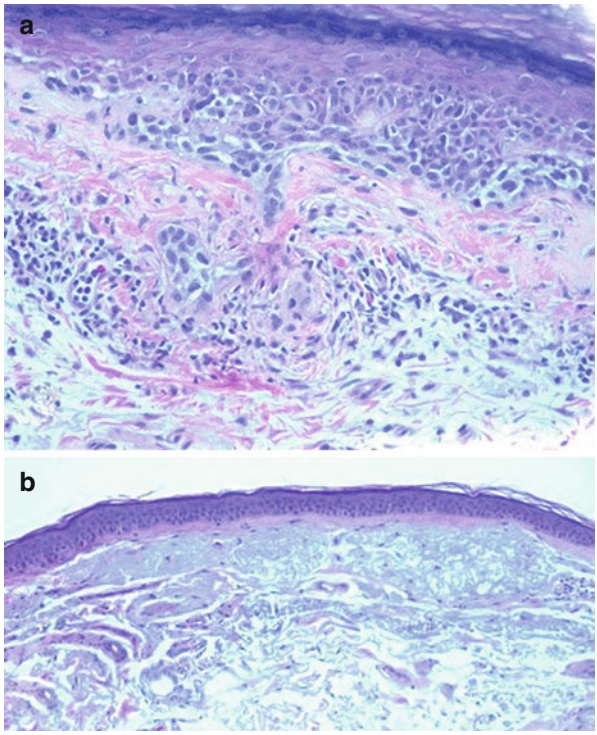


Fig. 8.14 Assessing field damage. (**a**) Microinvasive melanoma arising in heavily sun damaged skin. (**b**) Control "normal" biopsy

changes associated with chronic photodamage This evaluation is particularly challenging in frozen sections and en face sectioning where there is no built in "normal" control, in contrast to radial sectioning that has a clearer demarcation from involved tumor to sundamanged normal skin. Immunostains have been proposed to help ameliorate this complication, however all melanocytes stain positively with MART-1/Melan-A offering limited assistance [49].

In prior studies, photodamaged skin has demonstrated confluence of atypical melanocytes along the basal layer, adnexal extension, and suprabasial scatter, all features shared with LM/LMM as well [64]. One of the more reliable distinguishing features is the epidermal melanocyte density observed in LM/LMM, which differed significantly from negative, photodamaged controls, however this interpretation has a certain degree of subjectivity. Furthermore, some of the cytoplasmic immunostains, such as Melan-A, have reportedly stained keratinocytes and melanophages particularly in areas of inflammation where distinguishing between cell types is less reliable [65, 66]. Additionally, some have suggested taking a sample of "normal" yet equally sun-damaged skin to act as a control specimen to minimize this challenge (Fig. 8.14), however this results in an additional wound/scar for the patient, and some have found this technique unreliable [9, 45]. Each of these confounders may benefit from confirmatory sections sent for permanent paraffin-embedded comparison, however this requires additional processing and an additional time-delay.

Table 8.1 Comparison of lentigo maligna specimen histologic processing techniques

	Standard breadloaf	Mohs micrographic surgery	Staged excision with en face	Staged excision with radial sections
Tissue processing	Paraffin	Frozen	Paraffin	Paraffin
Immunostains	Infrequent	Routine use	Infrequent	Infrequent
% surgical margin evaluated	Limited	100 %	100 %	<100 %
Technical skill	Standard	High	High	Moderate
Margin of clearance	Yes	No	No	Yes
Differentiate lesion vs. Background	Yes	Challenging	Challenging	Yes
Potential Skip areas pitfall	No	Yes	Yes	No

Conclusion

In summary, LM/LMM is a subtype of melanoma most commonly occurring on sun damaged skin on the head and neck. This particular tumor subtype poses a therapeutic challenge as the tumor often extends well beyond what is clinically perceived. Furthermore, an unsuspected invasive component is demonstrated in a substantial percentage of cases due to inadequate biopsy sampling on cosmetically sensitive sites. Surgical excision remains the gold standard of treatment, with more recent evidence suggesting that modalities implementing more complete margin evaluation offer superior cure rates to traditional excision margins. Whether utilizing frozen section-MMS or rush permanent sections, accurate histologic margin assessment is crucial in ensuring complete tumor clearance and minimization of local recurrence and tumor metastasis (Table 8.1).

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Chapter 9
Management of Eyelid Lentigo Maligna

Brian P. Marr

Eyelid melanoma accounts for 1% of both cutaneous melanoma and malignant lesions of the eyelid [1]. The common clinical subtypes of superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma occur on the eyelid, as in other cutaneous areas. However, lentigo maligna (LM) and lentigo maligna melanoma (LMM) have been reported in higher frequency in the periocular area compared to other locations on the body [2]. LM, once called Hutchinson's melanotic freckle, is a slowly progressive irregular pigmentation of the skin confined to the epidermis, found in areas of solar damaged skin, and more commonly in fair skinned, older individuals. LM, over time, can transform into its invasive counterpart LMM or be associated with a desmoplastic melanoma [3]. Usually presenting as an enlarging area of pigmentation or a change in an area of pigmentation, delay in diagnosis of LM/LMM is not uncommon as these changes can be subtle and the features ill defined. Lentigo maligna is usually diagnosed by biopsy, showing a collection of atypical melanocytes confined to basal epidermis. LM/LMM of the eyelid and periocular area show no significant difference in their behavior and prognosis compared to similar lesions in the head and neck area [2, 4]. In this chapter we will discuss the management and special considerations associated with treatment of LM/LMM on and around the eyelids.

Eyelid Anatomy and Function

The eyelids and ocular adnexa are specially designed tissues that protect the eyes, and maintain the ocular surface. Their function is essential for good vision and their dysfunction can result in permanent visual impairment, pain, and dramatic

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_9

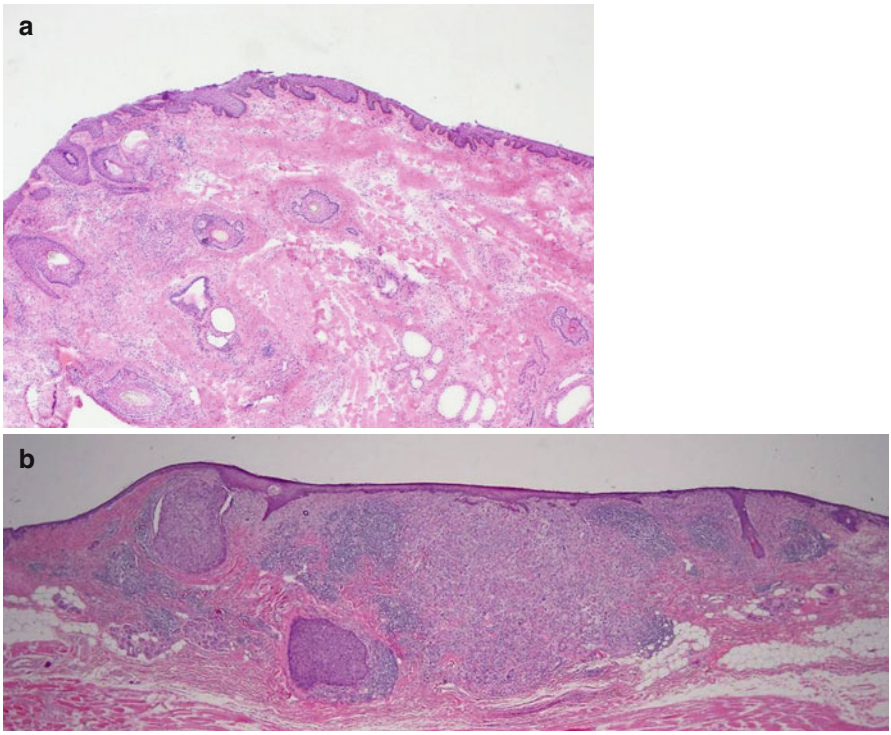

Fig. 9.1 (**a**) Histology of normal eyelid skin; (**b**) Eyelid melanoma, 1.7 mm breslow thickness

reduction in quality of life. It is important to consider this when treating any lesions in this area. The eyelids, due to their location and function, are commonly exposed to sunlight and ultraviolet radiation. Depending on facial anatomy and the use of sun protection, some ocular adnexal areas receive significantly more exposure than others. The chronic exposure may account for the higher rates and delayed onset of lentigo maligna in this area.

The skin of the eyelid is unique in that it is the thinnest skin on the face (Fig. 9.1a) averaging 759 μm [5] allowing the eyelid to move easily and quickly. However, this attribute makes replacement options more challenging during reconstruction and more importantly can complicate assignment of histopathologic criteria. Assignment of Clark levels in thin eyelid skin is challenging given the difficulty to define the junction between the papillary and reticular dermis. Because of this difficulty, Breslow thickness may be a more useful way to grade melanoma in this area. As in other areas of the body, the thickness of these lesions is the most important prognostic indicator for survival (Fig. 9.1b) [4].

The eyelid is made up of three functional lamellae, the anterior lamella which includes the skin and the orbicularis oculi muscle, the middle lamella which contains orbital septum, or lower eyelid retractors, and the posterior lamella which contains the tarsus and conjunctiva (Fig. 9.2). The eyelid margin is the mucocutaneous junction

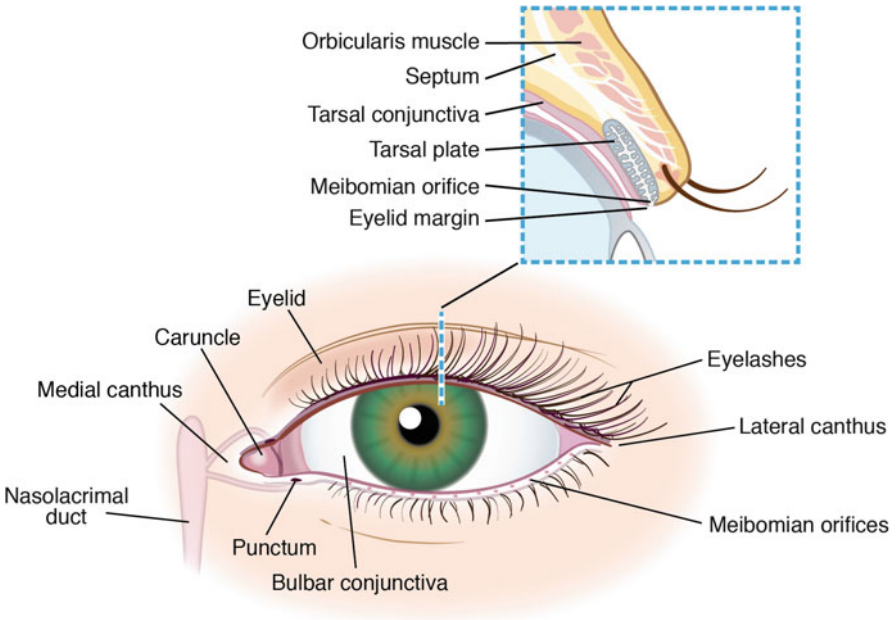

Fig. 9.2 Eyelid anatomy

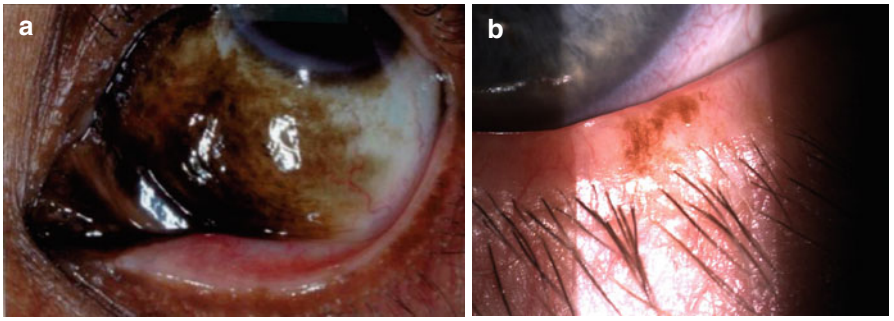

Fig. 9.3 (**a**) External photograph of a conjunctival melanoma extending into the medial canthal area, caruncle and onto the skin. (**b**) Slit lamp photograph of lentigo maligna on the eyelid margin

where skin transitions into conjunctiva. The presence of the adjacent conjunctiva can also complicate evaluation of the extent of the disease and even its origin. Conjunctival primary acquired melanosis can involve the tarsal conjunctiva and extend over and beyond the mucocutaneous junction, thus simulating or becoming lentigo maligna and vice versa [6]. Conjunctival melanoma can also invade the eyelid margin and continue onto the skin simulating primary eyelid melanoma. Care must be taken to fully examine the tarsal and bulbar surfaces of the conjunctiva when evaluating pigmented lesions around the eyes (Fig. 9.3). It should be noted that conjunctival mela-

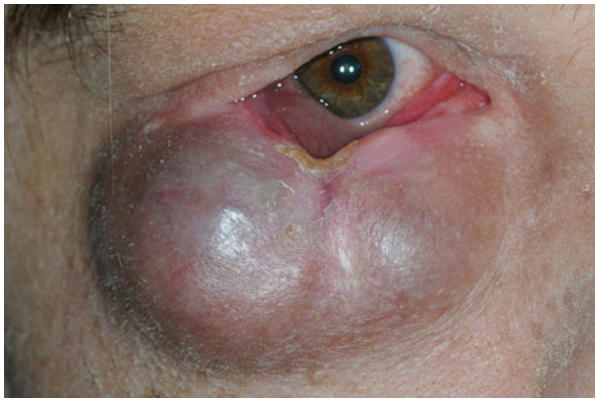

Fig. 9.4 A large recurrent eyelid melanoma after incomplete resection; patient developed nodal and distant liver metastasis

noma (mucosal melanoma) is staged differently than skin melanoma and has its own AJCC classification. This mucosal staging system should be used for lesions whose epi-centers are located unquestionably in the conjunctiva. As discussed earlier, in situ lesions involving the tarsal conjunctiva may also involve lid margin and eyelid skin this overlap and may be more similar to the cutaneous lentigo maligna.

Eyelid Lentigo Maligna Surgical Treatment

Treatment for LM and LMM can be divided into surgical and non surgical options. It is widely accepted that surgical resection of these lesions, with adequate margins, offers the best local control. However, currently there is some controversy on the optimal surgical margin for removal of eyelid lentigo maligna. In an evidenced based meta analysis of eyelid lesions, Cook and Bartley found conflicting papers, opinions, and consensus statements on margin recommendations for melanocytic lesions [7]. Historically a recommended surgical margin of 5 mm for LM and 10 mm for LMM has been advised. However, many reports have found these recommendations to fall short in recurrence control and have recommended various distances ranging from 5 to 12 mm for LM/LMM [8, 9]. One must also take in to account that many of these recommendations were derived from studies that excluded periocular lesions or contained a small portion of representative eyelid cases. In an eyelid melanoma-specific study, Esmaeli et al. found no correlation between margins and local recurrence [10]. It has also been observed that up to 16 % of histopathologically diagnosed LM on further examination harbored portions of LMM [11]. For LM and LMM, surgical control may be obtained with currently recommended or smaller margins by better identifying the actual margin of the lesion. Techniques for identifying melanoma in vivo include dermatoscopy and confocal laser microscopy [11–14]. These techniques in experienced hands have led to better identification of the extent of lesions resulting in enhanced care. However, if mismanaged, recurrence of these lesions can be significant and lead to metastatic disease (Fig. 9.4).

The surgical removal can be done primarily with standard wide margins, with Mohs micrographic surgery with frozen sections, or staged excision with rush permanent sections, interpreted by a pathologist rather than the surgeon interpreting frozen sections. The latter and variations of the technique are now preferred, offering more reliable control and tissue sparing [2, 15, 16].

The goal in working with lesions around the eyelid is to offer the best procedure to provide a cure while preserving the function and aesthetics of the eye. For lesions not involving the eyelid margin, a full thickness skin excision is recommended by the techniques previously explained. If the lesion involves the eyelid margin and/or the conjunctiva, a full thickness eyelid resection is recommended. If the lesion extends into the orbit, then an exenteration must be considered. Periocular LM is found most commonly extending from the cheek or forehead onto the eyelid area, followed by the lower lid, lateral canthus, medial canthus, and least commonly on the upper eyelid [17].

Eyelid Reconstruction

As there are many techniques for reconstruction of the eyelids and they are dependent on the location and extent of the lesion, careful planning is essential. The first step in determining how to repair the defect is to evaluate whether it involves the anterior lamella (skin and orbicularis oculi muscle) or extends into the posterior lamella (tarsus and conjunctiva.) Anterior lamellar defects can be repaired with full thickness skin grafts or sliding flaps. Lesions involving the posterior lamella require replacement of this layer with a mucosal surface. This can be harvested from buccal mucosa or hard palate, or a tarsal conjunctival graft can be used from an adjacent eyelid.

The procedure used for reconstruction of the lower eyelid is determined by the size of the defect; lesions involving under 25 % of the eyelid can usually be closed primarily including both full thickness defects and anterior lamellar defects. Defects involving 25–50 % will require a sliding skin flap for skin defects, and canthotomy with canthal lysis and advancement of adjacent lateral skin for full thickness defects. Defects greater than 50 % will require a vascularized tarsal conjunctival flap with free skin graft for full thickness lesions (Hughes procedure) (Fig. 9.5), or a rotational cheek flap with or without a free mucosal graft (Fig. 9.6). A similar approach is taken for the upper eyelid with the exception that the cheek flap cannot be used for the upper eyelid. In large, full thickness upper eyelid defects, the lower eyelid is rotated to replace the upper eyelid and later divided. Medial canthal lesions require evaluation of the nasolacrimal system. It is important to closely inspect the punctum for pigment as the disease can track down the canalicular system. Defects in this area all require probing and irrigation of the nasal lacrimal ducts to access patency of the system. If a defect is found, it can be repaired with use a bi cannular or mono cannular stent to maintain patency through the healing process.

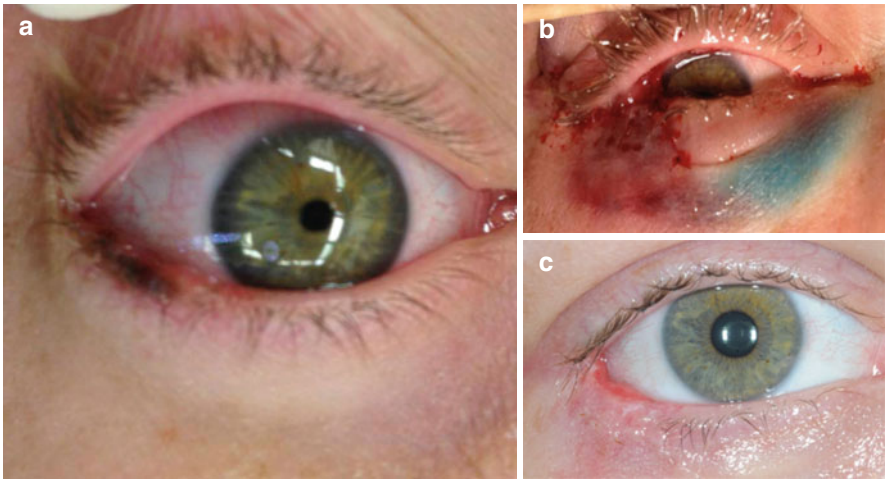

Fig. 9.5 (**a**) Eyelid margin melanoma of the right lateral lower eyelid. (**b**) Repair with a Hughes flap showing the vascular pedicle extending from the upper to lower eyelid laterally. Note the methylene *blue dye* used for sentinel lymph node mapping. (**c**) Appearance of the eye after dividing the tarsal conjunctival flap

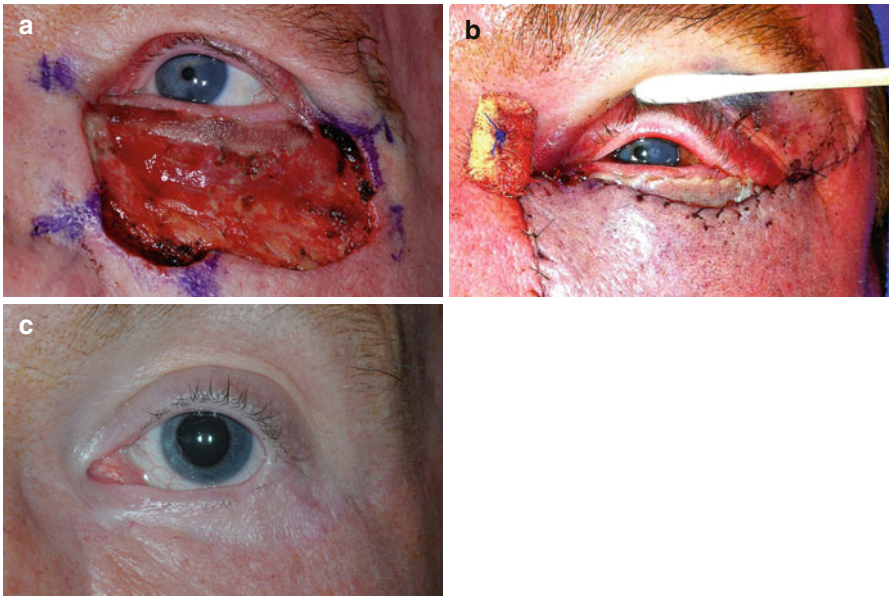

Fig. 9.6 (**a**) A large lower eyelid and cheek defect following the surgical resection of a lentigo maligna. (**b**) Repair of the defect using a cheek advancement flap. (**c**) The appearance of the eye and eyelid 2 months following the repair

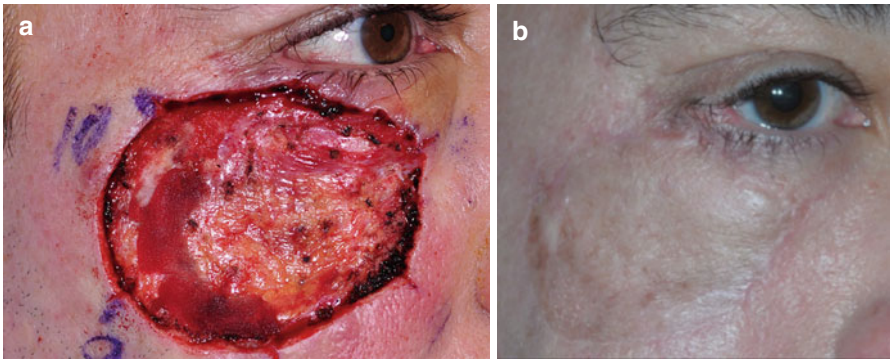

Fig. 9.7 (**a**) A large lower eyelid and lateral cheek defect following the surgical resection of a multiply recurrent lentigo maligna lesion. (**b**) Repair of the defect using a free skin graft

Defects for LM/LMM can be large, and skin grafts may be necessary, although they can have a significant affect on eyelid function and aesthetics (Fig. 9.7). In attempts to avoid some of the side effects from surgery on the eye and eyelid and for patients unable to undergo surgery, nonsurgical methods have been explored.

Eyelid Lentigo Maligna Non Surgical Treatment

A variety of nonsurgical methods have been used in the management of LM, such as cryotherapy, radiation therapy, and topical treatment with imiquimod [18]. Use of topical imiquimod has been an alternative treatment for patients with multiple comorbidities preventing surgery, and those where surgery would have significant functional and cosmetic affect. Imiquimod has been used as primary treatment for LM, neoadjuvant, and adjuvant treatment after surgical excision. Local recurrence rates at 5 years have been reported at 27.5 % and lower rates have been reported but with less follow up [19–23]. Currently there are highly variable treatment regimens and lack of long-term follow-up in the literature. Treatment involves applying the cream to the visible area of pigmentation daily for fixed duration unless a local reaction precludes further treatment. Histologic verification after treatment is recommended. Review of specimens post treatment has not been without cases with persistent disease or progression to invasive melanoma [23]. Surveillance with confocal microscopy has been used as well to guide treatment and assess response [19, 24, 25].

Topical imiquimod has been used successfully in the periocular region. Patient selection is important when considering use in this area, and patients must be compliant and have good dexterity to accurately apply the medication around the eye. When dealing with eyelid lesions, the topical medication can be applied up to the eyelash margin with care not to directly apply the ointment into the eye itself. Use of an ophthalmic ointment or gel prior to administration may help prevent

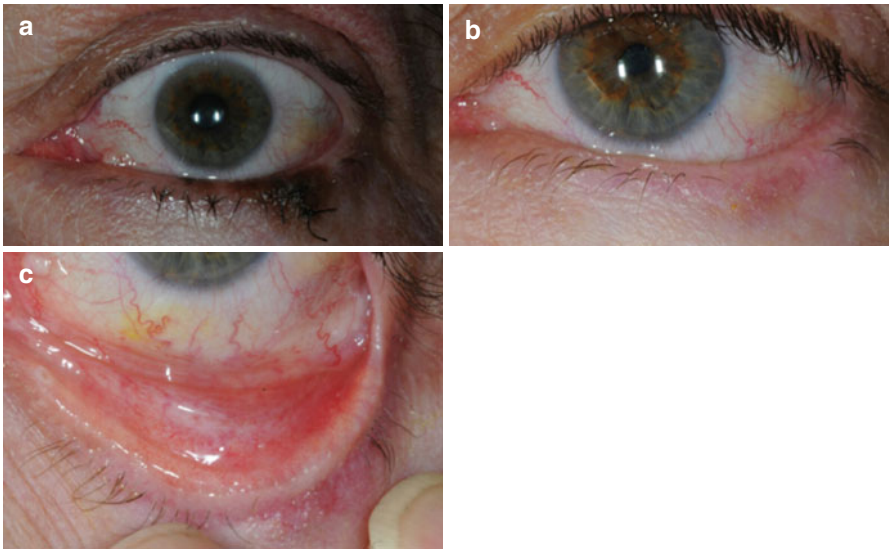

Fig. 9.8 (**a**) Eyelid margin lentigo maligna involving the skin and conjunctiva. (**b**) One year following treatment with local cryotherapy and adjuvant imiquimod without recurrence. (**c**) Tarsal conjunctival surface showing no residual pigmentation

conjunctival exposure. If inadvertently medication gets onto the conjunctiva an artificial tears solution should be used to promptly irrigate the area. During treatment a low-grade conjunctivitis may occur, If the conjunctivitis becomes symptomatic a low dose topical steroid can be applied until symptoms resolve. For more severe reactions temporary or permanent discontinuation of the medications advised.

Cryotherapy has been used commonly in the periocular region for treatment of conjunctival disease. It can also be used in the eyelid area and in lesions that involve the eyelid margin (Fig. 9.8). The use of the special ophthalmic cryotherapy unit, initially designed for treatment of intraocular disease in retina surgery, provides a controlled administration of the therapy around the eye. Lentigo maligna has been treated with cryotherapy in other areas with local control results ranging from 60 % and higher [26, 27].

Radiation therapy has also been successfully used to treat lentigo maligna of the periocular region when surgery is not feasible, when the patient has multiple medical comorbidities or surgery would negatively impact quality of life. Specialized shielding can be used to protect the eye and the patient must be warned about the potential for dry eye complications. Recurrence rates of 0–7 % have been reported following radiation [28, 29].

The treatment of periocular melanoma and lentigo maligna is ideally managed by a multidisciplinary team involving dermatologists, Mohs surgeons, ophthalmic oncologists, ocular plastic surgeons, plastic surgeons, pathologists, head neck surgeons, and radiation oncologists that can integrate and deliver comprehensive care.

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Chapter 10
Reconstruction

Leslie E. Cohen, Karen L. Connolly, and Joseph J. Disa

Introduction

Following surgical removal of lentigo maligna (LM) or lentigo maligna melanoma (LMM), confirmation of negative histologic margins is of primary importance, given the frequent propensity of LM/LMM to have significant subclinical extension. The reconstructive surgeon is often tasked with repair of a large defect, most commonly on the head and neck area. The cheek and nose are the most frequent sites involved, and require consideration of different reconstructive principles. Maintaining respect for anatomic subunits when planning reconstruction of any area is a key concept, particularly for nasal defects. Various techniques utilized in the repair of LM/LMM surgical defects include secondary intention healing, primary closure, skin grafts, local flaps, regional flaps, and occasionally free flaps. This chapter will describe advantages and disadvantages as well as appropriate application of this range of techniques.

Planning

In planning reconstruction following excision of lentigo maligna (LM) or lentigo maligna melanoma (LMM), several unique issues must be considered. Typically closure is delayed until after confirming a negative histopathologic margin.

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_10

By awaiting histopathology results and deferring closure, the surgeon prevents additional procedures or sacrifice of an elegant repair to pursue re-excision. Should a tumor be upstaged due to occult invasion, a staged excision avoids disruption of the lymphatic system by manipulation of surrounding tissues.

As LM is notorious for subclinical extension, the risk of re-excision following 5 mm margins is high, and is even higher with larger lesions. Huilgol et al showed that 30 % of LM's required >5 mm margins and for LMM lesions < 1 mm breslow thickness, 12 % required >1 cm margins for clearance. In recurrent LM, 56 % required >5 mm margins [1]. In a separate study, 58 % of LM required >5 mm margins for histologic clearance [2]. Further, occult invasion has been reported in up to 16 % of cases [3].

When collaborating with a multidisciplinary team for reconstruction, is it important to involve the reconstructive team early in the process. Communication between the reconstructive and ablative teams is crucial, especially when planning lines of excision along relaxed skin tension lines. It is also important to consider the location of an incision if a sentinel lymph node biopsy or neck dissection may be required to avoid violating any potential blood supply to the flap. If feasible, the reconstructive surgeon should be present for the markings of the initial excision.

Counseling

Reconstruction begins with adequate patient counseling in the office setting. Lentigo maligna is notorious for subclinical extension beyond the initial clinical lesion, necessitating larger margins of resection than meets the eye, as shown in Fig. 10.1a–g. A study

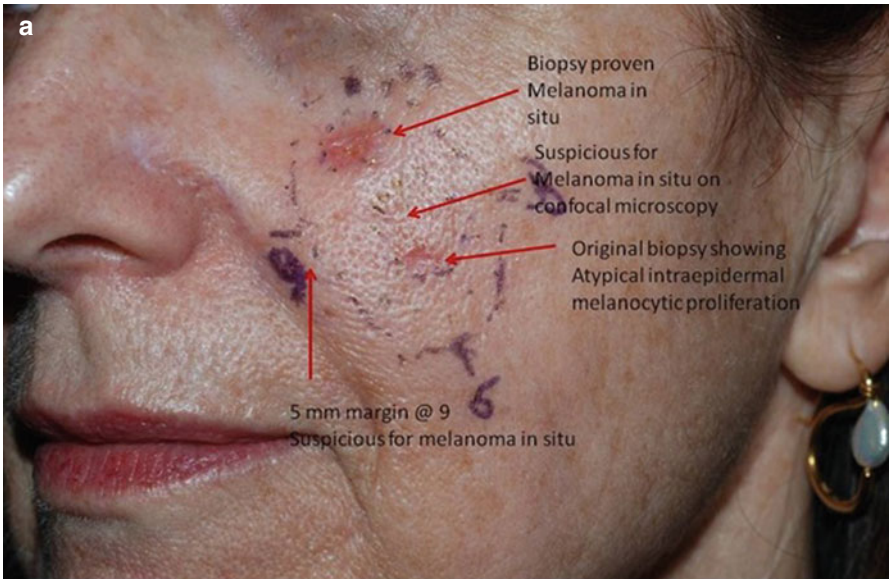

Fig. 10.1 (**a–g**) Left cheek lentigo maligna with final defect much larger than anticipated

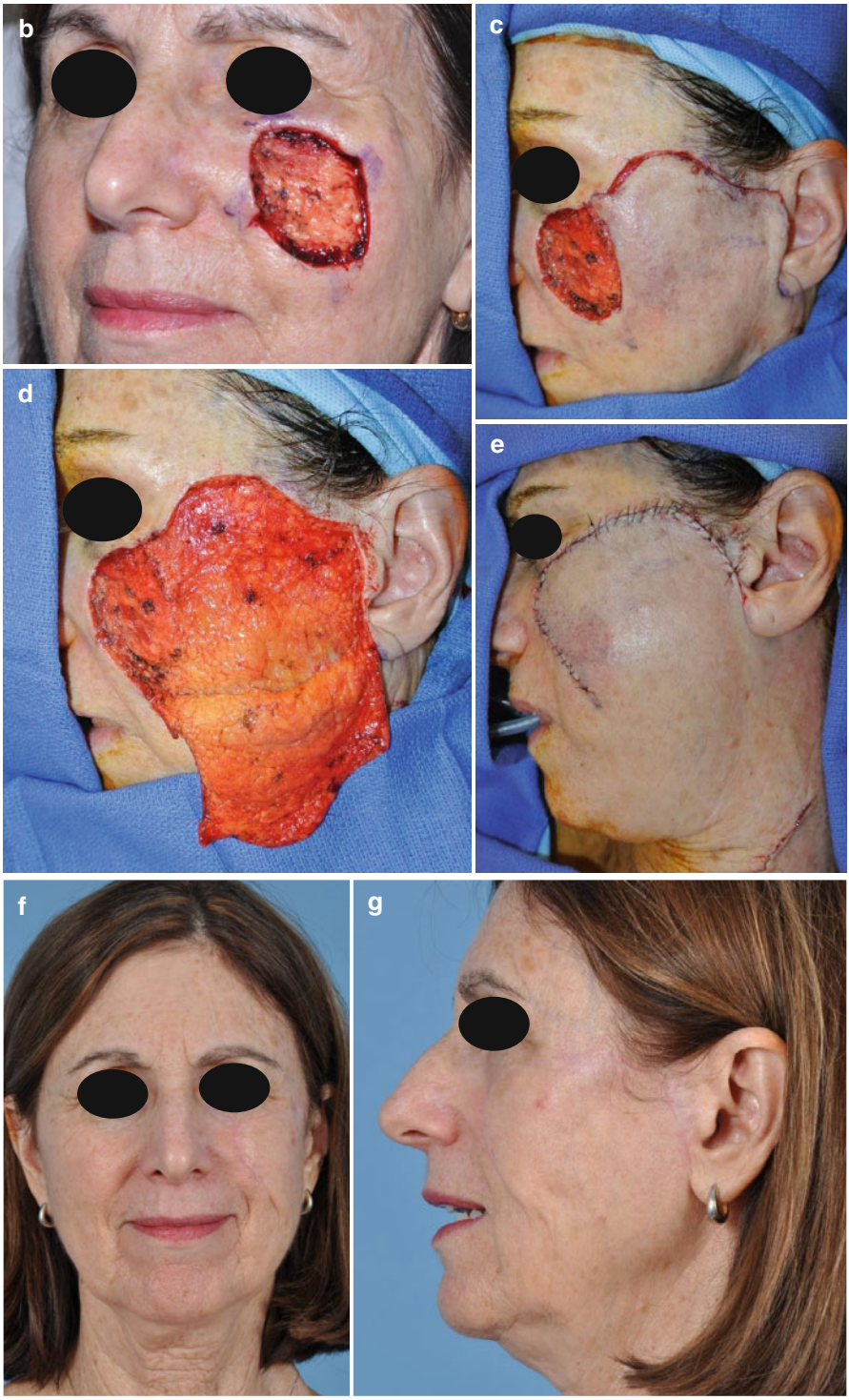

Fig. 10.1 (continued)

of 23 patients that underwent staged excision for melanoma of the lentigo maligna subtype of the head and neck showed that final surgical defect was 2–10 times the original defect lesion size [4]. The patient should understand that not only may the excision be larger than anticipated but that the reconstructive plan may change intra-operatively and that the final result may require revisions to achieve the best result.

Several studies have reported reconstruction techniques that were used following excision of LM/LMM. In the above noted study of 23 patients, 4 defects healed by secondary intention, 3 were closed primarily, 7 required skin grafts, 8 required local flaps, and 1 required a tissue expander with a subsequent flap [4]. In a study of 51 LM/LMM treated with staged excision, 36 % of patients were reconstructed with full thickness skin grafts, 22 % cervicofacial flaps, 14 % rhombic flaps, 12 % nasolabial flaps, 10 % rotation/advancement flaps, 4 % advancement flaps, and 4 % paramedian forehead flaps [5]. Temple and Arlette reported reconstruction techniques used in 166 LM/LMM patients treated with Mohs micrographic surgery. In this group, flaps were used in 59 patients, 48 had primary closures, 37 had skin grafts, 19 had a combination of grafts and flaps, and 3 underwent secondary intention healing [6].

With a mean age of 70 years [7], many patients with LM are elderly and may have multiple medical co-morbidities. Patient history including age, tobacco use, sun exposure, prior surgeries and a history of collagen vascular disease should be noted [8]. Exam should note skin laxity, location of langer's lines, old scars and other nearby pigmented lesions that may need monitoring.

During initial patient evaluation it is important to remember that certain patients may not tolerate larger reconstructions that employ more distant flaps. A thorough discussion of patient expectations for cosmetic outcomes and complexity of the anticipated repair must occur.

A patient with limited life expectancy or co-morbidities that may preclude a longer procedure may not be physically capable or wish to undergo a more complex or multi-stage reconstruction. Although the cosmetic result may be sub-optimal, these patients should be considered for an office-based reconstruction with primary closure when possible, simple skin grafting, small local flaps, or healing by secondary intention [9].

Common Locations of LM

Lentigo maligna most commonly affects the cheek, followed by the nose [3, 10]. The two areas should be approached differently.

The cheek is a broad region extending to the lateral mandibular border. Asymmetries in the lateral region of the cheek are more forgiving than more central areas such as the nose or lips. Defects of the cheek are generally repaired by taking advantage of the laxity of local tissues without strict attention to subunits.

On the other hand, defects of the nose are typically closed with respect to exact subunit borders. Defects following margin-controlled excision techniques can be very broad and irregularly shaped. These defects may involve multiple cosmetic subunits on the face, requiring a combination of reconstructive techniques, as shown in Fig. 10.2a–g.

Fig. 10.2 (**a–g**) Complex upper lip defect requiring two separate advancement flaps

Wound Bed Preparation

After excision, it may be several days before negative margins are confirmed. In the meantime, the wound bed should be kept clean with saline gauze dressings, changed up to three times a day. Once negative surgical margins are histologically confirmed, reconstruction can commence.

The wound bed must be addressed first. It is important to clean the open wound and freshen the edges with a sharp blade, particularly if the reconstruction has been delayed.

Reconstruction

Reconstruction of any defect should be approached using standard principles and the reconstructive ladder.

Secondary Intention

While not often reported as the first choice for closure, in well-selected wounds, secondary intention can be a very useful and aesthetically appropriate method for healing. Particularly in the very elderly with multiple co-morbidities, healing by secondary intention may be the right approach, even in a site that is not cosmetically ideal. With proper selection of wounds, favorable aesthetic outcomes can be achieved following secondary intention healing. Specifically, concave wounds in locations such as the medial canthus, nasoalar sulcus, nasofacial junction, alar groove, temple, concha, and triangular fossa have shown excellent cosmetic results following secondary intention healing [11, 12]. Once the wound has healed and contracted, the residual scar that is much smaller than the initial defect can be serially excised. Figure 10.3a–d depicts the significant contraction demonstrated in a cheek wound that healed by secondary intention and has not yet undergone final reconstruction which will subsequently be a more minor procedure.

Primary Closure

If healing by secondary intention is not reasonable, the next step is to assess how much potential local tissue advancement can be obtained by simply undermining the skin edges without violating any aesthetic subunits.

If a wound can be closed primarily on the cheek this should be done. Primary closure can match skin color, texture and thickness well. On the cheek it is crucial to ensure that a primary closure does not distort free margins such as the lower eyelid, causing ectropion [8].

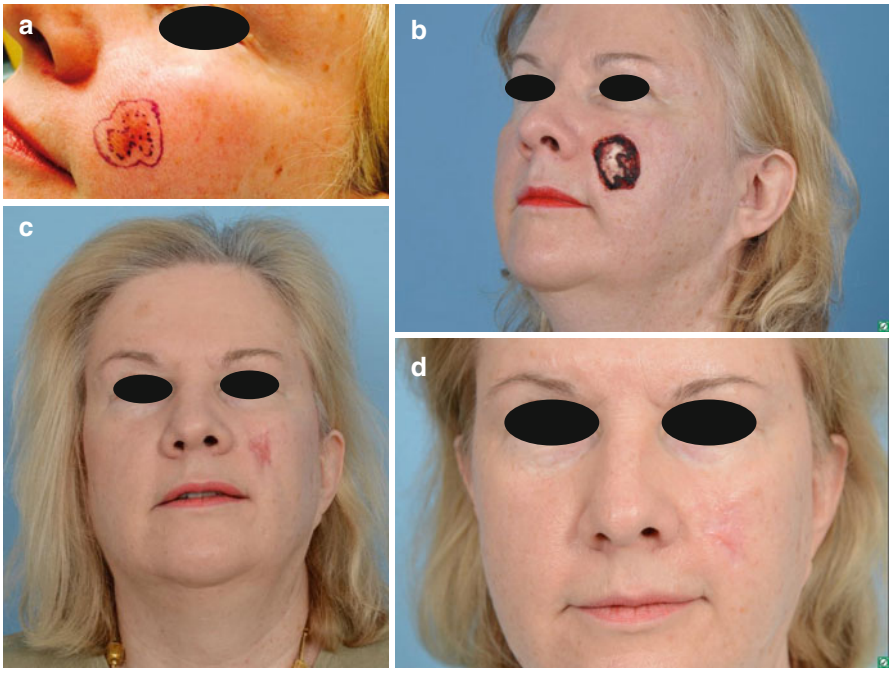

Fig. 10.3 (**a–d**) Medial cheek defect healed by secondary intention

Even if a primary closure can be achieved without free margin distortion, excessive tension on the wound should also be avoided. Undermining the soft tissues can create a fair amount of tissue recruitment especially in older patients with more skin laxity in order to achieve a tension free closure. Double-prong skin hooks should be used to retract the skin while undermining and sharp dissection is encouraged over bovie electro-cautery. Primary closure can be achieved by converting the defect into an ellipse, extending the length of the defect, but simultaneously avoiding dog ears. Another option is to utilize a purse-string closure for a circular defect; while the periphery of the wound may initially appear pleated, this effect resolves over time or could undergo a delayed secondary excision if necessary, working with a much smaller scar [13].

Skin Grafting

Although a skin graft does not always provide an optimal color and texture match, it is often the next best option for patients with significant medical co-morbidities who need stable coverage and cannot tolerate prolonged anesthesia. Skin grafts should not be used when there is exposed bone, nerves or blood vessels in the defect.

For cheek defects, a full thickness skin graft is preferred over a split-thickness graft. A full thickness graft provides a thicker substitute with a better texture match. They contract less over time, which is useful for near the eyelid, nose or oral commissure [8]. Donor sites for the cheek can include the axillary fold, supraclavicular region or pre-auricular region depending on the patient's skin color and quality.

"Pie-crusting" of the graft (creating small holes in the graft for fluid egress) should be minimized for aesthetic reasons however a secure bolster is crucial for graft survival. Bolsters should remain in place for 5–7 days especially given that the cheek is such a mobile area. For defects involving the face, the surgeon should always use a bolster to secure the graft in place, as it is a difficult region that cannot be immobilized.

Local Flaps

A local flap can be appropriate for a moderately sized defect because it replaces "like tissue with like tissue" and therefore can camouflage well with time. All local flaps are designed so that at least one border of the defect becomes one side of the flap. These flaps take advantage of skin laxity adjacent to the defect to achieve closure. In older patients with deep relaxed skin tension lines the incision can be well hidden when properly placed. When approaching the cheek it is crucial to remember key pearls when creating flaps in the three different zones of the cheek, shown in Fig. 10.4.

Zone I, the superior medial region, is amenable to hiding incisions in the nasolabial fold. Zone I often has less laxity than the other two zones. With the eyelid margin as the superior border, advancement of tissue should not be based inferiorly on the cheek to avoid lower eyelid pull and risk of ectropion.

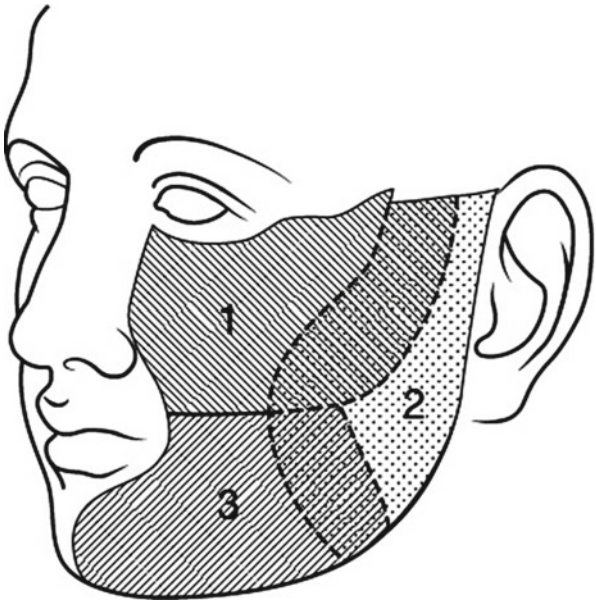

Fig. 10.4 The three zones of the cheek (Copyright ©2016, Memorial Sloan Kettering Cancer Center)

Zone II, the pre auricular region, often has a fair amount of laxity in older patients, however care should be taken not to distort the beard or sideburns. Zone III is lateral to the mouth and extending down to the neck. Flaps in this area should not put any tension on the oral commissure, in this region, redundant tissue may be borrowed from the neck, below the mandibular border [14].

In some areas, simple advancement or small rotational flaps may be superior to more geometric flaps such as a rhomboid or bilobed flaps that can result in scars oriented perpendicular to langer's lines [14]. Strict geometric flaps may cause unsightly scarring in the mid face, and prevent re-advancement of future flaps. An exception to this as mentioned is the V-Y advancement flap which uses the natural lines of the nasolabial folds to camoflauge the scars [15]. These decisions should be made on an individual case by case basis.

Regional Flaps

The cervicofacial flap is the workhorse for larger defects of the cheek, as shown in Fig. 10.5a–d. Historically the deltopectoral flap was used for cheek coverage but this has been replaced by the use of free flap alternatives and if nothing else then

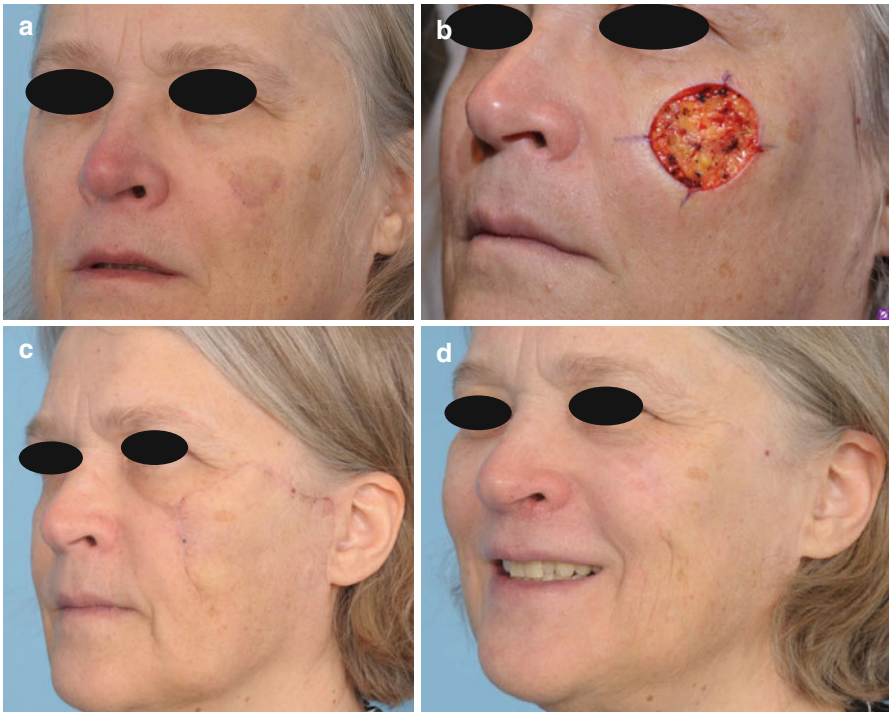

Fig. 10.5 (**a–d**) Cheek defect spanning zone 1 and 2 that was reconstructed with a cervicofacial flap

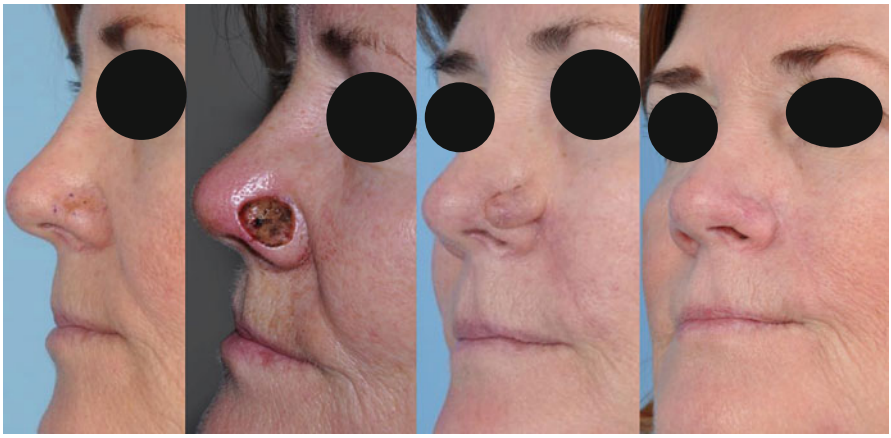

Fig. 10.6 Left alar defect closed with a nasolabial flap that was subsequently divided and thinned

the pectoralis major flap. The cervicofacial flap moves the lateral and inferior neck and cheek skin to cover medial and superior cheek defects and can be designed in a variety of ways. With this flap in particular the surgeon should remember to plan the incision in congruence with the incisions needed for any potential neck dissection. One may consider elevating the cervicofacial flap and then proceeding with the sentinel lymph node biopsy to obviate a second incision [8].

In designing this flap it may sometimes be useful to bring the flap above the lateral canthus of the eye to help avoid ectropion. It is generally recommended to use a subtarsal incision over a subciliary incision to lower the risk of ectropion [14].

If the LM defect is on the nose, local nasolabial or bilobed flaps may occasionally work but LM defects are commonly large enough to require a regional flap such as a forehead flap. Figures 10.6 and 10.7a–e demonstrate these two techniques.

Free Flaps and Perforator Flaps

More complex cheek defects may require free tissue transfer. Hayashi et al. reviewed 26 patients who underwent cheek reconstruction for melanoma. The range of skin defects with local flaps was 6 to 37.5 cm^2, and the range with free flaps was 39 to 121 cm^2. The dividing line between local and free flaps was approximately 40 cm^2. Free flaps were used more frequently in cases with great tumor thickness [16].

The most common free flap for cheek reconstruction is the radial forearm free flap. When stable coverage from a cervicofacial flap is not available either due to lack of tissue, previous surgery or the size of the defect, the radial forearm free flap is the first line choice for reconstruction in an otherwise healthy patient. In a thin patient, the anterolateral thigh fasciocutaneous flap is reasonable although a more bulky back up option to use. Both of these flaps are thin, pliable and well-

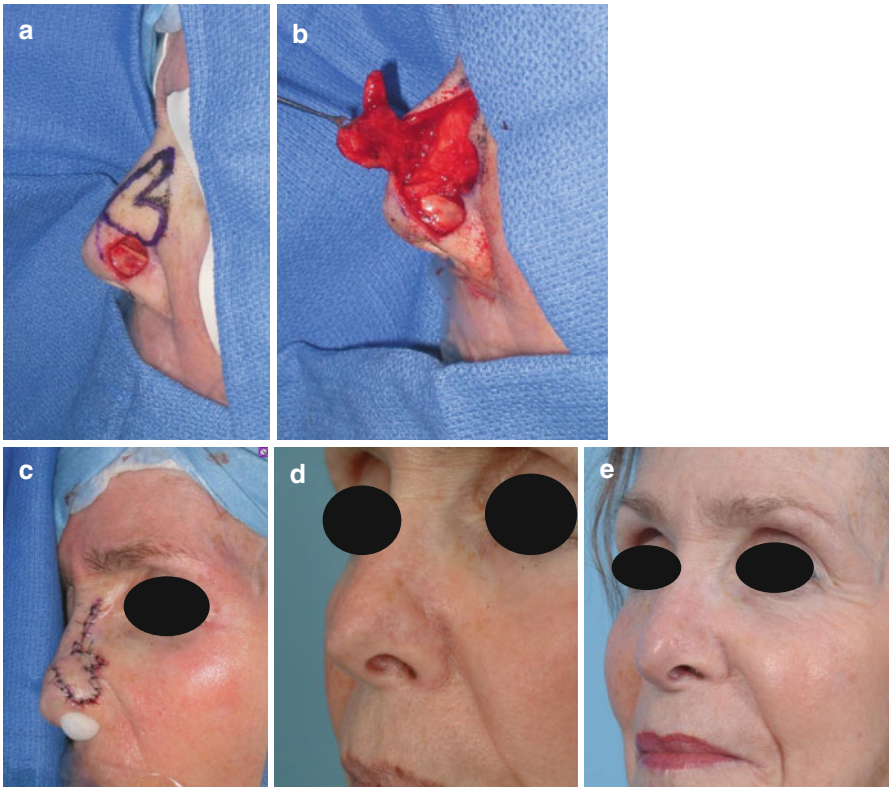

Fig. 10.7 (**a–e**) Left alar defect closed with a bilobed flap

vascularized. The radial forearm flap can also provide intraoral lining for full thickness cheek defects.

Finally, perforator flaps based off of the facial artery have been employed to move skin flaps lateral to the nasolabial fold and oral commissure into moderately sized cheek defects [17]. These flaps may give the flap a larger arc of rotation to be rotated into the given defect compared with a rotational flap [18].

Defects Crossing Subunits

Although lentigo maligna most often occurs on the cheek [19], when the area of resection crosses aesthetic subunits such as the cheek and the lateral wall of the nose then the defect must be approached carefully. To create the most aesthetically optimal result, we advise advancing the cheek tissue medially to the lateral border of the nose, and then reconstructing the lateral wall of the nose separately. The surgeon should consider doing this as a two-stage procedure.

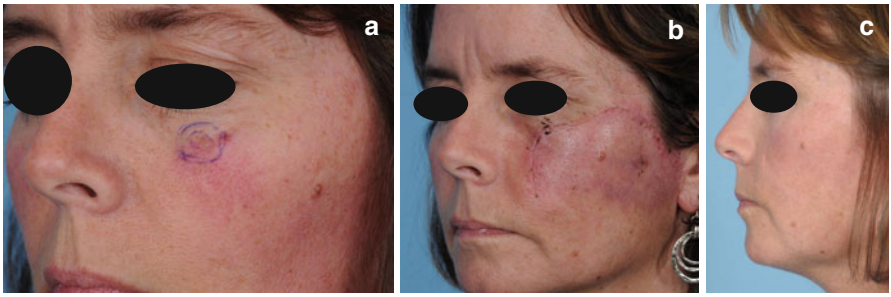

Fig. 10.8 (**a–c**) Improvement in scar contour and color of a cervicofacial flap after laser treatment

Scar Revision

Once the final repair is healed, minor revisions can be made for aesthetic improvement. Fat grafting or injection of dermal fillers can improve minor irregularities in contour, particularly in atrophic scars [20]. Intralesional corticosteroid injections can soften hypertrophic scars and improve scar contour in cases such as pincushioning. Some patients may be candidates for vascular or ablative laser treatments to decrease erythema or further blend incision lines of their scars, as demonstrated in Fig. 10.8a–c. Atrophic scars can also be treated using fractional ablative lasers [21]. Dermabrasion may be used to soften scar lines and contour irregularities with excellent results [22].

Surveillance

Post operatively, follow up should be multidisciplinary and monitoring for recurrence is paramount. If there is serious concern for recurrence based on initial size of the lesion or behavior of the lesion then a skin graft may be the best initial choice for coverage at the expense of aesthetic goals, however the literature is lacking. Hayashi et al found that type of reconstruction had no impact on prognosis and that recurrence rates were instead associated with the severity of the melanoma [16]. Bogle et al. compared rates of recurrence in 39 flap closures after wide local excision of head and neck melanomas with 560 patients who underwent primary closure or skin grafting. They found that flap closure did not appear to delay the detection of local recurrence [23].

Conclusion

In summary the most important tenets of reconstruction are as follows:

- Ensure final margins are negative
- Prepare a clean wound bed prior to flap placement

- Avoid tension in any closure
- Respect aesthetic subunits
- Plan incisions well to avoid burning bridges in the future, in case a recurrence requires flap re-advancement

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Part IV
Nonsurgical Management

Chapter 11
Role of Topical Therapy: Imiquimod

Elise Ng and Vicki Levine

Introduction

Complete surgical excision remains the standard of treatment for lentigo maligna. In certain cases, however, surgery is less reasonable or appropriate due to lesion characteristics or patient factors. Large, ill-defined or non-contiguous lesions in cosmetically or anatomically sensitive areas can be challenging to remove surgically and patient co-morbidities may preclude surgery in select cases. Patients may also decline surgical intervention. In such cases, various alternative modalities have been utilized, including cryotherapy, radiotherapy, laser therapy, and electrodessication and curettage with variable success. Topical therapies include tretinoin, azelaic acid, and 5-fluorouracil, but these have yielded disappointing results and there is limited evidence for their use [1].

Increasing evidence that immune surveillance plays an important role in melanoma pathogenesis spurred interest in the use of topical imiquimod for lentigo maligna. Imiquimod is a synthetic small-molecule that belongs to a family of compounds known as the imidazoquinolones, which modulate the immune system to exert antitumor and antiviral effects. It was the first agent in a new class of immune response modifiers to become commercially available. Topical imiquimod 5 % cream was first approved by the FDA in 1997 for the treatment of genital and perianal warts. It was subsequently developed in 2.5 % and 3.75 %

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_11

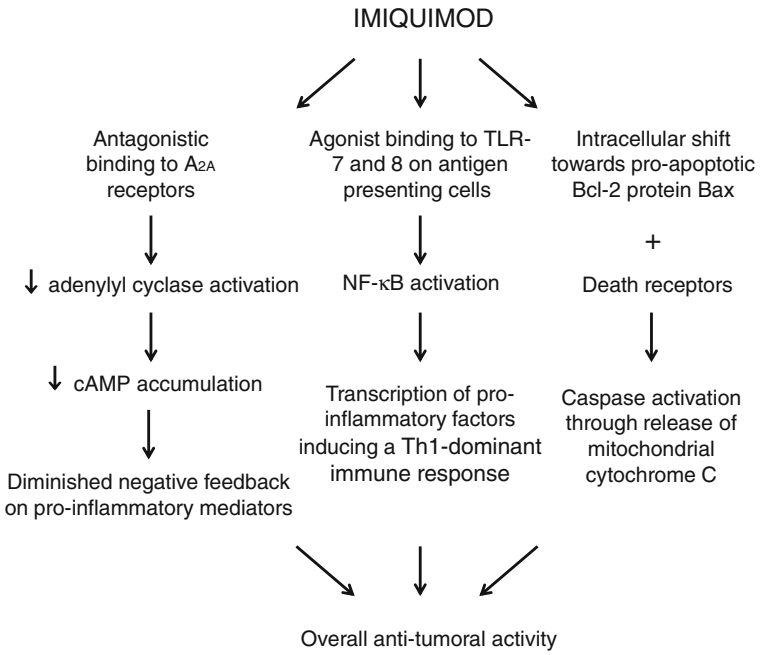

Fig. 11.1 Mechanism of action of imiquimod. Multimodal anti-tumoral activity is achieved via: (1) activation of the NF-kB pathway through TLR-7 and 8 signaling, (2) suppression of negative feedback on inflammatory responses through interaction with the adenosine receptor signaling pathway, and (3) induction of apoptosis through death receptor-dependent and independent mechanisms

concentrations. All strengths are approved for the treatment of actinic keratosis and the 5 % cream is also approved for a subset of superficial basal cell carcinoma. Aside from these indications, imiquimod is also used off-label for other skin malignancies, including nodular basal cell carcinoma, squamous cell carcinoma in situ, and lentigo maligna [2].

Mechanism of Action

Imiquimod acts primarily via binding to toll-like receptor (TLR)-7 and TLR-8 expressed on antigen presenting cells. Agonist activity toward these receptors leads to activation of the transcription factor NF-kB and transcription of pro-inflammatory cytokines and chemokines, including the Th1 cytokines interleukin (IL)-12, interferon (IFN)-a, IFN-g, and TNF-a, among others. These mediators induce a Th1-dominant cellular antitumoral immune response through recruitment of dendritic cells, particularly of the plasmacytoid subset, and other immune cells that drive the stimulation of cytotoxic T cells (Fig. 11.1) [3–7]. This immune response has been

corroborated clinically in lentigo maligna lesions treated with topical imiquimod. Studies characterizing cellular infiltrates during therapy have detected a predominance of CD8+ T cells [3, 8].

In addition to this predominant mode of action, imiquimod has been demonstrated to exert effects independent of TLR-7 and 8 binding. The compound has been shown to inhibit adenylyl cyclase activity, thereby suppressing adenosine receptor signaling pathways. Because these pathways normally inhibit inflammatory reactions, imiquimod augments pro-inflammatory pathways by limiting negative feedback on inflammation. Lastly, imiquimod has also been shown to possess direct pro-apoptotic activity independent of membrane-bound death receptors. Notably, this activity appears to preferentially affect transformed keratinocytes and melanoma cells over their normal counterparts [6, 7, 9].

Efficacy and Recurrence Rates

The first report of using topical imiquimod 5 % cream for the treatment of lentigo maligna was published in 2000. Ahmet et al. successfully treated a large lentigo maligna on the scalp with application of imiquimod over a 7-month period. The use of imiquimod led to gradual clinical clearing of the pigmentation and post-treatment incisional biopsy confirmed the resolution of lentigo maligna. The patient was followed for 9 months without evidence of clinical recurrence, but histopathologic confirmation was not performed [1].

Early case reports and small case series examining the efficacy of topical 5 % imiquimod for lentigo maligna reported clearance rates of up to 100 %, but multiple subsequent larger studies have produced variable results [10–20]. Complete histopathologic response rates have varied from 50 % to 93 %. Comparison between studies has been difficult due to differences in treatment regimen, assessment of outcome, and duration of follow-up. The majority of studies have assessed complete clinical clearance based on targeted biopsies. Among the three studies examining complete post-treatment excision specimens, clearance rates ranged from 53 % to 75 % [10, 11, 13]. A systematic review analyzing data at the individual tumor level calculated overall histologic and clinical clearance rates of 76 % and 78 %, respectively [21, 22].

Recurrence rates have varied from 7.1 % to 50 % with mean follow-up up durations ranging from 6 to 49 months [22]. These rates compare unfavorably to those seen with staged surgical excision and Mohs micrographic surgery, which range from 0 % to 9.7 % and 0 % to 6.25 %, respectively [23]. True recurrence rates with imiquimod may be even higher as the follow-up times in most studies have been shorter than the mean time to recurrence of 3.2 years reported in cases treated with surgery [22, 24]. Limited penetration and consequent incomplete eradiation of malignant cells within adnexa likely account for the higher recurrence rates seen with imiquimod compared to surgical therapy. Prognostic factors that may indicate an increased risk for local recurrence include the total number of melanocytes,

number of basal and suprabasal melanocytes, and number of pagetoid spreading melanocytes in the original biopsy specimen [25].

Clinical Treatment Regimen

No standardized application regimen for the use of imiquimod in lentigo maligna exists, and the optimal treatment regimen remains to be determined. Table 11.1 summarizes published treatment regimens for topical imiquimod 5 % cream for lentigo maligna with more than 20 patients. To date, all studies have employed imiquimod 5 % cream; use of the 2.5 % and 3.75 % concentrations has not been studied. A typical regimen is application for 5–7 days per week for 12 weeks with frequency titrated to inflammation [10, 13–15]. Figure 11.2 illustrates a brisk inflammatory response with topical imiquimod with subsequent clinical resolution of the lentigo maligna lesion. A total of greater than 60 applications or a regimen using greater than 5 applications per week has been found to be associated with a higher likelihood of histologic clearance [21]. One study in which subjects were treated for at least 12 weeks and were required to have clinically visible inflammation for at least 10 weeks found a high and sustained clearance rate. All 24 patients in this study experienced clinical and histologic clearance of lentigo maligna and recurrence occurred in only 1 patient after 39 months of follow-up [12]. Topical tazarotene 0.1 % gel may enhance penetration and response, but the clinical significance of this remains to be confirmed in larger studies [26].

Assessment of Treatment Response

Optimal technique for assessment of treatment response and outcome is uncertain. Clinical exam is not sufficient, as clinical clearance of pigmentation is known to be an unreliable marker for histologic clearance. Significant residual lentigo maligna can persist histologically despite minimal residual clinical pigmentation as depicted in Fig. 11.3a, b [11]. Conversely, post-treatment hyperpigmentation can be postinflammatory in nature and may not be associated with residual disease [4, 15, 27]. Monitoring for therapeutic response is further complicated by the fact that degree of inflammation does not necessarily correlate with degree of response [26]. While the presence of clinical inflammation tends to portend a histopathologic response, cases in which an inflammatory reaction did not lead to histopathologic clearance or those in which histopathologic clearance was achieved despite lack of clinical inflammation have been described [27]. In Fig. 11.3c, minimal inflammation was noted despite 12 weeks of topical imiquimod treatment for a biopsy proven lentigo maligna. As such, histopathologic examination is necessary to confirm clearance after treatment with topical imiquimod.

Table 11.1 Summary of methodology and results from studies of imiquimod 5 % cream for lentigo maligna enrolling more than 20 patients

Study	Type	No. of tumors	Lesion characteristics	Application regimen	Application area	Assessment of clearance	Complete clearance rate	Follow up period	Recurrence rate
Naylor et al. [14]	Prospective	28	Majority head (87 %)	Daily × 12 weeks, rest period if intolerable	Lesion + 2 cm margin	Four 2-mm punch biopsies at week 16	26/28 (93 %)	12 months	0 %
Cotter et al. [10]	Retrospective	40	Majority head/neck (90 %)	5 days/week × 12 weeks; tazarotene 0.1 % gel nightly added if no erythema at 4 weeks (for 10/40 pts)	Lesion + 2 cm margin	Staged excisions with 2-mm margin	30/40 (75 %)	18 months (mean)	0 %
Powell et al. [15]	Retrospective	48	Face	3 days/week × 10 weeks; frequency increased to five times per week if no inflammation at 4 weeks	Lesion + 2 cm margin	One 4-mm punch biopsy at week 12 (multiple biopsies if residual pigmentation)	37/48 (77 %)	48.6 months (mean)	0 %
Ly et al. [13]	Prospective	38	Head and neck	5 days/week × 12 weeks; rest period for excessive inflammation	Lesion + 1 cm margin	Wide local excision by week 16	20/38 (53 %)	N/A	N/A
Alarcon et al. [32]	Prospective	20	Face	5 days/week × 8 weeks; decreased to 3 days/week if excessive inflammation	Lesion + 1 cm margin	Dermoscopy + reflectance confocal microscopy + biopsy at 12 weeks and 12 months after treatment	15/20 (75 %)	34 months (mean)	0 %

(continued)

Table 11.1 (continued)

Study	Type	No. of tumors	Lesion characteristics	Application regimen	Application area	Assessment of clearance	Complete clearance rate	Follow up period	Recurrence rate
Kirtschig et al. [12]	Prospective	24	Face	Daily × 12 weeks titrated to inflammation	Lesion + 1–2 cm margin	Biopsy	24/24 (100 %)	39 months (mean)	4 %
Kai et al. [45]	Retrospective	40	Face	3 days/week × 8 weeks; increased to 5×/week at week 4 if no inflammation		Biopsy at 3 months after treatment	27/40 (68 %)	7.4 months (mean)	0 %

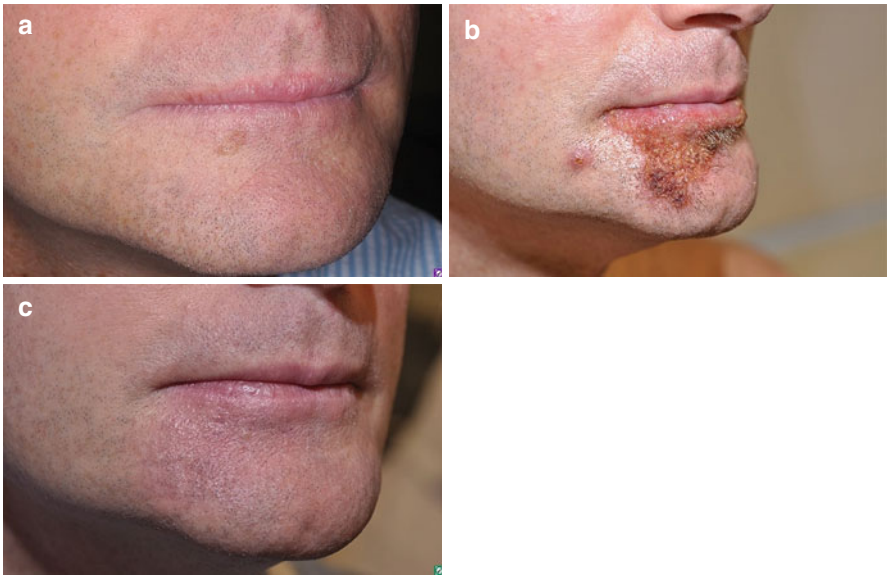

Fig. 11.2 Imiquimod clinical response. (**a**) Biopsy proven lentigo maligna on right chin. (**b**) Brisk inflammatory response after 2 months. (**c**) Clinical resolution of lentigo maligna lesion at 4 months

Clinical Monitoring and Follow-Up

There are no official recommendations regarding the appropriate the number, location, and timing of post-treatment biopsies and if biopsies are even indicated. It has been suggested that post-treatment biopsy should be deferred for at least 3 months after completion of therapy, as findings in those performed too soon after treatment may be obscured by an exuberant interface dermatitis reflecting continued inflammatory activity from treatment effect [15]. However, it is unknown how best to identify the correct site or sites for biopsy in order to avoid sampling error that may miss foci of residual disease and lead to false negative results. Appropriate monitoring for recurrence similarly remains to be established, as long-term follow-up studies are not yet available. Close, regular clinical follow-up with a high index of suspicion for any concerning areas is imperative.

Several modalities for improving selection of biopsy site and detection of residual or recurrent disease have been proposed. The most simple of these is use of the Wood's lamp, which has been shown to be helpful in the delineation of clinical borders of lentigo maligna by enhancing the appearance of pigment in the skin [28]. Dermoscopy and reflectance confocal microscopy, either alone or in conjunction, have also been studied for this use. Four dermoscopic features—(1) asymmetric pigmented follicular openings, (2) dark brown or black rhomboidal structures, (3) slate-grey dots, and (4) slate-grey globules—were initially described as correlating highly with lentigo maligna on the face [29, 30]. A subsequently observed finding of very fine, dust-like brown dots, thought to correspond to pagetoid cells migrating

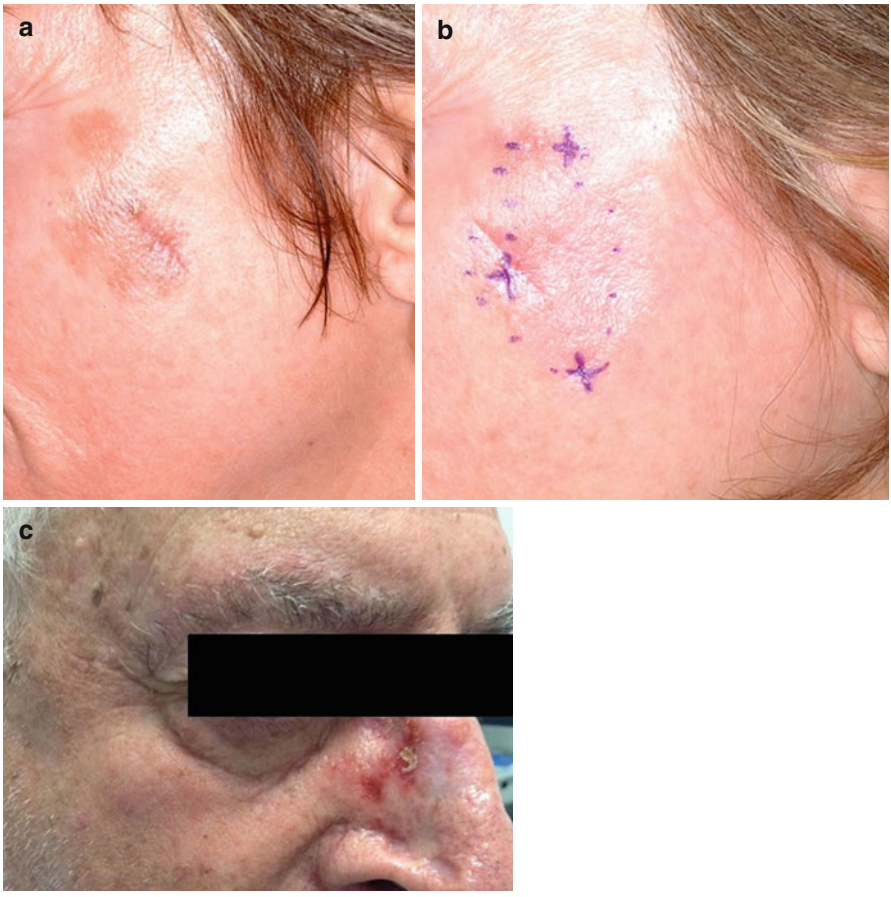

Fig. 11.3 Imiquimod limitations. (**a**) Broad lesion of lentigo maligna prior to treatment with topical imiquimod. (**b**) Clinical resolution of pigmented lesion after 12 weeks of topical imiquimod but persistent lentigo maligna histologically at biopsy sites. (**c**) Minimal inflammation with imiquimod despite 12 weeks of topical treatment

through the epidermis, has also been highly correlated to the presence of lentigo maligna [31]. Reflectance confocal microscopy, which allows for in vivo optical sectioning of the skin to a depth of 200 μm, has demonstrated superiority over dermoscopy for delineation of margins with lentigo maligna. Based on the identification of features comprising a lentigo maligna "score," reflectance confocal microscopy appears to provide greater sensitivity and specificity for detection of recurrent lentigo maligna over dermoscopy [31–35].

Post-treatment assessment and monitoring are crucial because development of invasive disease during or after imiquimod treatment for lentigo maligna has been observed [15, 26, 36]. It is unknown whether imiquimod has the potential to promote invasion. There is evidence that inflammation can paradoxically promote tumor progression through production of matrix metalloproteinases, but this has not

been demonstrated specifically with imiquimod [37]. An alternative possibility is that focal microinvasion was already present in these lesions prior to treatment and subsequent invasion in these cases simply represented disease progression. Indeed, approximately 8.1–16 % of tumors diagnosed as lentigo maligna on initial biopsy will have unsuspected invasion [38–40].

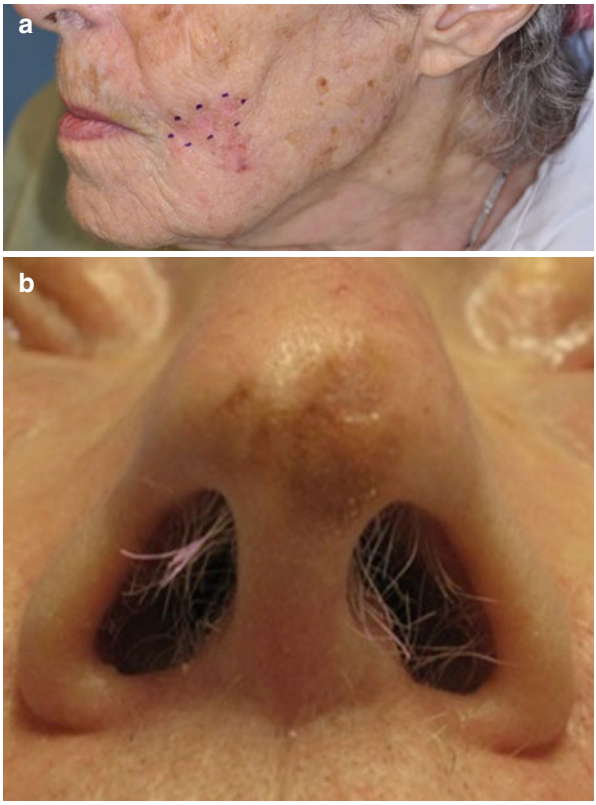

Fig. 11.4 Clinical role of imiquimod. (**a**) Lentigo maligna on left cheek in a 90 year old patient. (**b**) Lentigo maligna on nasal tip in an 85 year old patient

Clinical Role

The role of imiquimod in the treatment of lentigo maligna remains controversial. For primary treatment of lentigo maligna, it is best reserved for cases in which surgery is contraindicated or impractical. Figure 11.4a shows a very poorly defined lentigo maligna in a 90 year old patient where imiquimod offered an alternative to extensive surgical management. Figure 11.4b depicts an 85 year old patient with multiple medical comorbidities who declined extensive surgery and complex nasal reconstruction.

There is debate regarding its use for adjuvant treatment. Some advocate initial surgical removal followed by topical imiquimod to eradicate any residual atypical junctional melanocytic hyperplasia at the periphery of the original lesion [26]. However, the only study to examine the use of topical imiquimod after surgical resection of lentigo maligna or lentigo maligna melanoma found that 2 of 11 patients with narrowly excised lentigo maligna melanoma developed metastasis during the course of imiquimod treatment. Three of twenty-five patients with residual increased atypical junctional melanocytes at the margin developed metastasis during treatment [27].

Others have suggested that imiquimod prior to surgery may be useful for decreasing the size of a lesion or the necessary margin for complete clearance. This is based on the finding that some patients appear to exhibit a partial response to imiquimod with decrease in total lesion size despite residual disease [15]. However, some have raised concerns that the lentigo maligna lesion may not shrink concentrically, resulting in skip areas that can be missed in the subsequent surgical resection. For primary or adjuvant treatment, imiquimod should not be used in lesions with evidence of invasion, as lentigo maligna melanoma carries a risk of metastasis even after complete surgical resection [27]. Caution is also advised for the treatment of amelanotic melanoma given the inherent difficulty with clinical assessment and at least one report of failed use [41].

Advantages and Disadvantages

The advantages of imiquimod include superior cosmetic result and avoidance of morbidity from cosmetically disfiguring surgery or long-term effects of radiotherapy such as radiation dermatitis. Topical imiquimod also allows for the treatment of surrounding clinically normal appearing skin that may harbor atypical melanocytes. The major disadvantage is the lack of full histopathologic margin evaluation. There is also the potential for inaccurate post-treatment or surveillance assessment due to biopsy sampling error. Finally, long-term rates of relapse and progression to invasive disease have not yet been determined and it remains unknown whether imiquimod is superior to radiotherapy, which has been established as an efficacious non-surgical treatment modality for lentigo maligna [4, 22].

Imiquimod is generally well tolerated and adverse effects are typically limited to local skin reactions, including erythema, pruritus, pain, burning, vesicles, erosions, and crusting. These are dose dependent and usually subside following periods of rest. Persistent post-inflammatory pigmentary changes may also occasionally occur. Additional risks specific to use in the periocular area include conjunctivitis and keratitis. While there has been concern for increased susceptibility to ultraviolet radiation with the use of imiquimod, studies have failed to show any potential for inducing photocontact allergy or phototoxicity. Systemic side effects are rare and include flu-like symptoms related to production of pro-inflammatory cytokines such as fever, headache, myalgia, fatigue, nausea, and diarrhea [2, 42, 43].

Summary

The use of topical imiquimod for the treatment of lentigo maligna remains under investigation. High quality evidence is lacking and no prospective, randomized studies directly comparing imiquimod to other therapies have been performed [44]. Imiquimod should be used with caution in select patients with unresectable disease, and surgical excision should be pursued whenever possible. Close follow-up is essential, but guidelines for appropriate assessment of response and strategies for monitoring recurrence remain to be established.

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Chapter 12
Role of Radiation

Christopher A. Barker

Introduction

Lentigo maligna (LM) and lentigo maligna melanoma (LMM) often occur as large pigmented lesions on the face, scalp and neck of elderly individuals. For this reason, non-surgical treatments are considered to minimize the morbidity of treatment by preserving tissue, which in turn may prevent compromise of function and cosmesis. Radiation therapy is a non-surgical treatment which may be appropriate in some patients to accomplish these goals. In some instances, radiation therapy may be the preferred treatment because surgery is not possible, or incompletely removes the LM or LMM.

The use of radiation therapy for LM and LMM is not a new concept. Radiation therapy was first reported for LM in 1931 by an American physician [1], but its use has been limited in the United States because of poor outcomes in a small case series [2–4]. In contrast, investigators throughout Europe have reported on large series of patients [5] treated with very superficial forms of radiation therapy developed by Miescher [6]. Over several decades a body of medical literature has emerged generally demonstrating outcomes with radiotherapy comparable to those observed with surgery [4, 7–10]. Herein, the biologic basis, advantages, disadvantages, technique, patient selection, and outcomes of radiotherapy for LM and LMM will be discussed.

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_12

Biologic Basis of Radiation Therapy

Ionizing radiation therapy can be used to treat a variety of cutaneous neoplasms. The primary biologic effect of ionizing radiation is deoxyribonucleic acid (DNA) damage. Damage of DNA by radiation leads to cell injury and death, and in turn produces clinically evident phenomena such as tissue inflammation and necrosis. Secondary immunologic effects of radiotherapy are likely a component of the biologic response, although the specific sequence and components of the immunologic response to irradiated LM and LMM remain ill-defined. The general clinical effects of radiation therapy depend on the specific cells, tissues and organs that absorb radiation, and the amount of radiation they absorb. These parameters are associated with the quality of the radiation therapy delivered (Grenz rays, superficial x-rays, electrons, etc), as discussed further below in "Treatment techniques".

As the biologic effects of radiation are strongly correlated with the absorbed dose of radiation, a discussion of how this has been expressed over the last century is worthwhile. Radiation dose is now expressed in units of gray (Gy, equivalent to 1 J of energy per kilogram of mass). Older studies expressed radiation dosage as "radiation absorbed dose" (rad or r, equivalent to 100 cGy), or in units of ionization in air, or roentgen (R, equivalent to 2.48×10^{-4} C of electric charge per kilogram of mass). Of note, these dose units all reflect physical dose and the heterogeneity in the clinical response to radiation can be significant. Prior to having equipment to measure physical dose, clinicians used "erythema dose" to indicate the amount of radiation that was absorbed. While biologically interesting, this parameter is too inconsistent and subjective to be useful when administering radiotherapy.

In clinical radiotherapy, the total dose of radiation that is required to produce elimination of a neoplasm is often divided in to a series of smaller doses, a process called fractionation. The rationale for fractionating radiotherapy is that normal cells and tissues are thought to be better able to repair the damage from radiotherapy than dysfunctional and genomically unstable cancer cells. By giving fractionated radiotherapy over several weeks, normal cells and tissues can repair radiation injury while cancer cells accumulate injury, and are ultimately eliminated. The balance of limiting normal tissue injury while producing disease control is often referred to as a therapeutic ratio. Mathematical equations have been devised to determine equivalent doses and compare schedules of radiotherapy, with the contemporary method in widespread use based on a linear-quadratic equation.

Treatment Techniques

The two predominant forms of radiotherapy for LM and LMM are *teletherapy* and *brachytherapy*. Teletherapy refers to the projection of radiation through space as a beam, while brachytherapy refers to the placement of a radiation source directly inside or adjacent to the target for treatment. Teletherapy is the predominant mode

Table 12.1 Radiation qualities used for treatment of lentigo maligna and lentigo maligna melanoma

Radiation quality	Energy (kV)	D50[a] (mm)
Grenz rays (ultrasoft, supersoft, Bucky therapy)	10–20	0.2–1.0
Soft x-ray	20–100	1–20
Superficial x-ray (low voltage x-ray therapy)	60–150	7–10
Orthovoltage therapy (deep x-ray therapy, conventional x-ray therapy)	150–400	50–80
Megavoltage therapy (betatron, particle, linear accelerators)	>1000	10–200

kV kilovolt

[a]D50 refers to the depth from the skin surface at which 50 % of the total radiation is absorbed

of treatment for LM and LMM, with wide range treatment units available to produce a variety of radiation qualities (see Table 12.1). While some have suggested that the quality of radiotherapy is important for determining outcomes, an abundance of outcomes based studies have characterized good results with different qualities of radiotherapy, as discussed further below in "Outcomes".

The original reports of Miescher and the subsequent reports using his technique involved very low energy x-ray teletherapy (10–20 kV, also known as Grenz rays). With Grenz ray therapy, the majority of the radiation dose is absorbed in the most superficial millimeter of skin, with little to no radiation absorbed beyond 2 mm. Soft or superficial x-rays (20–150 kV) are absorbed over 1–20 mm of skin and subcutaneous tissues. An example of this is presented in Fig. 12.1. Even higher energy x-rays (orthovoltage, 150–400 kV) deposit the majority of radiation dose over 50–80 mm of skin and subcutaneous tissues. The aforementioned forms of radiation are preferable for neoplasms originating in the skin, but they are not widely available because most radiation oncology departments use linear accelerators to produce megavoltage electrons and photons which intentionally spare the skin surface. Through specific manipulations, megavoltage electron radiation can deliver radiation to the skin surface, and unlike x-rays have an advantage of delivering radiation to a limited, finite range of skin and subcutaneous tissue, ranging from 10 to 200 mm deep to the skin surface. Examples of this are presented in Figs. 12.2 and 12.3.

Brachytherapy has been less often used and reported on, but should not be overlooked as a valuable component of the radiotherapeutic armamentarium for LM and LMM. The primary advantage of brachytherapy is the ability of this modality to conform to irregular skin surfaces (i.e., those that are not relatively flat), and deliver a uniform and homogenous dose of radiation across the area. A notable example of this is a case of extensive, unresectable LMM affecting the entire scalp of a patient. As the curved, large surface of the scalp could not be adequately targeted with a superficial teletherapy technique, investigators performed skin surface brachytherapy using catheters afterloaded with Ir-192, with a satisfactory result [11]. Other investigators used interstitial brachytherapy to treat 3 patients with LMM that were deemed inappropriate for surgery. With a median follow-up of 4 years, these patients had good control of the LMM, with no significant side effects [12]. Brachytherapy has not enjoyed a significant amount of

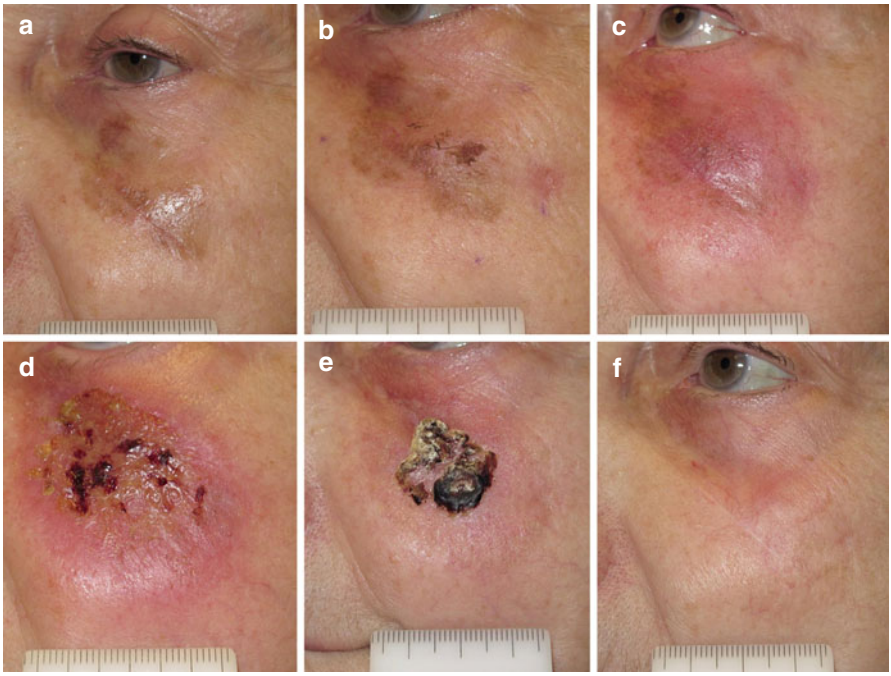

Fig. 12.1 Definitive radiation therapy for lentigo maligna of the left cheek with soft/superficial x-rays to a total dose of 57.5 Gy in 23 fractions of 2.5 Gy. (**a**) before treatment; (**b**) during first week of treatment; (**c**) last day of treatment; (**d**) 2 weeks after completion; (**e**) 4 weeks after completion; (**f**) 12 weeks after completion

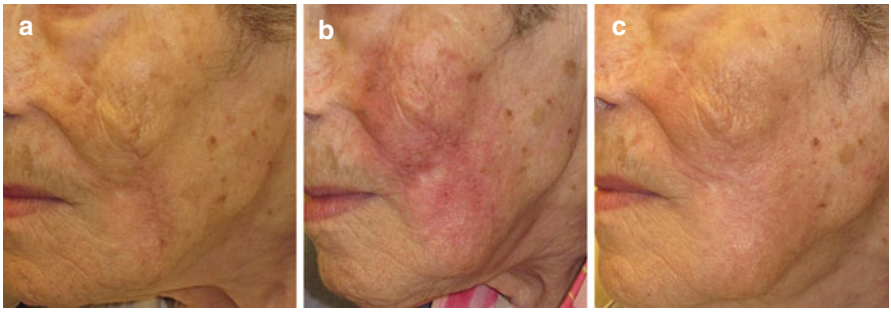

Fig. 12.2 Adjuvant radiation therapy for lentigo maligna melanoma of the left cheek with megavoltage electrons to a total dose of 32 Gy in 4 fractions of 8 Gy after excision of microinvasive component. (**a**) before treatment; (**b**) last day of treatment; (**c**) 6 months after completion

usage in the treatment of LM and LMM, probably owing to the technical demands and resources required to perform this successfully. Moreover, custom skin surface brachytherapy techniques generally require access to radioisotopes, which are generally not at the disposal of dermatologists who collectively treat the vast majority of patients with LM and LMM.

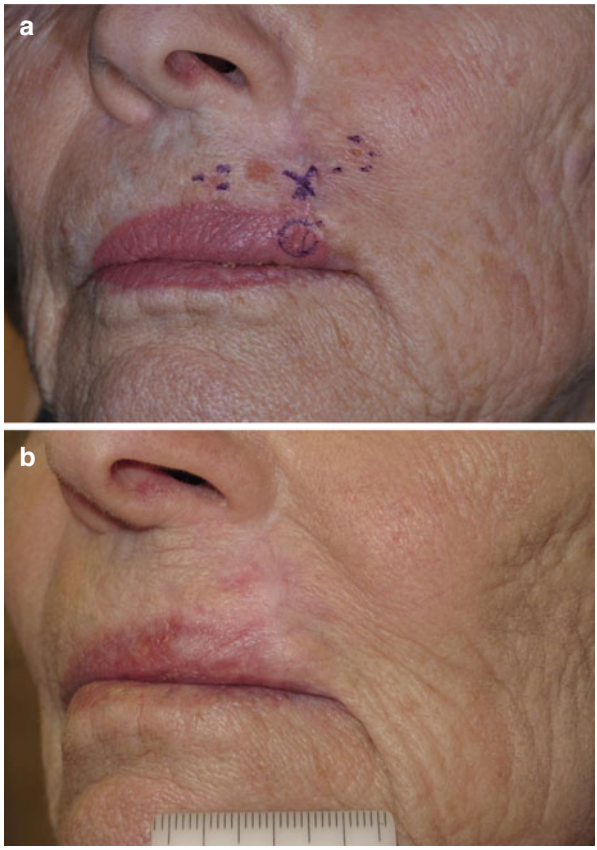

Fig. 12.3 Definitive radiation therapy for *recurrent* lentigo maligna of the left upper lip with megavoltage electrons to a total dose of 57.5 Gy in 23 fractions of 2.5 Gy after prior surgical excision. (**a**) before treatment; (**b**) 3 years after completion

Regardless of the specific treatment technique used, defining the target for radiotherapy is paramount to successful treatment. The grossly evident "tumor" or gross tumor volume, (GTV) is typically delineated as the pigmented lesion on the skin surface. In some instances, there is sharp demarcation between the pigmented lesion and the surrounding normal tissue, but this is not always the case. Adjunctive imaging techniques may help identify the target and include Wood's lamp (ultraviolet light) which requires visualization in a dark room [13]. Conventional radiographic imaging (CT, MRI, PET) is unlikely to be informative given the superficial nature of LM and LMM, but other modalities such as reflectance confocal microscopy, high frequency ultrasonography and optical coherence tomography may be valuable [14]. Once the GTV has been identified and marked on the skin surface, one must determine the subclinical extent of disease, often referred to as the clinical target volume (CTV). A study of 1,120 patients with LM excised using variable margins indicated that 6–9 mm of normal appearing skin radially around the GTV, will yield a negative margin in 86–99 % of cases [15]. Extrapolation of this suggests that a CTV of 6–9 mm radial margin is appropriate. While the depth of invasion of LM and LMM is expected to be limited, however, perifollicular extension is common, and some have reported this extending to 3–5 mm from the surface of the epidermis. Finally, to

account for movement, setup uncertainty, and other factors, a planning target volume (PTV) must be generated, which will depend on the specific parameters of the treatment setup. Once the PTV has been created, determination of the appropriate radiation application parameters (including shielding) is carried out. Taking all of this into account, investigators have employed margins of 5–20 mm from the edge of the pigmented skin lesion to the edge of the treatment field, although the specific parameters of the treatment technique will ultimately dictate the margin width necessary.

Advantages and Disadvantages

The primary advantage of radiotherapy for LM and LMM is that cutaneous and subcutaneous tissue is preserved during treatment. In some instances, tissue preservation is an important goal in order to maintain form and function. For example, resection of LM or LMM on or near the eyelid could lead to tissue defects compromising the ability to close the eyelid, and this can result in secondary ophthalmic complications. Likewise, a large scar or graft from reconstruction on the face may be cosmetically unacceptable to some patients.

The primary disadvantage of radiotherapy for LM and LMM is that there are no pathologic assurances of the extent of disease (depth of invasion), or whether the LM or LMM was completely eradicated during treatment. The presence of invasive melanoma, and the depth of invasion, is a primary prognostic determinant to estimating the probability of metastasis and death from melanoma. These cannot be fully assessed through partial sampling of LM and LMM, and therefore introduce uncertainty into the anticipated natural history of the disease. Furthermore, after treatment of LM and LMM with radiotherapy, one cannot be assured about the presence of residual and viable melanoma cells until recurrence occurs. This uncertainty may prove vexing for both the clinician and the patient.

Patient Selection

Guidelines on the use of radiotherapy for LM and LMM from around the world have been published, with relatively consistent themes. Generally, they support the use of radiotherapy in situations when surgery is contraindicated, or when surgery does not remove all of the LM or LMM. The National Comprehensive Cancer Network indicates, “For selected patients with positive margins after optimal surgery, consider topical imiquimod (for patients with melanoma in situ) or RT [radiation therapy],” and that “Imiquimod and/or RT [radiation therapy] can be considered as non-standard options in highly selected cases” [16]. In the United Kingdom, it has been noted that “for some particular clinical situations, treatment by other methods such as radiotherapy, or observation only, may be appropriate” [17]. Guidelines from Brazil indicate that radiation is “justified in cases where surgery can cause

great aesthetic/functional damage or in patients unable to undergo surgery" [18]. In China, "if a histologically negative margin cannot be achieved by surgery alone, local application of imiquimod or radiotherapy may be considered (Category 2B)." [19]. The Spanish Society for Medical Oncology considers radiation therapy "in case of inadequate resection margin of lentigo maligna" [20]. The European Society of Medical Oncology also indicated that "radiotherapy for local tumor control should be considered in cases of inadequate resection margins of lentigo maligna melanoma" [21]. The German Dermatological Society indicates that "in lentigo maligna melanomas not suitable for surgical therapy due to size, location, and/or age of the patient, primary radiotherapy should be employed. Good tumor control rates can be achieved with this." [22]. Finally, the American Academy of Dermatology indicated that "Primary radiation therapy for lentigo maligna with or without prior excision of nodular component of lentigo maligna melanoma may be considered when complete surgical excision is not a realistic option" [23].

Radiotherapy with curative intent may be considered in two general circumstances. The first as the sole or *definitive* therapy used for treatment of LM or LMM. This may be prior to any other treatment, as upfront therapy, or after another modality has failed, as a salvage therapy. The alternative to *definitive* radiotherapy is *adjuvant* radiotherapy. This type of treatment is used to reduce the risk of recurrence after an alternative treatment has been used as the definitive therapy, typically surgery. Radiotherapy may be selected as an adjuvant to surgery in case of positive margins, or when the risk of recurrence is estimated to be high. Radiotherapy can also be used with palliative intent, although this situation would be unusual in LM and LMM.

There are few absolute contraindications to radiotherapy for LM and LMM. Patients with active collagen vascular or autoimmune disease including skin manifestations, or with genetic syndromes rendering hypersensitive to radiotherapy are probably not ideal candidates for radiotherapy. Typically skin radiotherapy is reserved for older patients, because of the risks of late side effects. Prior radiotherapy to the area of LM and LMM is also a relative contraindication, given concerns about cumulative toxicity of radiotherapy, although a number of studies have reported good outcomes after reirradiation for recurrent LM and LMM at the edge of prior radiotherapy fields. In the past, radiation was used to treat non-malignant skin conditions such as acne; however this practice is no longer continued presently. Prior radiotherapy for non-malignant skin conditions which are presumed to entail a low dose of radiation, are not necessarily a contraindication for radiotherapy.

Outcomes

Definitive Therapy

As noted in Table 12.2, a broad range of outcomes of definitive radiotherapy have been reported from around the world over the last seven decades [4, 5, 7–10, 12, 24–31]. These data suggest local recurrence occurs after radiotherapy for LM and

Table 12.2 Studies of definitive radiation therapy for lentigo maligna and lentigo maligna melanoma

Study author	Study period	Diagnosis, patients (n =)	Recurrence, local (n =, [crude rate])	Recurrence, nodal (n =, [crude rate])	Recurrence, distant (n =, [crude rate])	Follow-up (years)	Radiation quality
Arma-Szlachcic	1941–1965	LM, 61	2 [3.3 %]	0 [0 %]	0 [0 %]	Most ≥5	Grenz
		LMM, 18	0 [0 %]	5 [27.8 %]	NR	Most ≥5	Soft/Superficial
Panizzon	1941–1988	LM, 129	2 [1.6 %]	0 [0 %]	0 [0 %]	Mean 9.3	Grenz
		LMM, 27	2 [7.4 %]	0 [0 %]	0 [0 %]	Mean 9.3	Soft
Farshad	1950–2000	LM, 93	5 [5.4 %]	0 [0 %]	0 [0 %]	Mean 8	Grenz
		LMM, 54	0 [0 %]	2 [3.7 %]	0 [0 %]	Mean 8	Soft
Braun-Falco	1955–1970	LM, 68	0 [0 %]	0 [0 %]	0 [0 %]	Mean 3	Grenz
De Groot	1958–1968	LM, 21	1 [4.8 %]	0 [0 %]	0 [0 %]	Median 3	Grenz
Pitman	1955–1977	LM, 8	3 [37.5 %]	0 [0 %]	0 [0 %]	Median 3.5	Grenz
		LMM, 5	4 [80 %]	2 [40 %]	0 [0 %]	Median 5	Grenz
Harwood	1958–1982	LM, 23	2 [8.7 %]	0 [0 %]	0 [0 %]	Median 2.2	Superficial
		LMM, 28	2 [7.1 %]	1 [3.6 %]	1 [3.6 %]	Median 2	Superficial/Orthovoltage
Tsang	1968–1988	LM, 36	4 [11.1 %]	0 [0 %]	0 [0 %]	Median 6	Soft/Superficial
Campolini	1987–1992	LM, 7	0 [0 %]	0 [0 %]	0 [0 %]	Mean 1.5	Soft
		LMM, 6	0 [0 %]	0 [0 %]	0 [0 %]	Mean 1.5	Soft
Schmid-Wendtner	1987–1998	LM, 42	0 [0 %]	0 [0 %]	0 [0 %]	Median 1.3	Grenz
		LMM, 22	2 [11.1 %]	0 [0 %]	0 [0 %]	Median 1.3	Grenz
Christie	1979–1995	LM, 7	0 [0 %]	0 [0 %]	0 [0 %]	Median 1.3	Soft/Superficial
Mortier	1995–1998	LMM, 3	0 [0 %]	0 [0 %]	0 [0 %]	Median 4	Brachytherapy
Zalaudek	1990–2000	LM, 15	2 [13.3 %]	0 [0 %]	0 [0 %]	Not reported	Grenz
Hedblad	1990–2009	LM, 188	27 [14.4 %]	0 [0 %]	0 [0 %]	Median 2–3	Grenz
		LMM, 162	33 [20.4 %]	0 [0 %]	1 [0.3 %]	Median 2–3	Grenz
Lee	1991–2010	LM, 31	9 [29 %]	0 [0 %]	0 [0 %]	Median 3.9	Soft/Superficial
Pooled estimates		LM, 729	57 [7.8 %]	1 [0.1 %]	3 [0.4 %]		
		LMM, 325	43 [13.2 %]	10 [3.1 %]	4 [1.2 %]		
		LM & LMM, 1054	100 [9.5 %]	11 [1.0 %]	7 [0.7 %]		

LM lentigo maligna, *LMM* lentigo maligna melanoma

LMM in about 10 % of patients, with regional and distant metastatic recurrence occurring in 1 %. A limitation of these data is the limited follow-up, which ranges from a median of 1.3–9.3 years. This is likely a reflection of the elderly patient population preferentially selected for radiotherapy, and the limited ability of these patients to follow-up over the long term [8]. Several other trends in the published literature are noteworthy.

The technique used for the treatment of LM and LMM has varied, and appears to be correlated with clinical specialist rendering treatment (dermatologist vs radiation oncologist). In Europe, the use of high dose (60–120 Gy), minimally penetrating radiation (Grenz rays) given once or twice a week in 6–12 fractions has predominated amongst dermatologists for LM. When treating LMM, some of these groups have used soft radiation and used lower total doses of radiation. Primarily in Canada and Australia, the use of soft, superficial and orthovoltage radiation has predominated amongst radiation oncologists. Generally, radiation oncologists have used lower doses of radiation that penetrates the skin to a greater depth. The differences in technique have likely been driven by the resources available to the practitioners in these areas. Notably, there appears to be no major difference in outcome based on the therapeutic technique used.

Not surprisingly, the risk of local, regional/nodal, and distant/metastatic recurrence appears to be higher after treatment of LMM (compared to LM). Moreover, recurrence after radiotherapy for LM may be related to incomplete pathologic assessment of these tumors, based on a partial sampling prior to treatment. For this reason, comparison of outcomes in patients with LM who underwent complete excision and pathologic staging is problematic.

The poor outcomes reported by the New York University group in 3 reports between 1972 and 1979 deserve special mention, as these outcomes deviate significantly from the observations of other groups, and have significantly influenced practice in the United States [2–4]. The reason for these outcomes are not entirely clear, but are likely related to several factors. First, the investigators indicate their Grenz ray machine required recalibration, resulting in an overestimation in the depth of penetration of the radiation by 80 %. This technical factor could have resulted in underdosing of the LM and LMM and contributed to the relatively high rate of failure [3]. Second, the investigators appeared to reserve radiotherapy for patients with previously treated, recurrent LM and LMM, such as the patient presented in Fig. 12.3. The presence of scar tissue from prior treatments likely increased the depth of the LM and LMM, which was not accounted for in the investigators treatment technique, which used very superficially penetrating Grenz rays. In addition, evolution from melanoma in situ to invasive melanoma after recurrence, before radiotherapy has been suggested as the reason for these poor outcomes [32]. Finally, authors reported on 16 patients with “melanotic freckle” in 1976, but in their final report on the topic in 1979, only describe outcomes of 9 patients. Ultimately, these three reports of small numbers of patients (total of n = 16 or less), should probably not be overemphasized among a body of literature reporting on over 1000 patients (Table 12.2).

Adjuvant Therapy

Two studies have reported on the outcomes of adjuvant radiotherapy after surgical excisions have been reported. Interpreting these data are somewhat challenging, because the indication for radiotherapy was not always specified in the analyses, there are no randomized comparative analyses of surgical excision with or without adjuvant radiotherapy. Moreover, the natural history of incompletely resected LM or LMM, or LM or LMM at high risk for recurrence after complete excision is not well-known.

Investigators from Germany reported on a group of 22 patients with LMM treated with excision of the nodular component of the LMM, followed by adjuvant radiotherapy to a dose of 100 Gy in 10 fraction using Grenz rays. Local recurrence was reported in 2 patients (10 %) and distant metastatic recurrence occurred in 1 patient. No comparison to patients treated by excision alone was performed [30].

More recently, investigators from Sweden reported on adjuvant radiotherapy within 6 weeks of patients undergoing partial, or complete/margin negative excision of LM or LMM. Adjuvant radiation was delivered using Grenz rays to a dose of up to 160 Gy in fractions of 10–20 Gy, 2–5 times/week. Of 71 patients undergoing partial excision and adjuvant radiation, 7 recurred (9.8 %), while of 172 undergoing complete margin negative excision and adjuvant radiation, 6 (3.5 %) recurred. This was compared to a group of patients undergoing radiotherapy alone, with similar doses of radiation. Among 350 patients treated with radiotherapy alone, 60 (17.1 %) experienced local recurrence. A limitation of the study is that the criteria for patients undergoing excision (vs radiotherapy alone) was not described, and therefore the outcomes are likely confounded by selection bias. Ultimately, the authors recommended partial or complete excision for LMM with adnexal extension deeper than 0.8 mm [5]. An example of this is depicted in Fig. 12.2.

Comparative Analyses

Several studies have attempted to compare outcomes of patients treated with various therapeutic modalities, in a retrospective fashion [4, 7–10]. As noted in Table 12.3, these studies have yielded disparate results, with some suggesting superiority, and others reporting equivalence of treatments. Importantly, the first prospective randomized study of non-surgical therapy (imiquimod vs. radiotherapy) for LM and LMM has been initiated, with results expected in several years (NCT02394132).

While radiotherapy is thought to be a less effective treatment modality than surgery, no head-to-head prospective comparisons of surgery and radiotherapy for LM and LMM have ever been carried out. As noted in Table 12.3, several retrospective studies suggest numerically higher rates of local recurrence after radiotherapy, compared to surgery, but none were statistically significant differences [4, 8–10]. On the contrary, one report demonstrated higher rates of recurrence after excision, compared

Table 12.3 Studies comparing radiation therapy to other treatment modalities for lentigo maligna and lentigo maligna melanoma

Study author	Study period	Treatment modality	Diagnosis, patients (n=)	Recurrence, local (n=, [crude rate])	Recurrence, nodal (n=, [crude rate])	Recurrence, distant (n=, [crude rate])	Follow-up (years)
Panizzon	1941–1988	RT	LM, 129	2 [1.6 %]	0 [0 %]	0 [0 %]	Mean 9.3
		RT	LMM, 27	2 [7.4 %]	0 [0 %]	0 [0 %]	Mean 9.3
	1967–1986	Surgery	LM, 13	2 [15.4 %]	0 [0 %]	0 [0 %]	Mean 7.8
		Surgery	LMM, 45	7 [15.6 %]	0 [0 %]	0 [0 %]	Mean 7.8
Pitman	1955–1977	RT	LM, 8	3 [38 %]	0 [0 %]	0 [0 %]	Mean 3.2
		EDC	LM, 8	2 [25 %]	0 [0 %]	0 [0 %]	Mean 3.2
		Cryotherapy	LM, 4	2 [50 %]	0 [0 %]	0 [0 %]	Mean 3.2
		Surgery	LM, 22	2 [11 %]	0 [0 %]	0 [0 %]	Mean 3.2
		RT, EDC, and/or Cryotherapy	LMM, 5	4 [80 %]	3 [60 %]	1 [20 %]	Mean 2.75
		Surgery	LMM, 11	0 [0 %]	1 [9 %]	1 [9 %]	Mean 2.75
Tsang	1968–1988	RT	LM, 36	4 [11.1 %]	0 [0 %]	0 [0 %]	Median 6
		Surgery	LM, 18	1 [5.6 %]	0 [0 %]	0 [0 %]	Median 3
Zalaudek	1990–2000	RT	LM, 15	[13.3 %][a]	0 [0 %]	0 [0 %]	Not reported
		Surgery	LM, 1041	[6.8 %][a]	0 [0 %]	0 [0 %]	
		Cryotherapy	LM, 22	[34.2 %][a]	0 [0 %]	0 [0 %]	
		Laser	LM, 8	[42.9 %][a]	0 [0 %]	0 [0 %]	
Lee	1991–2010	RT	LM, 31	9 [29 %]	0 [0 %]	0 [0 %]	Median 3.9
		Surgery	LM, 27	4 [14.8 %]	0 [0 %]	0 [0 %]	Median 1.4
		Laser	LM, 15	0 [0 %]	0 [0 %]	0 [0 %]	Median 6.5

RT radiation therapy, *LM* lentigo maligna, *LMM* lentigo maligna melanoma, *EDC* electrodessication and curettage
[a]Estimated 5-year rate of recurrence

to radiotherapy, despite no difference in the tumor thickness and level between the treatment groups [7]. It is worth noting that in most of these series, radiotherapy was selected for older patients, and those with LM and LMM on the head and neck [8].

Response Assessment and Surveillance

During radiotherapy, the developments of acute, inflammatory effects are expected (Fig. 12.1c). Response assessment during radiotherapy has been reported to potentially be associated with subsequent control of LM and LMM. Investigators have reported that patients that do not exhibit a strong inflammatory reaction during radiotherapy may be at risk for local recurrence [5]. Beyond this, no predictors of recurrence after radiotherapy are known.

Typically, at the conclusion of radiotherapy for LM and LMM radiation dermatitis will be present and can take 2–6 weeks to resolve (Fig. 12.1d–f), depending on the radiotherapy regimen. Supportive care with gentle skin cleansing, emollients, topical corticosteroids and analgesics may be necessary and appropriate. After the acute inflammatory effects of radiotherapy have resolved, pigmentation at the LM and LMM may resolve over 2–24 months (Fig. 12.1f). While this appears to represent clinical response to treatment, it is not a perfect indicator of response. Investigations of other response assessment tools are ongoing, and may include modalities such as reflectance confocal microscopy [33, 34].

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Chapter 13
Incorporating Patient Preferences and Quality of Life

Karen L. Connolly and Erica H. Lee

Introduction

In slowly progressive cancers such as lentigo maligna (LM) and lentigo maligna melanoma (LMM), individual patient characteristics and preference play an essential role in the informed decision-making process. LM and LMM mortality rates are exceedingly low. As LM and LMM tend to occur in an elderly population, with a mean age of 65 years from SEER estimates [1], this group may have competing risks such as advanced comorbidities, which should be part of the discussion to guide management. Patient considerations such as their overall health status, ability to withstand a surgical procedure and perform post surgical care, as well as their social support system should all factor into treatment decisions. Further, the importance of comorbidity when making treatment decisions has been shown to play a larger role in patients with slowly progressive cancers, as consideration of associated risks should be included in the physician-patient discussion [2]. Often, it is helpful to include family members or caregivers and the patient's primary physician for a more comprehensive understanding of the patient's overall health status to help decide on the best approach.

Noninvasive Management

Despite advances in the nonsurgical treatment of LM, surgical management remains the gold standard. However, a reasonable option for elderly patients with advanced comorbidities may be minimally invasive treatment or observation for LM/LMM. In select patients with an understanding of the natural history of their diagnosis, along with the

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_13

potential implications and risks of no treatment, close clinical follow up may be an appropriate choice after detailed discussion. Non-invasive technologies such as dermoscopy and reflectance confocal microscopy may be used as adjuncts to evaluate for changes suggestive of invasive disease when monitoring LM or to guide nonsurgical treatment.

Shared Decision-Making Models

While basal cell carcinoma (BCC) is a lower-risk malignancy than LM/LMM in terms of risk for metastasis and disease-related death, this slow-growing cutaneous malignancy similarly may present in an elderly patient population with multiple comorbidities, and has been a model for discussions about shared decision-making. Elements to guide the decision-making process for BCC, as suggested by Lee and colleagues, may also be applied to LM/LMM. These authors recommend addressing each of the following during a discussion about patient treatment: tumor biological behavior, biopsy findings, various options for treatment with anticipated outcomes, expected time to complete treatment, and financial aspects of care [3].

Patient-Specific Goals

Defining a patient's specific goals for treatment and elucidating their concerns is a key aspect of the shared decision-making process, as goals of treatment may vary widely between individuals. A patient may be most concerned about the impact of LM/LMM on their facial appearance, and may feel stigmatized by having a dark skin lesion in a prominent location. This same patient may not wish to undergo an extensive surgical procedure with scarring and may prefer a non-invasive treatment with superior aesthetic results such as topical imiquimod or superficial radiation therapy. Others may be more concerned with a LM diagnosis and prefer definite treatment with a surgical approach, or a combined approach, depicted in Fig. 13.1.

In a study evaluating responses of patients with facial skin cancers, all patients were concerned with removal of the skin cancer. However, some patients experienced continued distress over the appearance of their scar, as well as anxiety during early postoperative sequelae such as edema and a large bandage [4]. Patient-reported outcomes have not been studied specifically in the facial LM/LMM population, but some of these findings may be extrapolated to this population due to the propensity of LM/LMM to occur on sun damaged skin.

Reconstruction Considerations

Reconstruction following a surgical procedure should be a consideration in the informed decision-making discussion. While a staged reconstructive procedure may offer the optimal cosmetic outcome, some patients with medical comorbidities may

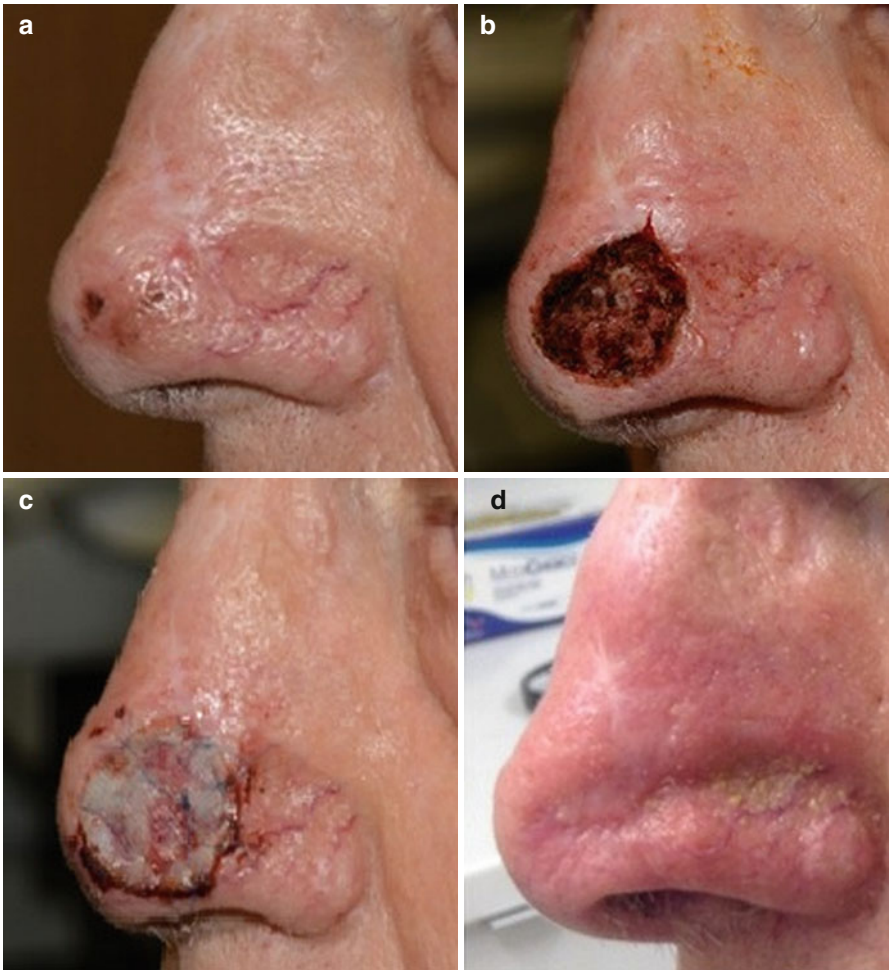

Fig. 13.1 (**a**) 95 year old male presented with a LM on the nasal tip. (**b, c**) An excision with narrow margins was performed and repaired with a porcine xenograft followed by 12 weeks of topical imiquimod to treat any residual disease. (**d**) Patient had a satisfactory result at 12 months postoperatively

opt for a less invasive approach yielding a less than ideal aesthetic result. The ability of wounds to heal by secondary intention must not be overlooked and can be a very reasonable option for patients unwilling or unable to undergo reconstruction, as demonstrated in Fig. 13.2.

Anticipated aesthetic outcome following tumor excision and reconstruction should be comprehensively discussed. An elderly patient who would potentially need to undergo a disfiguring surgery may choose to observe a lesion or opt for a less invasive approach rather than live out their final years with a significantly altered facial appearance. The use of facial prosthetics should also be considered in cases of extensive LMM in which very large defects result or entire anatomic units such as the ear or nose are removed.

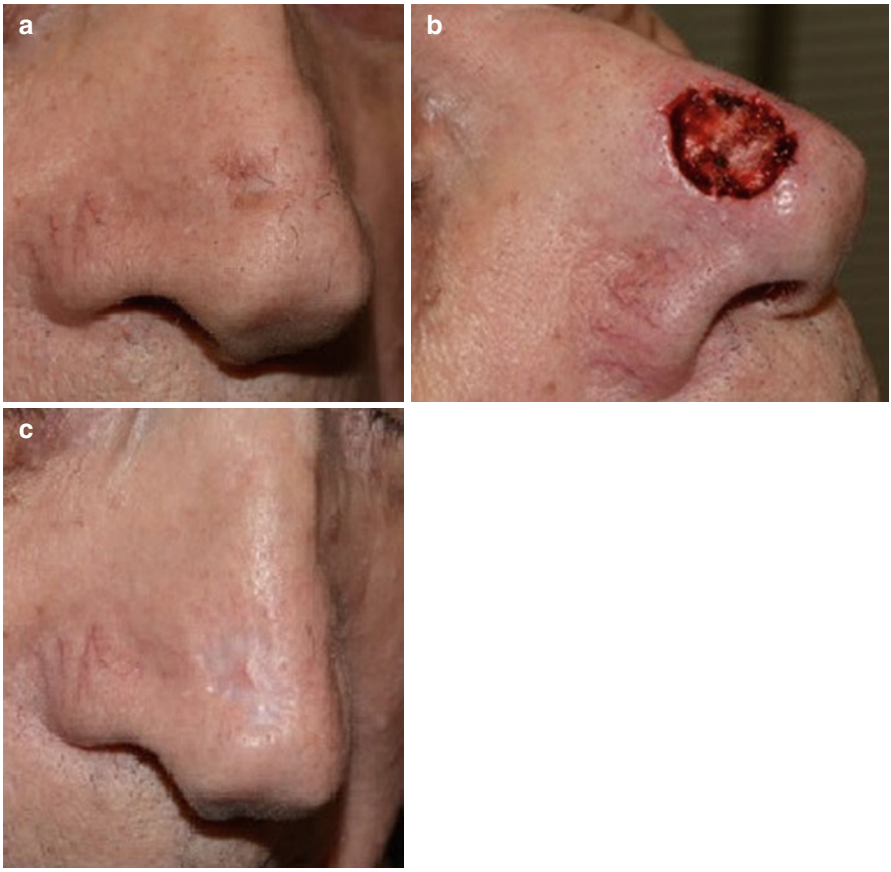

Fig. 13.2 (**a**) 87 year old man with a 0.4 mm LMM on the nasal dorsum who chose treatment with staged excision. (**b**) Surgical defect with clear margins. (**c**) Patient declined reconstruction due to multiple medical comorbidities and the defect healed by secondary intent. He had a reasonable result at 4 months postoperatively

Health related Quality of Life

While the majority of studies on quality of life in melanoma patients focus on advanced and metastatic disease involving systemic treatments, there are several studies evaluating health related quality of life (HRQOL) predictors and influencers in localized melanoma. Lehto and colleagues showed that psychosocial factors were a stronger predictor of quality of life for localized melanoma patients than cancer type or treatment, when compared with a cohort of breast cancer patients. Both increasing age greater than or equal to 70 years and increased number of comorbidities have been shown to negatively influence quality of life in melanoma patients [5]. Psychological distress is higher in patients with melanoma in visible areas, including on the face, relevant to many patients with LM/LMM [6]. A systematic

review identified 13 studies that included an HRQOL measure used for melanoma. The most frequently used measures were the Short Form-36 (SF-36) and European Organization for Research and Treatment of Cancer (EORTC QLQ-C30). The Functional Assessment of Cancer Therapy—Melanoma (FACT-M), is a melanoma-specific questionnaire, and may be useful in clinical trials [7].

Conclusions

The optimal management of LM/LMM may vary widely among different patients. An individualized plan accounting for patient comorbidities, social support, and aesthetic concerns should be developed using a model of shared decision-making. In some cases, close clinical follow up alone may be the preferred management option for LM.

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Part V
Future Direction

Chapter 14
Emerging Novel Non-invasive Imaging

Brian P. Hibler, Miguel Cordova, Milind Rajadhyaksha, and Anthony M. Rossi

Introduction

Lentigo maligna (LM) and lentigo maligna melanoma (LMM) are diagnostically and therapeutically challenging due to their diverse presentations, often with poorly defined, irregular borders on a background of photodamaged skin. Moreover, these lesions often occur on cosmetically-sensitive areas of the head and neck. As such, "blind" mapping biopsies for diagnosis, or potentially disfiguring surgical excision as treatment, may not be welcomed [1–3]. Patients may have had prior treatment that further obscures clinical borders, or the lesion may be multiply recurrent due to inadequate excision or failure of nonsurgical therapy. Initial biopsies diagnostic for LM may miss areas of occult invasion, due to sampling error. In all of these cases, there is a critical need for better visualization and evaluation of the lesion pre-treatment to inform the patient and physician, and to guide optimal therapy. There is a need for novel imaging modalities to better visualize these lesions for diagnosis and improve monitoring for recurrence after both surgical and non-surgical treatment. Advances in newer imaging technologies, including reflectance confocal microscopy (RCM), have improved our ability to better diagnose and manage these challenging lesions. Herein, this chapter will discuss the advantages and limitations of confocal microscopy for LM and review other emerging, non-invasive tools employed to manage cases of LM.

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_14

Reflectance Confocal Microscopy

RCM is a non-invasive imaging tool that uses a low-power laser system to provide real-time imaging of the epidermis and superficial papillary dermis with cellular-level resolution, and has been demonstrated to improve diagnostic accuracy for melanocytic lesions [4–7]. Imaging can be readily obtained at a defined depth (up to 200 μm) and captured in an en face orientation.

At any chosen depth (z plane), a two dimensional sequence or matrix of neighboring images can be captured and then stitched into a mosaic to display extended areas of skin (x-y plane). Thus, capturing vertical stacks of images combined with multiple mosaics at different depths can allow for 3D approximation of lesion margins [8, 9].

Studies have demonstrated the effectiveness of RCM for delineating surgical margins, assessing physiologic responses to therapy, and evaluating the response to non-surgical treatments in vivo for LM [1, 3, 10–13]. One major advantage of this non-invasive imaging modality is the ability to repeat studies on the same area of skin over time. This opens the door for longitudinal studies of cutaneous responses to nonsurgical therapies and the ability to non-invasively monitor for recurrence in vivo.

RCM for LM Diagnosis

Traditionally, non-invasive tools for assessment of LM have included dermoscopy and Wood's light. These instruments have been utilized to assist in the clinical examination of LM and better define the extent of the lesion. However, our ability to reliably discriminate LM from benign pigmented lesions can be challenging, especially in the context of recurrent disease or background of significantly photodamaged skin; therefore, histopathology remains the gold standard in diagnosis [14–16]. Because LM may be large and tends to occur on cosmetically and functionally sensitive areas, biopsies for diagnosis of LM or demarcation of margins may add morbidity for patients in the form of pain, infection, and scarring. It is important to note that even with an adequate tissue biopsy, sampling error or a high degree of background melanocytic hyperplasia may result in imprecise histopathologic interpretation of suspicious lesions. Ultimately, improved technologies and techniques are warranted to augment existing methods for pigmented lesion analysis.

Reflectance confocal microscopy (RCM) provides real-time, non-invasive imaging of intact skin at a resolution comparable to conventional histology. Several studies have demonstrated that RCM may improve diagnostic accuracy of melanoma compared to dermoscopy or Wood's light examination [5, 7, 17–19]. RCM correlates of dermoscopic findings have also been shown to be helpful in distinguishing LM from pigmented nonmelanocytic macules [20].

Guitera et al. looked at various RCM features identified in a sample of clinically equivocal macules of the face, of which 81 were LM and 203 were benign [4]. From

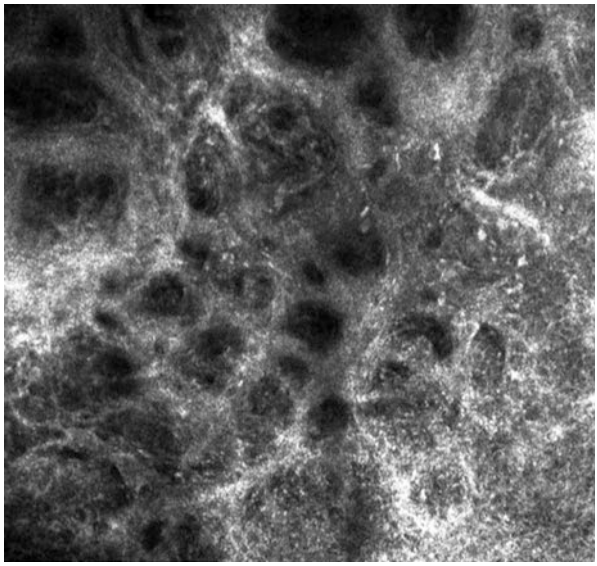

Fig. 14.1 RCM feature of LM: nonedged dermal papillae

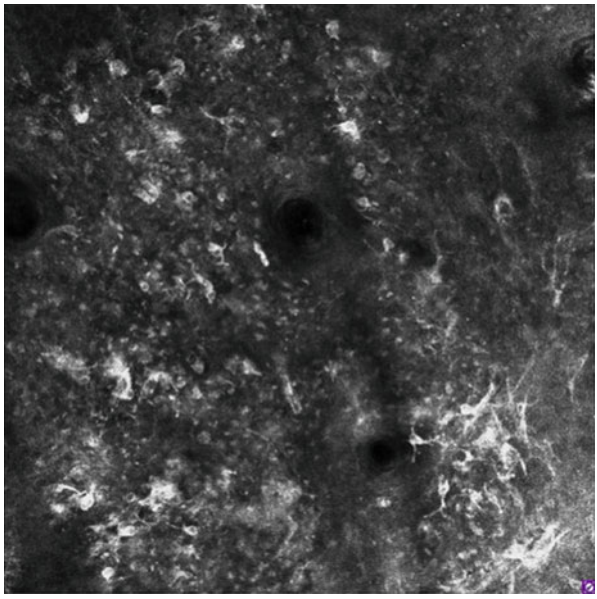

Fig. 14.2 RCM feature of LM: round large pagetoid cells

this study, they determined features suggestive of LM and created a scoring algorithm to distinguish LM from benign macules. The two major features (scoring +2 points each) were nonedged papillae (Fig. 14.1) and round, large pagetoid cells (Fig. 14.2) greater than 20 um. The three minor features (+1 point) included: atypical cells at the dermoepidermal junction (three or more found in five 0.5×0.5 mm^2 fields) as seen in Fig. 14.3, follicular localization of atypical cells (Fig. 14.4), and

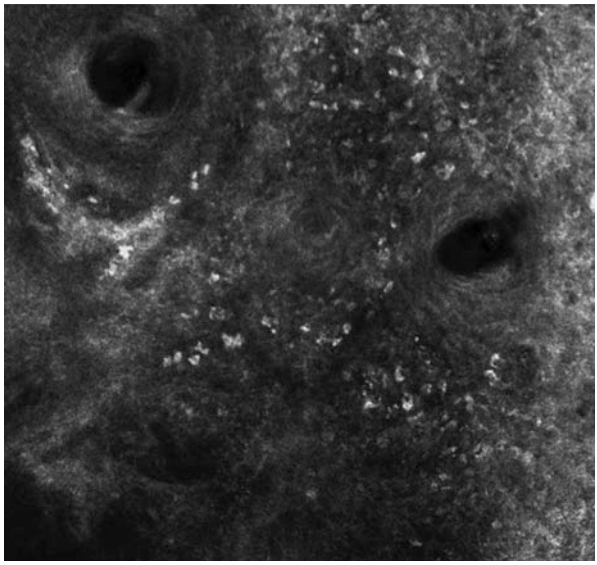

Fig. 14.3 RCM feature of LM: atypical cells at the dermal-epidermal junction

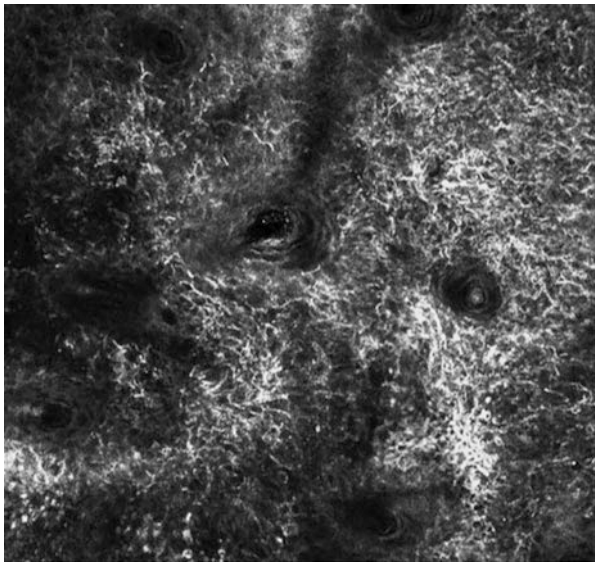

Fig. 14.4 RCM feature of LM: follicular localization of atypical cells

nucleated cells within the dermal papillae. A broadened honeycomb pattern was less indicative of LM, and scored −1 point. Overall, an LM score of 2 or greater yielded a sensitivity of 85 % and specificity of 76 % for the diagnosis of LM (Table 14.1). Other studies have found comparable features including nests of atypical melanocytes surrounding and/or infiltrating adnexal structures, sheets of dendritic melanocytes, and cord-like rete ridges at the dermoepidermal junction to be suggestive of facial LM/LMM [21]. Similar features have held true in the case of amelanotic LM as well [22].

Table 14.1 RCM score for diagnosis of lentigo maligna

RCM feature	Points
Major criteria	
Nonedged dermal papillae	+2
Round large pagetoid cells	+2
Minor criteria	
Nucleated cells in dermal papillae	+1
Atypical cells at DEJ	+1
Follicular localization of atypical cells	+1
Broadened honeycomb pattern	−1

Suspicious for at least melanoma in situ with score ≥2 (Guitera et al. [4])

Rossi et al. studied the use of a handheld confocal microscope and compared it to histopathology in the diagnosis of 60 equivocal pigmented lesions in patients concerning for LM. In this study, RCM and histopathology interpretations were concordant in 89 % of cases (56/63). While there were no false-negative outcomes on RCM, 7 false-positive results were seen, a majority being diagnosed on histopathology as pigmented actinic keratotis. Features suggestive of LM in the false-positive group include the presence of numerous hyperreflectile large cells at the dermoepidermal junction and follicular localization of these cells [23].

A recent meta-analysis found a sensitivity and specificity of 93 % and 76 %, respectively, for RCM when used as a second-level test for diagnosing pigmented lesions that are clinically equivocal [24]. Others have also reported sensitivities of 100 % using RCM to detect LM, further supporting the idea that RCM is a reliable method for diagnosing LM or monitoring for treatment failure in vivo [12, 14]. Using RCM to non-invasively identify LM without biopsy is an exciting improvement in the management of patients with chronically sun-exposed skin.

Another important function of RCM is to improve the ability to hone in on optimal areas for mapping biopsies and detect possible occult invasion in LM lesions. Blind mapping biopsies of LM are prone to sample bias and depend greatly on biopsy technique. Even adequate biopsies of LM can be challenging to definitively interpret under standard hematoxylin and eosin histology due to its occurrence in areas with a background of melanocytic hyperplasia. Studies have demonstrated that occult invasion in LM with standard biopsy technique was not consistently apparent until complete surgical excision was performed. For example, Agarwal-Antal et al. reported on 92 cases of LM of which 16 % were found to have unsuspected invasion on final excisional pathology [25]. Due to the cosmetically-sensitive nature of the lesions, physicians may feel discouraged to take numerous mapping biopsies, even in cases of large lesions. This makes it quite difficult to adequately evaluate the breadth of the lesion or detect occult invasion. Moreover, biopsies are subject to sampling error due to the heterogeneous nature of LM and its characteristic subclinical extension. The costs and morbidity associated with multiple biopsies in patients with a high burden of actinic disease can be substantial. Utilizing real-time video imaging of the dermoepidermal junction at the margin and within the lesion has allowed for the detection of deep atypical melanocytes suspicious for invasion to

better hone in on suspicious areas and guide mapping biopsies. Being able to detect the relative depth of invasion pre-treatment through RCM imaging or by guiding mapping biopsies is essential for not only counseling the patient about disease risk but also imperative for choosing an appropriate treatment modality.

RCM for LM Management (Surgical)

Surgery is considered the first line treatment for LM; however, it is not without associated morbidity. Wide surgical margins, especially on cosmetically-sensitive areas such as the face, are not always possible to obtain, and become further complicated when trying to maintain adequate functional and aesthetic outcomes. The margins required for surgical clearance may not be straightforward for facial lesions. A study by Hazan et al. reviewed 117 cases of LM and LMM and found that the total surgical margin required for excision of LM was 7.1 mm and for LMM was 10.3 mm. Moreover, of the tumors that were initially diagnosed as LM on biopsy, 16 % were found to have unsuspected invasion [26].

As surgical excision remains the standard of care for LM, it is important to optimize surgical methods and because there may be extensive subclinical extension, there is a need for better pre-treatment margin evaluation in LM. RCM is emerging as an adjunct to existing technologies, including dermoscopy and Wood's lamp, to better delineate borders. Utilizing RCM pre-surgically offers the benefit of surgical planning, as it helps define the extent of subclinical spread prior to initiating the surgery. This informs both the surgeon and the patient to assist in reconstructive design and patient expectations. While RCM may be used to show that margins need to be increased due to subclinical spread, it may also allow for confirming narrower surgical margins in critical anatomical areas, facilitating reconstruction and decreasing patient morbidity. Thus, RCM provides valuable clinical information to potentially guide surgical management, and may lead to favorable cosmetic outcomes and a better prognosis.

One approach to using RCM to guide surgical management of LM is to first demarcate the lesion clinically with the aid of Wood's lamp and dermoscopy, followed by placing appropriate surgical margins at 5–10 mm depending on clinical and histologic criteria. RCM may then be used within the lesion to identify features of the melanoma, thus serving as a control. An imaging "map" (Fig. 14.5) may be made by dividing the lesion into quadrants and capturing RCM video imaging along the periphery of surgical margins of each quadrant at the level of the dermoepidermal junction (main region to detect features of LM and LMM). In areas where positive findings including hyperreflective dendritic cells, large, round pagetoid cells, and epidermal disarray are seen, the margins are extended out radially. Video capture can be used to recreate video mosaics by stitching together sequences of images captured to re-create a larger field of view. As such, RCM is a valuable adjunct to the clinical exam and dermoscopy to determine clinical margins and define the gross tumor volume.

Advancements have been made in RCM technology, overcoming limitations of earlier iterations of the device. The newer, handheld Vivascope 3000 (Caliber ID,

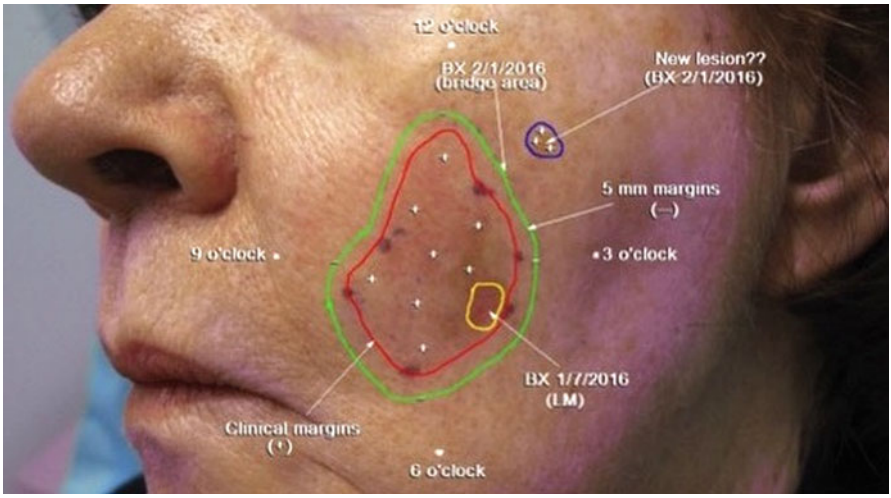

Fig. 14.5 RCM "map" created to delineate surgical margins of LM

Rochester, NY) offers the advantage of real-time assessment in areas that may not have been amenable to previous versions of the device. Employing RCM during the initial consultation may help clinicians characterize subclinical spread of LM and therefore better counsel patients about the extent of their lesion. Additionally, Hibler et al. described the use of the handheld Vivascope 3000 intraoperatively to provide the surgeon with real-time assessment of tumor margins in vivo [27]. This may be a valuable approach for large cases of LM being performed in the operating room under general anesthesia, where the benefits of obtaining immediate visual confirmation of margins to ensure clearance may prevent a return trip to the operating room, saving costs and avoiding risks of additional anesthesia. Using RCM in this mapping fashion could ultimately allow for improved clearance of LM, thereby decreasing the likelihood of recurrence and the need for re-excision, while also maximizing tissue conservation and lowering morbidity.

RCM for LM Management (Non-surgical)

While surgical excision is the treatment of choice for LM, factors including advanced patient age, multiple comorbidities, large lesion size in functionally or aesthetically-sensitive areas, and indiscriminate borders on photodamaged skin may make surgical excision complicated or not a feasible option. For patients unable to pursue surgical treatment and in cases where surgery would cause excess morbidity or deformity, multiple nonsurgical treatment options have been pursued. The use of superficial radiation or off label use of topical therapies, i.e. Imiquimod, has been reported in the literature as alternative non-surgical treatment options [28, 29]. However, the lack of histological confirmation, and possibility for undetected

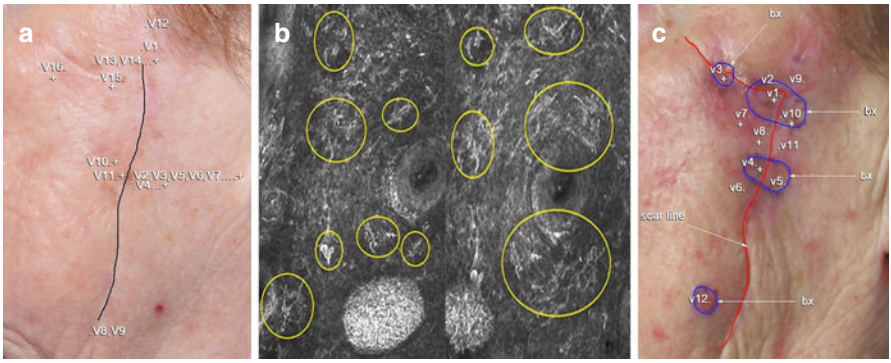

Fig. 14.6 RCM used to detect recurrent LM. (**a**) Pre-confocal mapping of *brown pigmentation* along scar from excision of invasive lentigo maligna melanoma 15 years prior. 'V' indicates sites where images were captured in the z-plane. (+) indicates features of lentigo maligna on confocal microscopy. (**b**) Reflectance confocal image: *Yellow circles* indicate suspicious features for lentigo maligna: hyper reflective dendritic cells surrounding hair follicles. (**c**) Shave biopsies (*blue circles*) guided by confocal all showed melanoma in situ and patient opted for treatment with Imiquimod to avoid surgical morbidity

invasive spread have been limits to these modalities. Similarly, close monitoring for disease recurrence and progression is of utmost importance. Typically this is carried out by clinical examination, without adjunctive imaging beyond dermoscopy. RCM is emerging as an imaging technology that is proving useful to aid in the assessment of disease extent, treatment response and disease recurrence for LM after non-surgical therapy [1]. This is illustrated in Fig. 14.6.

In the same way that RCM may provide enhanced delineation of lesion margins for surgical intervention, it may also be capable of better defining a treatment field for radiation or topical therapies (Fig. 14.7). LMs treated with radiation or non surgical treatment modalities need close follow-up to detect recurrences [28]. Detecting recurrence can be a challenge clinically, as the lesion may recur as an amelanotic lesion, or can be further obscured by radiation-induced inflammation and post-radiation pigment changes. Because RCM allows for the same area of skin to be re-examined over time, this technology can also be applied to monitor for recurrence in LMs [30]. Changes in tissue architecture have been observed in LMs after radiation, including: superficial necrosis and apoptotic cells, dilated vessels, and increased inflammatory cells in both the dermis and epidermis [10]. After radiation, LM-specific large pagetoid cells were decreased or even resolved in the epidermis, dermal-epidermal junction, and in the follicles [10]. When using RCM to monitor for recurrence post-treatment, it is important to wait until the inflammation and post treatment changes have subsided to ensure any acute radiation-induced changes in skin architecture have resolved and will not cause false positives [31]. Epidermal regeneration post-radiation therapy begins 3–5 weeks after treatment and heals within 1–3 months, suggesting that radiation-induced changes on RCM might persist for this duration of time, although this has not been formally studied [32]. The ability to visualize and define changes during and after RT suggest RCM may be useful for monitoring for treatment failure. Examination with RCM may augment our ability to better define the radiation field pre-treatment and has been shown to

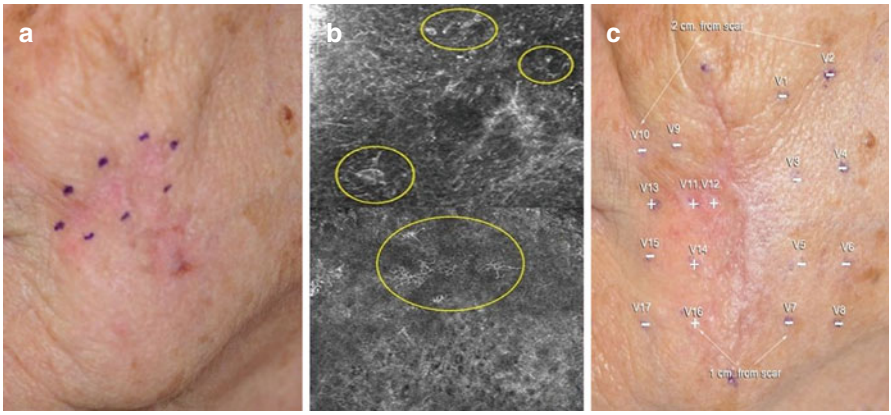

Fig. 14.7 RCM used to plan radiation treatment margins. (**a**) Initial lesion with irregular pigmentation confirmed as lentigo maligna on biopsy. Patient elected treatment with Imiquimod due to her advancing age and medical comorbidities. Follow-up biopsies found melanoma invasive to 0.37 mm and patient underwent surgery to excise the invasive melanoma but in situ LM remained at surgical margins. (**b**) Reflectance confocal mapping for radiation therapy planning. *Yellow circles* indicate areas of dendritic pagetoid hyper reflecticle cells suspicious for lentigo maligna. (**c**) RCM map at 1 cm and 2 cm margins from surgical scar created to guide further radiation planning. 'v' indicates stacks of images captured in the z-plane. (+) indicates findings suspicious for lentigo maligna

be capable of detecting areas concerning for residual or recurrent disease post-treatment before clinical repigmentation [33].

In a similar manner, RCM may be utilized to monitor response after treatment with off label Imiquimod cream [34]. While the use of Imiquimod for LM has been well documented in the literature, the application, duration of therapy, and response to treatment vary greatly. Furthermore, factors accurately predicting a positive response to treatment have yet to be fully elucidated, as the degree of inflammatory response and erythema have not correlated well with overall clearance. The benefit of RCM after topical therapy is that it represents a non-invasive modality to monitor response to treatment and may help assess the need for increased duration of treatment. Moreover, similar to the changes induced post-radiation, treatment with Imiquimod may cause an alteration of the clinically apparent pigment, and it is therefore difficult to assess treatment success by clinical inspection alone. The use of RCM before, during, and after treatment provides a longitudinal assessment of the lesion, and may augment our ability to determine treatment success or failure.

RCM Limitations and Future Directions

As outlined above, RCM is a non-invasive technology with the potential to significantly augment our ability to counsel and treat patients regarding their skin cancer diagnoses, management, and expected outcome. Yet, a number of

limitations of this technology currently exist, including the time needed to image, limited depth of imaging, technology access and cost, and associated learning curve. The field of view for RCM is limited, so for larger lesions it may take time to assess the entirety of the lesion. The advent of video mosaicing and the handheld RCM has improved upon the time required to assess lesions [9], yet it may still be time consuming in the case of large lesions. Moreover, the restricted depth of imaging (~200 μm) restricts evaluation of the dermis to the superficial papillary dermis. Additionally, widespread adoption of this technology is limited by its high cost relative to dermoscopy and associated learning curve [35].

There is a learning curve associated with RCM imaging; however, the training required for accurate RCM interpretation has been reported to be less than that of dermoscopy [36]. Importantly, studies have shown that key RCM diagnostic criteria for lesions including melanoma and basal cell carcinoma are reproducibly recognized among RCM users, and that diagnostic accuracy increases with experience [37]. Although more onerous and time-consuming than dermoscopy, RCM provides detailed images of live tissue with cellular-level resolution and can reconstruct 3D areas for evaluation, critical for assessing heterogeneous lesions such as LM with poorly defined borders that may have significant subclinical extension. Due to these limitations, the use of RCM is highly individualized depending on the size and nature of the lesion, its location, and patient comorbidities.

Handheld and Video Mosaicing

The handheld Vivascope 3000 overcomes limitations of the stationary Vivascope 1500 device, and offers advantages such as being able to assess lesions in difficult locations on the face [38, 39]. Compared to previous non-handheld RCM devices the use of the HRCM does not need to attach a ring to the skin and is less bulky. This permits its use at the bedside of the patient or even intraoperatively [27]. Furthermore, the ability to create video mosaics overcomes the limited field of view provided by standard RCM imaging, and allows for rapid and accurate assessment of large lesions in real time [9]. This may permit complete examination of the periphery of lesions, critical for evaluation of subclinical extension of LM and verifying clearance after surgery. Indeed, studies have found good correlation between handheld RCM findings and histological findings after surgery for LM/LMM, suggesting that it is a valuable technique to guide surgical excision [40]. Handheld RCM is a noteworthy ancillary tool as it can be readily performed at the bedside of the patient or even intraoperatively, and may represent a faster approach than conventional RCM in cases where large areas need to be mapped.

Other Non-invasive Tools for LM

Apart from RCM, there are other non-invasive imaging modalities that have been applied for melanoma detection. Depending on the imaging technology, the practical in-vivo use of such compared to RCM may be limited. Technologies such as optical coherence tomography and ultrasound have been applied to melanoma diagnosis and while they are able to penetrate deeper than RCM, the level of resolution is macroscopic compared to RCM's cellular resolution. Therefore reliable diagnostic criteria have not been fully elucidated in regards to melanoma diagnosis.

Devices that are based on multispectral imaging (MSI) have also become available for the diagnosis of melanoma. MSI works through using multiple wavelengths, ranging from 400 to 1000 nm, to enhance detection of dermoscopic features within the lesion. Different skin chromophores absorb and reflect different wavelengths to create an "image" which is then analyzed algorithmically [41]. Spectrophotometric intracutaneous analysis (SIAscopy), is one of two types of MSI devices applied for the detection of melanoma, however, there have been multiple studies that reveal differing results in the ability to detect melanoma in vivo [42, 43].

Smartphone (Melanoma in General)

The mobile market has experienced a rapid expansion in the number of dermatological applications marketed to educate individuals and monitor lesions. There are over 200 dermatology-related mobile applications, with the most common being general dermatology references, self-surveillance/diagnosis tools, disease guides, and educational aids [44]. Most of these applications (51 %) are targeted towards patients, while 41 % of applications are targeted towards medical professionals, and 8 % target both. Consumers are able to rapidly access and use mobile applications. Moreover, the mobile market makes it possible to reach more remote locations with these educational resources and diagnostic aids.

While this technology is widely distributed, few studies have evaluated the accuracy of smartphone applications. Of major concern is that diagnostic inaccuracy may result in delayed treatment due to false reassurance that a lesion is benign. For example, 3 of 4 smartphone applications incorrectly identified at least 30 % of melanomas as "unconcerning," and the sensitivity of such applications ranged from 6.8 to 98.1 %, highlighting the drastic variability among current applications [45]. A recent review of dermatology-related mobile applications found that none of the applications that provided risk-assessment of lesions appeared to have been validated for diagnostic accuracy, and there was limited information regarding the credentials of those involved with making the application—some applications were not updated in over 3 years [46]. As such, creators may make unsubstantiated

assertions in order to influence users to download and use their application, and have even been fined by the Federal Trade Commission for unproven claims [47]. Therefore, regular appraisal of dermatology-related mobile applications may be warranted to objectively review the spectrum of applications available and to make recommendations.

Conclusion

LM and LMM present diagnostic and therapeutic challenges due to the heterogeneous nature of the lesions, occurrence on cosmetically and anatomically sensitive areas, and indistinct clinical margins. As such, the need for non-invasive devices to detect and diagnose LM is clear. While many different technologies have been applied to this task, RCM has had the most promising results thus far for real time in vivo use. RCM has been utilized to diagnose challenging lesions, "map" out subclinical margins, and detect recurrence of LM. With the advent of newer technologies, improved laser/light optics, and enhanced algorithmic capacities, there will continue to be much progress in this arena.

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Chapter 15
Follow Up and Recurrence

Karen L. Connolly, Stephen W. Dusza, Kishwer S. Nehal, and Erica H. Lee

Introduction

This chapter describes the unique challenges of clinical follow up of lentigo maligna (LM) and lentigo maligna melanoma (LMM), including difficulty of identifying local recurrence (LR) in a background of actinically damaged skin. Methods used to assist in monitoring for recurrence, and reported time to recurrence subsequent to various surgical techniques are discussed. The prognosis of local recurrence will also be discussed.

Local Recurrence Rates

The reported incidence of LR following therapeutic intervention for LM and LMM ranges from less than 5 % with margin-controlled surgical techniques to greater than 25 % with destructive and other nonsurgical techniques [1]. Table 15.1 and Fig. 15.1 present the published literature regarding LR for LM and LMM, stratified by procedure type (excision versus Mohs). The varied studies using a margin-controlled surgical technique tend to give very consistent results. The overall pooled estimate for LR from these 34 studies was 0.04 (4 %); 95%CI: 0.02–0.06. When restricting the analysis to studies that focused solely on various excision techniques, the LR rate was 0.05 (5 %); 95 % CI: 0.02–0.10, and for studies focusing on Mohs, LR was 0.01 (1 %); 95 % CI: 0.00–0.03. Further, those with a history of lentigo maligna have an increased likelihood of developing subsequent primary invasive melanoma, emphasizing the importance of close, regular dermatologic follow up [2]. Therefore,

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_15

Table 15.1 Recurrence rate (effect size) and 95 % confidence interval stratified by procedure type (Excision or Mohs)

Study	Recurrence rate	95 % CI		% weight
		Lower	Upper	
Excision				
Pitman [34]	0.09	0.01	0.29	2.31
Hill [35]	0.02	0	0.08	3.05
Argawal-Antal [36]	0	0	0.04	3.2
Osborne and Hutchinson [11]	0.2	0.12	0.3	3.14
Malhotra et al. [25]	0.03	0.01	0.07	3.34
Bub et al. [30]	0.05	0.01	0.13	3.02
Huilgol [37]	0.02	0.01	0.06	3.37
Mahoney [38]	0	0	0.28	1.72
Jejurikar [39]	0	0	0.08	2.79
Walling et al. [29]	0.07	0.02	0.2	2.78
Lee [40]	0.06	0	0.3	2.04
Abdelmalek [41]	0.02	0	0.04	3.45
Chin-Lenn [42]	0.08	0.03	0.15	3.19
Akhtar [43]	0.03	0	0.1	3.06
Hou et al. [26]	0.06	0.03	0.09	3.47
Joyce et al. [6]	0.02	0.01	0.04	3.53
Matos [44]	0.41	0.34	0.48	3.43
Rawlani [45]	0.22	0.06	0.48	2.14
Random pooled rate (Excision)	**0.05**	**0.02**	**0.1**	**53.05**
Mohs				
Robinson [27]	0.06	0	0.3	2.04
Cohen [46]	0.03	0	0.14	2.73
Clayton [47]	0.01	0	0.07	3.12
Bienert [48]	0	0	0.05	3.11
Bricca et al. [7]	0	0	0.02	3.50
Bhardwaj [49]	0	0	0.03	3.42
Temple [50]	0.03	0.01	0.06	3.42
Walling et al. [29]	0.38	0.15	0.65	2.04
Bene [51]	0.01	0	0.05	3.34
Kunishge [52]	0	0	0.01	3.60
Chin-Lenn [42]	0.05	0.01	0.14	3.00
Newman [53]	0.02	0	0.04	3.47
de Vries [54]	0.04	0.01	0.10	3.23
Etzkorn et al. [4]	0	0	0.01	3.56
Hou et al. [26]	0.03	0.01	0.07	3.36
Random pooled recurrence rate (Mohs)	**0.01**	**0**	**0.03**	**46.95**
Overall random pooled recurrence rate	**0.04**	**0.02**	**0.06**	**100**

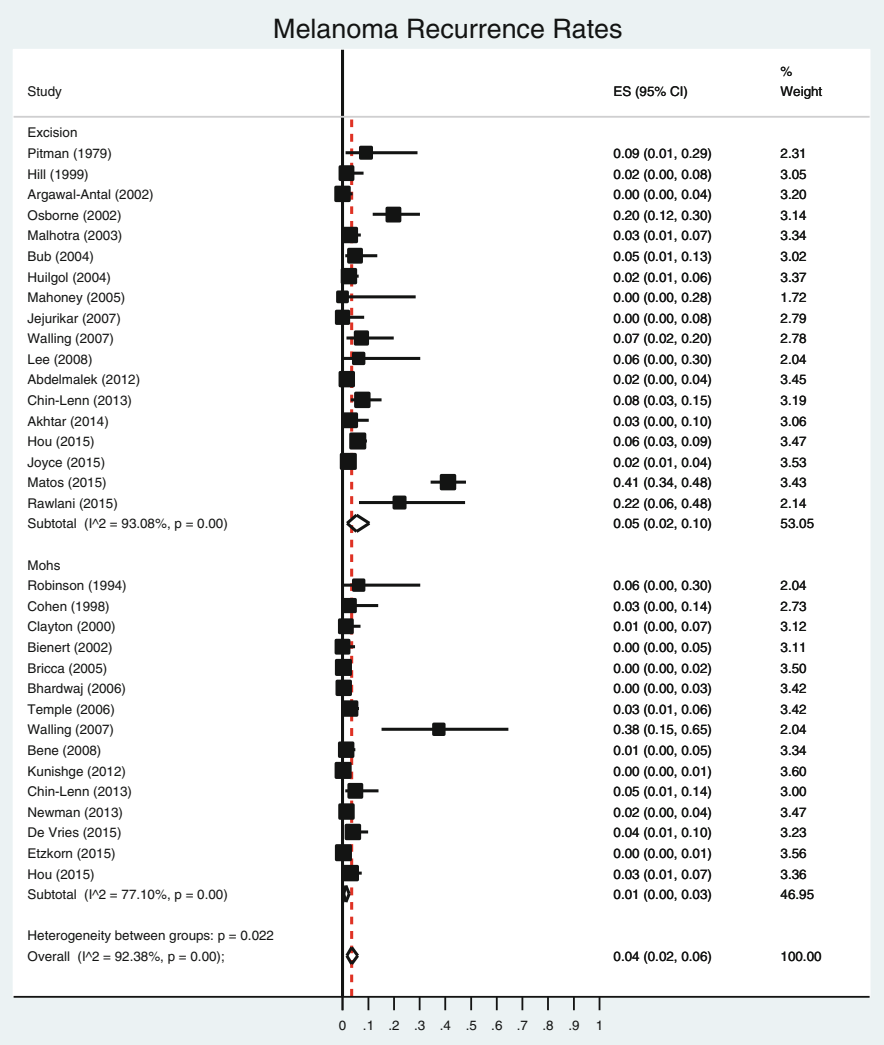

Fig. 15.1 Forest plot of the recurrence rates for melanoma, stratified by procedure type (excision vs. Mohs)

regardless of the technique used for treatment of LM/LMM, the importance of routine clinical follow up to monitor for both recurrence and subsequent skin cancers is paramount. In a large study of 1,996 melanomas of various subtypes treated at a single institution by surgical excision, LM/LMM accounted for only 6.5 % of all melanomas treated, but 37 % of all local recurrences [3]. Several reasons for higher

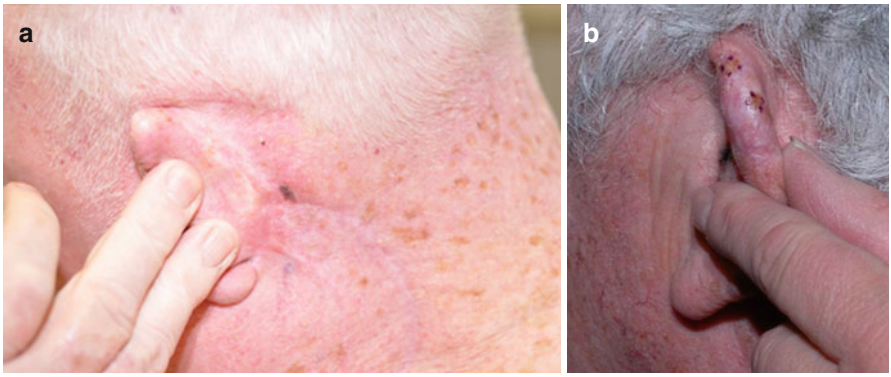

Fig. 15.2 (**a**) Recurrent LMM at the margin of the previous surgical scar. (**b**) Recurrent LM in a graft (hyperpigmented macules marked in *purple*)

rates of LR in LM/LMM have been proposed by the authors, including the increased risk of subclinical extension, difficulty in distinguishing field damage from the trailing edge of LM/LMM, location on anatomically sensitive areas in the head and neck area, and frequent use of smaller surgical margins to minimize morbidity.

Defining Local Recurrence

Local recurrence of LM/LMM typically presents as hyperpigmented macules or patches along a scar or within a graft in the area of prior intervention as depicted in Fig. 15.2.

The exact definition of LR for LM/LMM varies from publication to publication. Most commonly, LR for LM/LMM is defined as hyperpigmentation just along a prior surgical scar from primary treatment to LM within 5 cm of the initial scar [4, 5] with additional definitions in the medical literature. LR can present a challenge to define in a cancer that by definition tends to occur in severely sun-damaged skin; field damage with subsequent primary lesions occurring in close proximity to the initial lesion is not uncommon. Figure 15.3 illustrates this challenge.

The authors prefer the definition of a subsequent biopsy-proven melanoma within or adjacent to the surgical scar, within the site of the initial surgical defect, consistent with studies where a definition was reported [4, 6–8]. Clinical photography can be essential in determining whether a lesion should be classified as a local recurrence. Standard follow up examination of patients with a history of LM/LMM must include both inspection of the prior treatment site/scar as well as a thorough exam of the adjacent and/or draining lymph node basin. While the interval for follow up varies depending on suspected risk of recurrence (e.g. shorter follow up intervals for patients with more invasive disease), at least annual follow up is recommended for any patient with a personal history of melanoma [9].

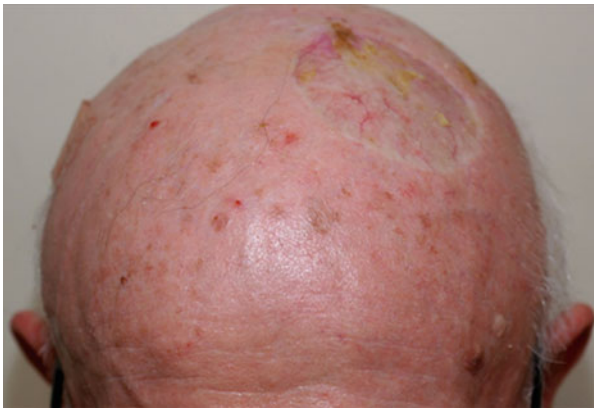

Fig. 15.3 Patient with extensive photodamage who developed multiple primary melanomas on the scalp

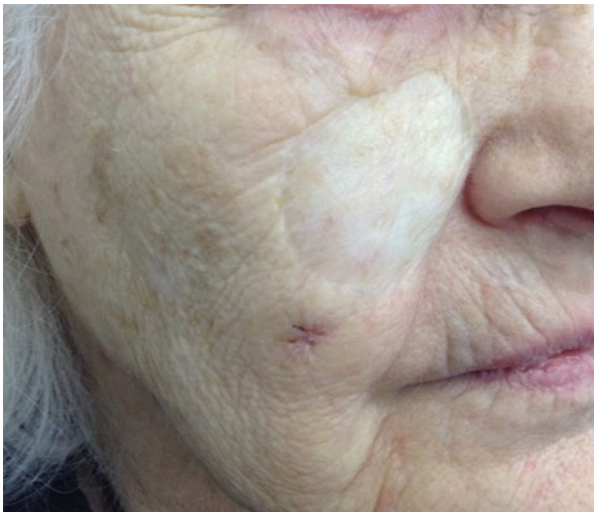

Fig. 15.4 This 88 year old woman developed a second primary lentigo maligna melanoma just inferior to the graft scar of a lentigo maligna treated 7 years prior. Her background skin demonstrates extensive photodamage

Monitoring for Local Recurrence

Monitoring for recurrence of LM poses several special challenges. First, lentigo maligna occurs on skin with chronic actinic field damage. Therefore, patients are also predisposed to development of additional primary melanomas in the initial treatment area due to the field effect of chronic cumulative ultraviolet radiation exposure in that specific region, as seen in Fig. 15.4.

While benign lentiginous hyperpigmentation may occur within a skin graft (Fig. 15.5), or along the scar of a prior LM [10], the clinician should maintain a high index of suspicion for LR, as recurrence rates can be as high as 20% in those treated with standard wide local excision [11], and even higher with other techniques such as laser and cryotherapy [12]. As hyperpigmentation cannot be readily differentiated from recurrence (Figs. 15.5 and 15.6), a histopathologic diagnosis is recommended in this situation.

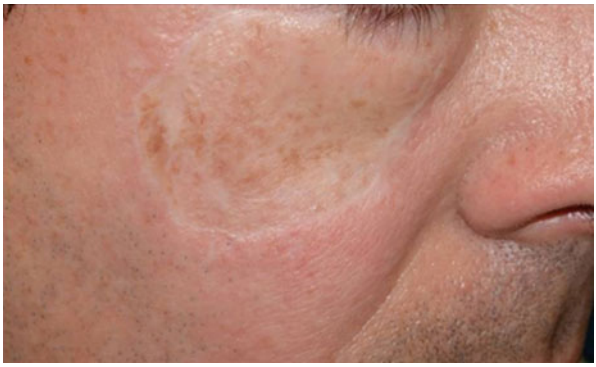

Fig. 15.5 Benign lentiginous hyperpigmentation in a skin graft following reconstruction

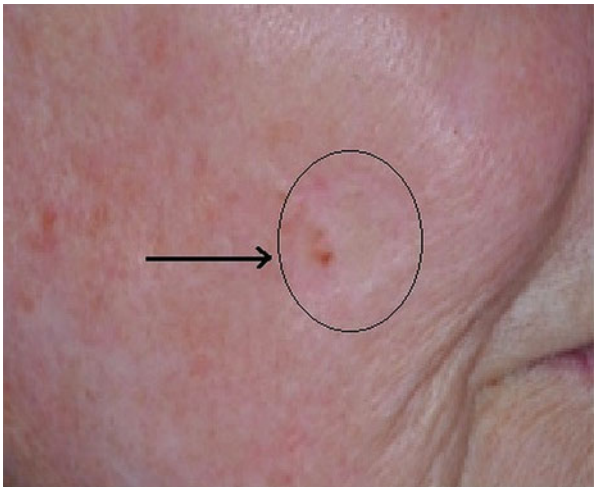

Fig. 15.6 Recurrent LM within a graft, eight years following the initial surgery

Few studies have demonstrated long-term recurrence rates in patients treated with topical therapies (i.e. imiquimod); however, failure of treatment has been reported in as many as 23 % of cases when long-term follow up is provided [13]. Recurrence of previously pigmented LM as amelanotic LM presenting as erythematous dermatitic plaques has also been described, necessitating a high index of suspicion for any new lesion or suspected dermatitis in a prior surgical site for LM [14, 15].

Recurrence of Lentigo Maligna as Invasive or Metastatic Disease

The most pressing concern when monitoring for recurrence of LM/LMM is presence of invasive melanoma or lymph node metastasis as the first sign of recurrence. Case reports exist of LM, previously thought to be in situ, treated nonsurgically and

recurring as invasive or metastatic disease [16, 17]. For example, Woodmansee and colleagues reported a case of a biopsy-proven LM treated nonsurgically with imiquimod with clinical and histologic resolution of tumor from sampling biopsies. Approximately 2 years following treatment, the patient developed nodules in the previously treated area, which were biopsy-proven to be 1.13 mm depth melanoma. As is the case with typical nonsurgical treatment, a tumor debulking specimen was not initially sent for histopathologic examination, suggesting that there may have been an undetected microinvasive component, later developing into clinically evident invasive disease. This patient went on to develop both pigmented and nonpigmented subsequent recurrences [16]. Fisher and colleagues reported a large recurrent lentigo maligna that underwent 13 pretreatment biopsies, all confirming in situ disease, and treated with topical imiquimod and showing initial clinical response. However, multiple invasive satellite nodules up to 3.3 mm in Breslow depth developed at the periphery of this lesion, and on Mohs surgery, a tumor debulking specimen showed only melanoma in situ in the central lesion. Fortunately, the patient had surgical removal of the invasive disease and remained free of disease at 17 months [17]. Similarly, Guitera and colleagues reported a series of nonsurgically-treated LM with two invasive treatment failures at several months post treatment, with Breslow depths of 0.4 and 0.6 mm, respectively [18]. For this reason, the authors recommended surgical treatment if possible for any recurrent lesion, to rule out occult invasive disease.

Various imaging modalities exist to assist in evaluating for LM recurrence, including dermoscopy and reflectance confocal microscopy. Both dermoscopy and reflectance confocal microscopy can be particularly useful in patients who are treated nonsurgically and wish to avoid additional procedures such as biopsies. It is important to obtain baseline lesion imaging as well as post-treatment imaging in these cases, to evaluate for resolution of features specific to LM [19]. Features on dermoscopy that have been reported in recurrent LM include typical features of asymmetrical follicular openings, grey or brown dots, and structureless areas [18, 20]. Reflectance confocal microscopy, while less widely available than dermoscopy, achieves cellular-level resolution at a depth up to 200 μm noninvasively, and offers superior sensitivity and specificity for diagnosing LM than dermoscopy [18]. Reflectance confocal microscopy may demonstrate atypical pagetoid and dendritic cells, disruption of a typical honeycomb pattern, and bright, non-nucleated cells representing melanophages [20]. In a broad lesion with multifocal hyperpigmented areas, RCM and dermoscopy may be used to guide biopsy location [21, 22]. Wood's light is an additional commonly used modality to facilitate follow up of LM, requiring minimal training. However, Wood's light will also enhance surrounding the surrounding lentigines commonly found on the photodamaged skin of LM, sometimes limiting its use in this setting [23]. While RCM and dermoscopy have demonstrated good sensitivity and specificity for the diagnosis of LM, the gold standard for diagnosis is histopathologic diagnosis. Even RCM, which allows examination at the histologic level, still has inferior resolution to light microscopy [24].

Prognosis of Recurrent Lentigo Maligna

The prognosis of locally recurrent LM/LMM is generally considered more favorable than local recurrence of other melanoma subtypes, with a low reported incidence of subsequent invasive disease following treatment of LM. Malhotra and colleagues reported that a history of recurrence of periocular LM was not associated with subsequent invasive disease, with only 1 of 29 previously recurrent LM presenting as LMM, and 2 of 109 surgically treated LM recurring as LMM [25]. Osborne and Hutchinson noted that previously recurrent lesions of LM that were retreated with wide local excision tended to recur more quickly than primary lesions treated by the same method, implying that the biological behavior was different among these lesions. In this series, only one patient developed subsequent invasive LMM on recurrence, with the remainder of recurrences representing in situ disease [11]. In a series of 423 LM treated surgically by Hou and colleagues, no invasive disease or metastases occurred related to an LR [26]. However, reports do exist of invasive disease in an LR of LM, with histological examination of a tumor debulking specimen, indicating that unsuspected invasive disease was initially ruled out [6]. Therefore, while the incidence of subsequent invasive disease, metastasis, and death following recurrence of LM/LMM has not been systematically studied, small series suggest that these outcomes are uncommon, and the prognosis of locally recurrent LMM appears favorable in comparison with other melanoma subtypes. In a large, single institution study, 12.5 % of patients with locally recurrent LMM died of disease, compared with 28 % of all other patients with locally recurrent melanoma [3]. An additional study showed that locally recurrent LMM had superior 5- and 10-year survival rates to all other types of melanoma, at 69.4 % and 46.1 % respectively [5].

Time to Local Recurrence

The time to LR for LMM has not been well-defined, and reports range from 154 days [4] to 8 years [27], with a recent study showing a mean time to recurrence of 5.9 years for primary LM treated with staged excision [28]. Multiple studies have shown a mean time to recurrence exceeding 3 years [26, 29–31], suggesting that surgically-treated LM can recur later than other melanoma subtypes. As LM may have a very long latency to LR, the authors recommend long-term clinical follow up to monitor for recurrence. Figure 15.7 exemplifies a patient who continues to be followed 10 years after initial surgical treatment.

Critical Assessment of Reported Recurrence Rates

There should be some caveats when viewing data on recurrence from LM/LMM, and these are mainly due to the natural history of the disease. Lentigo maligna and lentigo maligna melanoma tend to occur in older individuals. Based on SEER

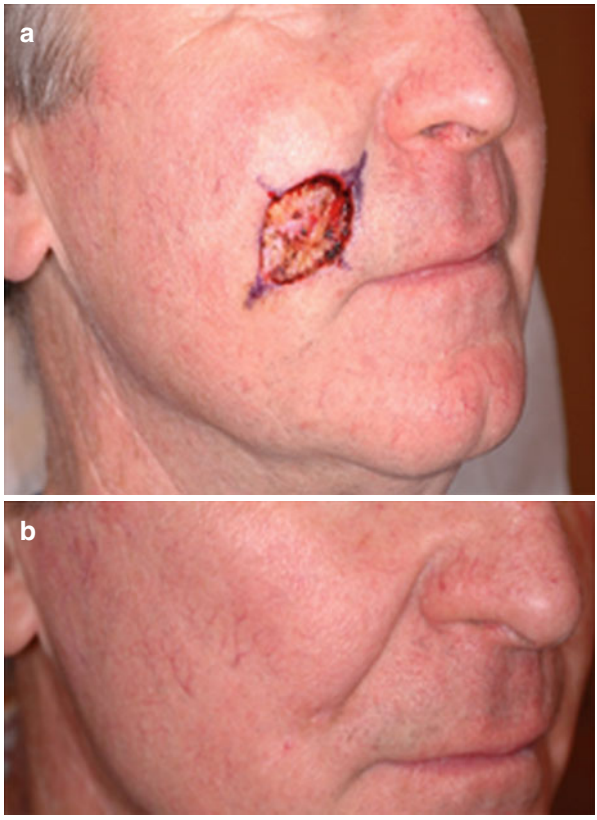

Fig. 15.7 (**a, b**) Patient with 10 years of follow up after excision of lentigo maligna and no signs of recurrence

estimates, the median age at LM/LMM diagnosis is 65 years, compared to superficial spreading and nodular melanomas that tend to have a median age of onset in the 1940s and 1950s [32]. Recurrences from LM/LMM, as noted above, can occur years after initial disease. Since these individuals are older, they tend to have other comorbidities and competing risks that can obscure the estimates of disease recurrence. A competing risk is any condition or event that limits our ability to accurately measure the disease or event of interest. For example, if someone dies of a myocardial infarction several months after surgical resection of their LM/LMM, their LM/LMM did not have much of a chance to recur. Although statistical methods have been designed to mitigate the bias effects of competing risks [33], these methods have not been evenly applied in clinical publications. Another potential factor limiting accurate recurrence estimation is patients lost to follow up. Keeping cohesive cohorts of LM/LMM patients for the extensive periods of time necessary for accurate recurrence data is logistically challenging. Patients lost to follow up may be inherently different on a disease severity basis than those who remained under surveillance. The effects of these differences are difficult to quantify and are infrequently reported in the literature.

Conclusion

Long term follow up is necessary following treatment of LM. Defining LR is important when studying entities such as LM, where development within an area of field damage is quite common and should be consistently reported in studies. Fortunately, it appears that LR of LM has a favorable prognosis in comparison to other subtypes of melanoma. Newer tools such as dermoscopy and reflectance confocal microscopy are helpful adjuncts for monitoring for recurrence, especially as use of nonsurgical treatment becomes more prevalent.

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Part VI
Case Presentations: Multidisciplinary Management

Chapter 16
Case A: Multiple Mapping Techniques to Guide Staged Excision for a Challenging Lentigo Maligna Melanoma

Michael C. Cameron and Chih-Shan Jason Chen

Case Presentation

A 69-year-old man presented with a biopsy-proven lentigo maligna melanoma (LMM) with a Breslow thickness of 0.37 mm on top of the head. On examination, there was a very ill-defined, large, irregular pigmented patch involving most of the frontal scalp (Fig. 16.1) in a background of extensive photodamage. Three distinctive biopsy scars were identified at the mid anterior region of the patch. All three biopsies were reported as lentigo maligna (LM) or LMM. Wood's light examination delineated a 9×9 cm pigmented patch (Fig. 16.2). Dermoscopic examination showed multiple features of LM/LMM such as asymmetrical pigmented follicular opening, circles in circles, and peppering within the margins determined by Wood's lamp (Fig. 16.3). Confocal microscopy detected features of melanoma such as epidermal disarray, pagetoid cells, and dendritic cells (Fig. 16.4), distributed similarly to the dermoscopic mapping in this case. Based on the above findings, scouting biopsies were performed for histologic confirmation of the mapped surgical margin (Fig. 16.5a). Figure 16.5b illustrates the composite map combining Wood's light, dermoscopy, confocal and biopsy findings.

A staged excision was then performed. In the initial stage, the entire lesion plus a narrow margin was excised down to the deep dermis and superficial subcutaneous plane (Fig. 16.6) with orientation preserved with suture markings. The specimen

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_16

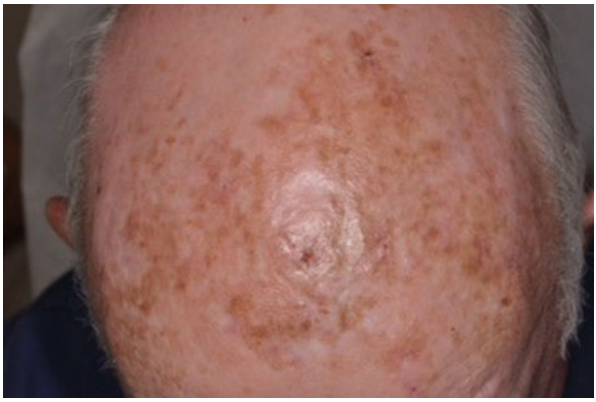

Fig. 16.1 Biopsy proven lentigo maligna melanoma with ill-defined clinical borders

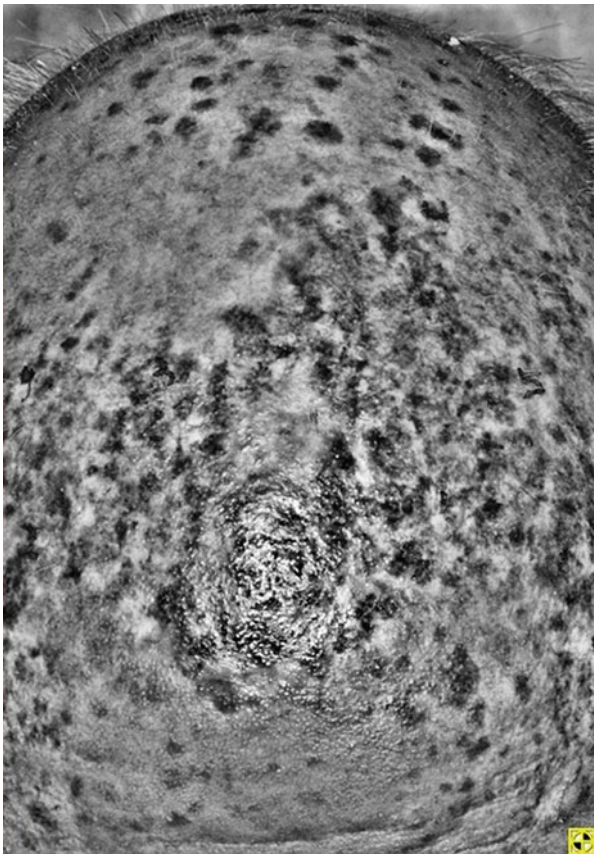

Fig. 16.2 Wood's light examination of pigmented lesion

was sent rush for paraffin-embedded pathology step sections from tip-to-tip in a breadloaf fashion. Because only a small portion of this large lesion was sampled, this sectioning approach allowed for comprehensive pathologic assessment, including additional information on tumor thickness and initial margin assessment

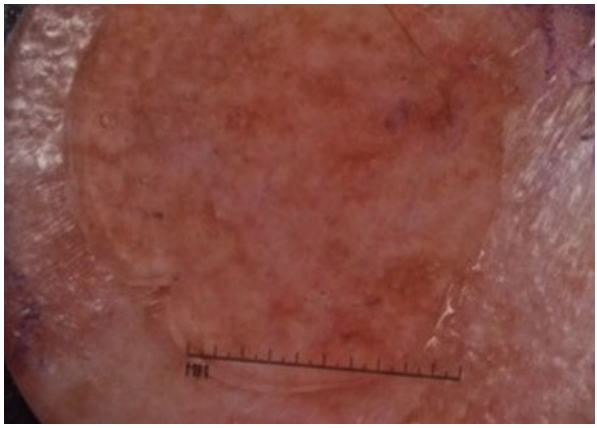

Fig. 16.3 Dermoscopic examination of pigmented lesion

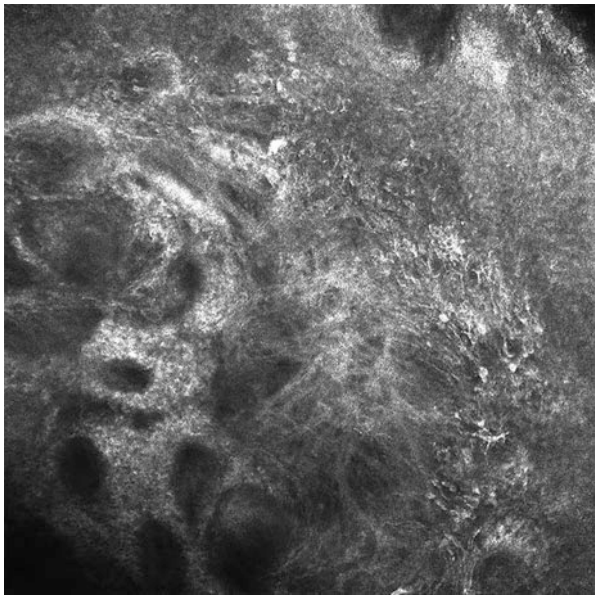

Fig. 16.4 Reflectance confocal imaging of pigmented lesion

(i.e. the distance of excision margin to the tumor, or its trailing edge). Pathology showed residual lentigo maligna with isolated atypical intraepidermal melanocytes focally within 1 mm of side margins. Based on these findings, a second and final staged excision was performed and sent for rush permanent sections to achieve sufficiently therapeutic lateral and deep margins (Fig. 16.7). Final pathology showed all margins were cleared with no melanoma seen.

Once the final excision is completed and the surgical margins are histopathologically clear, wound reconstruction can be performed. In this case, the surgical defect measured 7.2 × 5 cm. After discussion of reconstruction options, the patient opted to allow the defect to heal by second intention after wound reduction with a purse-string suturing technique (Fig. 16.8).

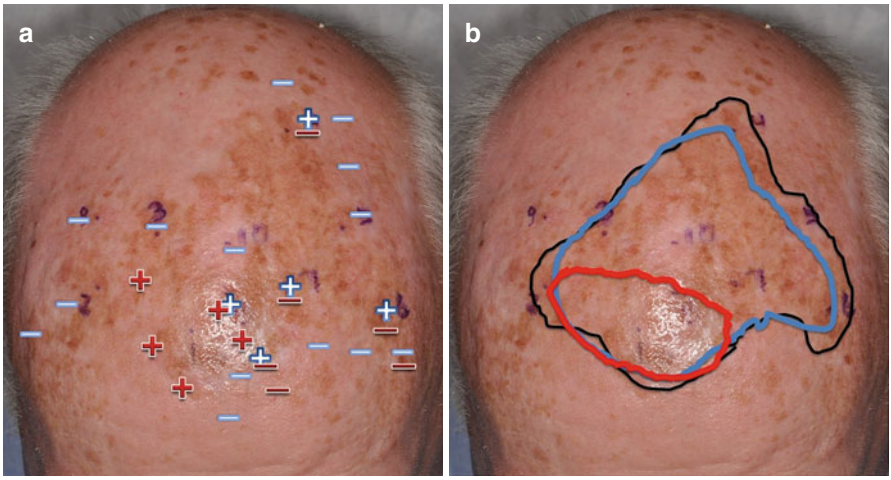

Fig. 16.5 (**a**) Scouting biopsies (*Red*: negative for melanoma positive for melanoma) guided by confocal microscopy (*Blue*: negative for melanoma positive for melanoma). (**b**) Presurgical mapping of melanoma borders using Wood's light examination (*black line*), dermoscopy and confocal microscopy (*blue line*), and scouting biopsies (*red line*)

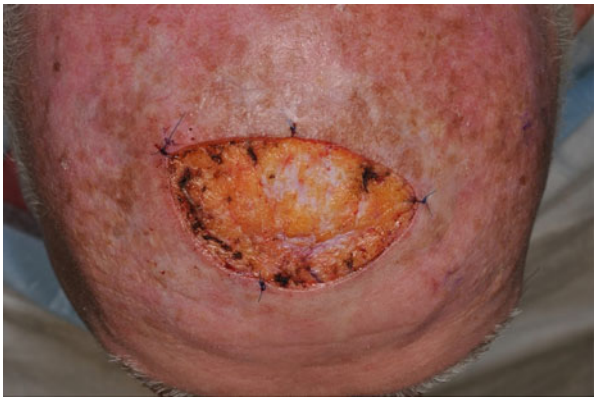

Fig. 16.6 Surgical defect after initial staged excision

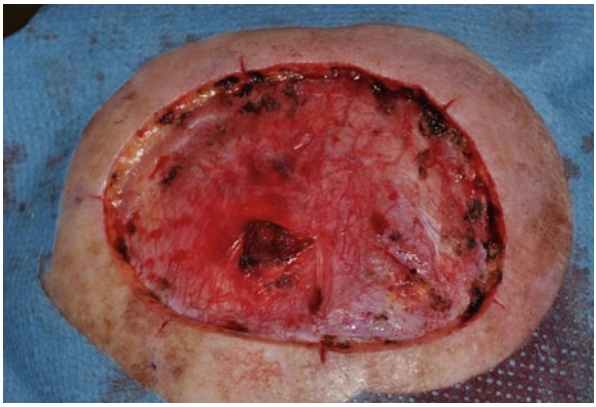

Fig. 16.7 Final excision with clear histologic margins

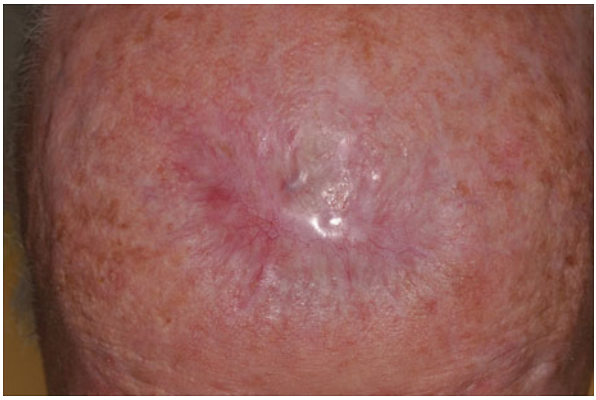

Fig. 16.8 The final defect was reduced with purse string suturing technique and allowed to heal by second intention

Discussion

For LM/LMM, surgical excision is the treatment of choice and is associated with the highest cure rates, primarily because it allows for complete histological evaluation of margins and removal of periadnexal melanocytes and invasive components of lesions [1–3]. While the proper surgical margin can vary widely, excision with adequate margins results in good cure rates [4–7]. Multiple factors make determining the true margin of these lesions for pre-surgical planning difficult. LM/LMM (especially on head and neck) often occur in the background of photodamaged skin, as demonstrated in this case, with solar lentigines, seborrheic keratoses, actinic keratoses, and other chronic-UV light changes obscuring true LM/LMM margins [8]. They often have unpredictable subclinical extension of atypical junctional melanocytic hyperplasia beyond the visible pigmented margins. Since these lesions most often occur on the head and neck, maximal preservation of cosmesis and functionality are additional priorities for the surgeon during pre-operative planning.

As visual assessment of tumor borders is often inaccurate, pre-operative assessment to estimate true margins can be aided by the following techniques: Wood's lamp examination, dermoscopy, confocal microscopy, and scouting biopsies [9]. Wood's lamp light (320–400 nm) takes advantage of melanin's absorption of radiation in the UV range. Lesions that possess increased melanin will appear brighter in contrast to normal skin when exposed to Wood's lamp light [10]. As a result, the instrument provides increased contrast between normal and pigmented skin, allowing for improved delineation of LM/LMM clinical borders.

Dermoscopy is a non-invasive technique to examine pigmented anatomic structures of the epidermis, dermoepidermal junction, and superficial papillary dermis not visible to the naked eye [11]. For experienced users, dermoscopy has been shown to be more accurate than clinical examination for diagnosis of melanoma [12]. Specific features in helping to identify LM/LMM on dermoscopy include asymmetric pigmented follicular openings, pigmented lines forming rhomboidal structures, slate-gray globules, circles within circles, atypical blood vessels, and slate-gray dots [13]. In a study comparing LM/LMM clinical borders identified by routine clinical examination, Wood's lamp, and dermoscopy prior to Mohs surgery excision, the

borders determined by both dermoscopy and Wood's lamp were larger than those by routine examination [14]. The borders determined by dermoscopy were also larger than those of Wood's lamp. Still, most lesions had to undergo an additional 5 mm excision beyond the clinical border even defined by dermoscopy. These findings are further evidence of both the improved accuracy of Wood's lamp and dermoscopy, as well as of the common subclinical extension of LM/LMM.

Reflectance confocal microscopy (RCM) allows for non-invasive, video-rate imaging of thin sections of human skin in vivo [15]. With a penetration depth of approximately 250 μm (superficial reticular dermis), an axial resolution of 3–5 μm, and a lateral resolution of approximately 1 μm, RCM images are comparable in resolution to routine histology sections [16]. Natural cutaneous chromophores and their varying refractive indices provide the contrast of RCM imaging; melanin, in particular, serves as a strong natural contrast agent [17]. Morphologic features on RCM positively predictive of malignant melanoma include disarray of epidermal honeycomb pattern, pagetoid cells in epidermis, non-edged dermal papillae, cellular atypia at the dermal-epidermal junction, atypical melanocytic nests, and bright nucleated cells in upper dermis [18, 19] In a study involving 51 patients with dysplastic nevus syndrome, RCM served as a helpful adjunct to serial imaging and was shown to have a sensitivity and specificity for the diagnosis of malignant melanoma of 100 % and 69 %, respectively [19]. Such diagnostic accuracy, in addition to its non-invasive real time imaging, allows RCM to play an important adjunct role in helping to define LM/LMM borders.

Histopathology examination with or without immunostaining remains the gold standard for defining benign versus malignant melanocytic lesions. In background skin with severe sun-damage, the specificity in diagnosing melanoma may be reduced when using dermoscopy and confocal microscopy. In such circumstances, scouting punch biopsies are helpful in identifying subclinical extension of LM/LMM lesions. In patients that were found to have melanoma in situ at margins after standard excision, Dengel et al presented the technique of placing 2-mm punch biopsy sites (which heal rapidly and scar minimally) in a ring 1 cm beyond the scar and/or residual melanoma lesion [20]. The use of ultraviolet light (Wood's lamp) to guide scout punch biopsy sites has also been reported. UV light-assisted scout biopsy margin mapping is shown to avoid repeat surgery and may reduce recurrence [21].

Since difficult-to-treat LM/LMM lesions often occur in sun-exposed areas, the histopathology will commonly show an increased number of basal layer melanocytes, some of which may be atypical. Histopathologic criteria for the diagnosis of a positive margin for melanoma in situ (as opposed to melanocytic hyperplasia) have been outlined by Weyers et al and include: the presence of melanocytic nests, irregular distribution of pigment, non-uniform distribution of melanocytes, melanocytes far down the adnexal structures, melanocytes above the dermoepidermal junction, and atypical melanocytic nuclei [22]. Multinucleated melanocytes with a "starburst" appearance (because of their prominent dendritic processes) are another useful finding to distinguish LM/LMM from melanocytic hyperplasia from sun damage [23].

Once appropriate surgical margins have been estimated with visual inspection, Wood's lamp, dermoscopy, confocal microscopy, and/or scouting punch biopsies, the LM/LMM lesion can be excised using a margin controlled surgical technique to ensure complete margin control prior to closure. After initial tumor debulking, the specimen is sent for rush paraffin-embedded permanent section processing with complete histological evaluation of borders. If a margin is determined to be positive (i.e. melanoma in situ within 3 mm of border), then re-excision is performed at that site and the process repeats until complete margin control is obtained prior to closure [1]. The use of permanent sectioning (serial perpendicular or "breadloaf fashion") allows easier lab processing, complete assessment of melanoma prognostic factors, and the ability of the dermatopathologist to assess changes in cell density from center to periphery of tumor, which can be critical for assessing these challenging lesions.

This case example illustrates a variation in the staged excision technique with rush permanent section evaluation of the surgical margins. The initial staged excision only removed a narrow margin (Fig. 16.6), and the pathology assessment determined how much additional margin was needed. For example, if the 3 o'clock margin is read as positive for LM/LMM (while the 6 o'clock margin is read as tumor-free margin with tumor 3 mm away from this margin, and the 9 o'clock is read as narrow margin with tumor seen within 1 mm of the lateral margin), then the second staged excision may be planned as the following: 7–8 mm at 3 o'clock, 2–3 mm at 6 o'clock and 4–5 mm at 9 o'clock. This detailed, stepped planning allows for increased tissue conservation and accuracy compared to a standard wide excision. The initial staged excision also provides the pathologist a thinner specimen piece compared to a traditional full layer wide excision. The thinner specimen is more easily processed with less embedding artifact (compared to a thick, fatty wide excision specimen), making it easier to read. The initial staged excision defect is also more superficial compared to a full thickness excisional wound bed, and therefore has less risk of hemorrhagic complication while awaiting the pathology report. In summary, this case presents the complexities and challenges in assessing the extent of LM/LMM in a background of severe sun damage.

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Chapter 17
Case B: Unsuspected Invasion and Upstaging in Lentigo Maligna Melanoma

Brienne D. Cressey, Klaus J. Busam, and Kishwer S. Nehal

Case

A 61-year-old Caucasian male, skin type I with hazel eye color, presented with an irregular light brown patch on the left mid cheek. His past medical history included hypertension, insulin dependent diabetes, arthritis, glaucoma, obesity, and cervical spine spondylolisthesis. He had history of basal cell carcinomas and actinic keratoses. His personal melanoma history included melanoma in situ lesions excised from the left lateral cheek (15 years prior), left mandibular cheek (10 years prior), and left neck (5 years prior). Family history was significant for melanoma in his mother. Due to personal and family history of melanoma, this patient was followed with frequent skin examinations at regular intervals.

The new pigmented lesion on the left mid cheek had developed recently, and his referring dermatologist performed three small biopsies within the large pigmented lesion (Fig. 17.1) with very poorly defined clinical borders, as a complete excisional biopsy was not feasible. Pathology demonstrated a primary melanoma of the lentigo maligna subtype, in situ (Fig. 17.2) and focally invasive to Breslow depth 0.5 mm at

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_17

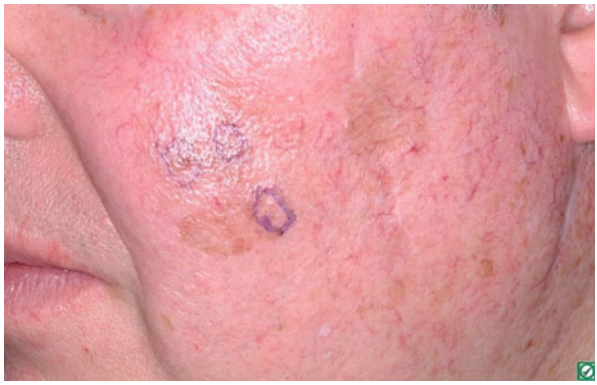

Fig. 17.1 Irregular brown patch on the left cheek in background of solar lentigines; biopsy sites marked in *purple*

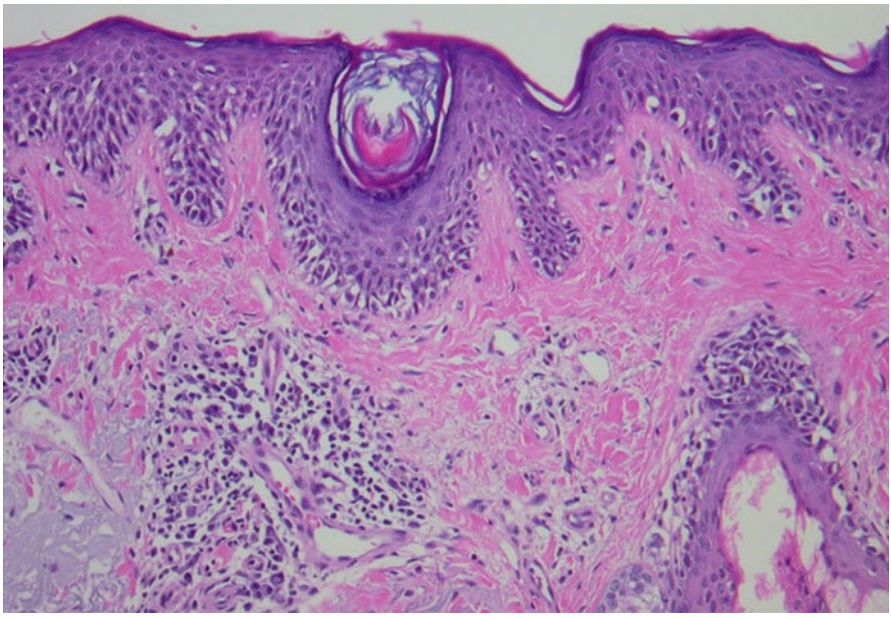

Fig. 17.2 Melanoma in situ of the lentigo maligna type: confluent proliferation of atypical melanocytes with pagetoid spread and follicular involvement and dermal solar elastosis (H&E, 20×)

least. The biopsies were reviewed and the LMM diagnosis confirmed by our pathology department.

At presentation, a detailed review of systems was negative and the biopsied lesion was asymptomatic. On clinical exam, a faint brown patch on the left mid cheek was present in a background of multiple solar lentigines and was distinctly separate from a scar along the left lateral cheek from treatment of a prior melanoma in situ. The clinical lesion appeared to measure 2–3 cm, but, due to the extensive background of photodamage, the true clinical margins of the lesion were difficult to delineate visually. Wood's light exam accentuated the pigmented lesion, but the

borders of the lesion still remained vague. No palpable lesions were appreciated on palpation of the lesion and surrounding tissue and head and neck lymph node basins. In order to better estimate extent and depth of the melanoma, another biopsy was performed of a slightly darker mark within the pigmented lesion and showed only chronically sun damaged skin. A control biopsy of normal appearing sun damaged skin was also performed to establish a baseline. Pathology showed marked solar elastosis, but intraepidermal melanocyte density was within normal limits.

Based on biopsy pathology information, an initial diagnosis of a thin melanoma was made. No further lab or imaging work was performed according to guidelines for an otherwise asymptomatic patient with pT1a melanoma [1]. An excision with 1 cm margins to the deep subcutaneous plane was performed using our staged excision with radial sectioning technique and tissue was sent for 24-hour rush paraffin-embedded permanent sections (Fig. 17.3). The tumor debulking centrally showed residual melanoma with invasion to 2.2 mm Breslow depth, Clark IV, non-ulcerated,

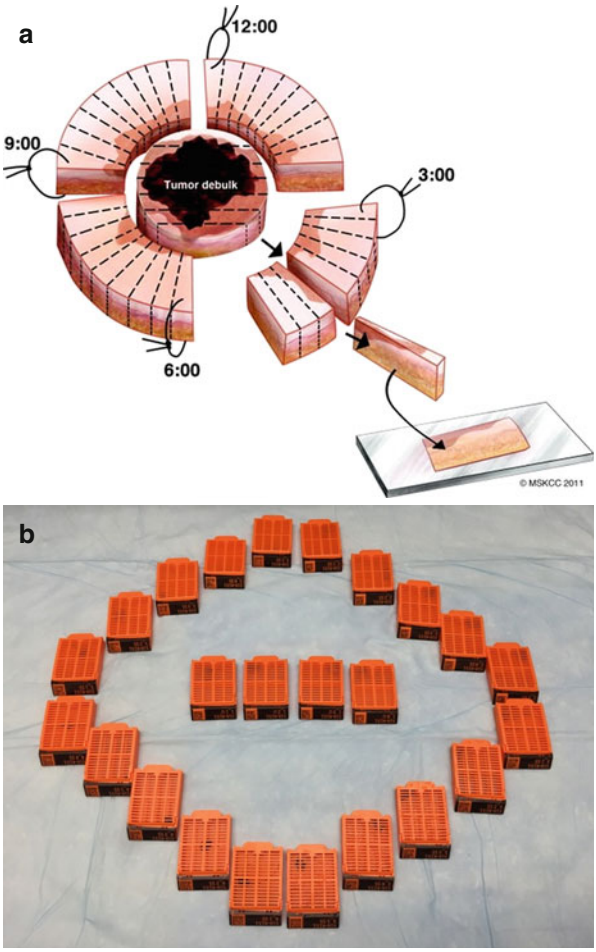

Fig. 17.3 Staged excision with radial sectioning technique: (**a**) The tumor is debulked centrally and margins excised and evaluated with vertical sections (**b**) The divided tissue is placed into cassettes for processing and embedding with complete preservation of tissue orientation

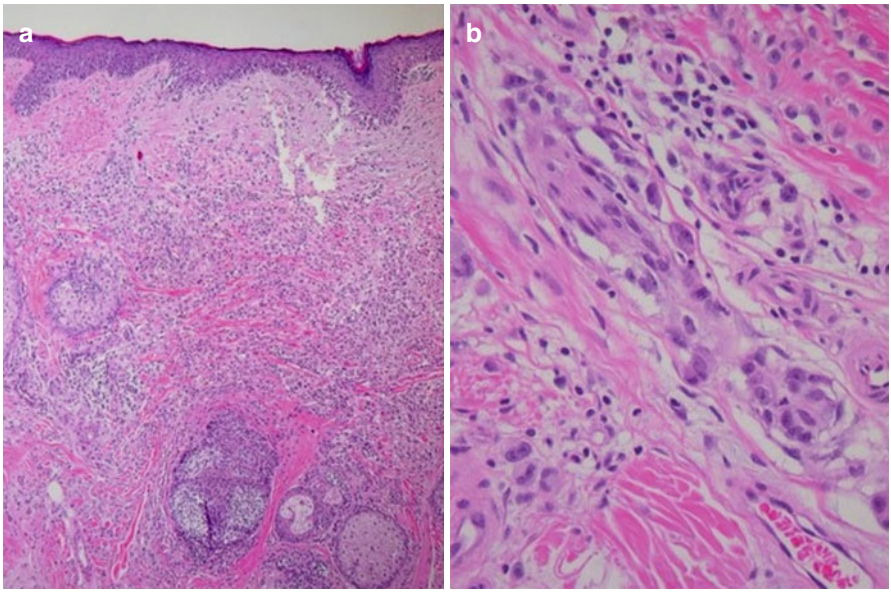

Fig. 17.4 (**a**) Melanoma Breslow thickness 2.2 mm extending to reticular dermis (H&E, 4×); (**b**) melanoma invading a nerve (H&E, 40×)

mitotic rate 1/mm^2, with no lymphovascular invasion, and no satellites (Fig. 17.4a). Perineural involvement was noted at the base of the tumor (Fig. 17.4b). The peripheral margins were clear in all four quadrants.

A consultation with head and neck surgery was arranged immediately given pathologic upstaging to a pT3a melanoma with associated risk of nodal and systemic metastasis. After a discussion with the patient and consulting physicians, a decision was made to not pursue sentinel lymph node biopsy (SLNB) given the 5 cm surgical defect (Fig. 17.5) and potential inaccuracy in this situation where the nodal mapping may not be relevant. Additional margins were excised to exclude in transit metastasis and pathology showed no residual melanoma. After consultation with plastic and reconstructive surgery, decision was made to reconstruct the surgical defect with a full thickness skin graft given melanoma upstaging, size of defect, and multiple medical co-morbidities. Following reconstruction, the graft healed well and cranial nerve VII function was preserved. Further lab and imaging workup did not reveal any evidence of regional or systemic disease. In summary, the melanoma was upstaged to Stage IIA disease. The patient continued melanoma follow up every 3–4 months with interval clinical exams and imaging.

One year following initial surgical treatment, clinically palpable left cervical lymphadenopathy developed and CT scan of the neck showed two enlarged lymph nodes in the submandibular space suspicious for malignancy. Fine needle aspiration confirmed metastatic melanoma. After a systemic workup with medical oncology showed no other concerning findings, the patient underwent left superficial parotidectomy and left modified radical neck dissection. 0/16 parotid nodes and 2/15 neck

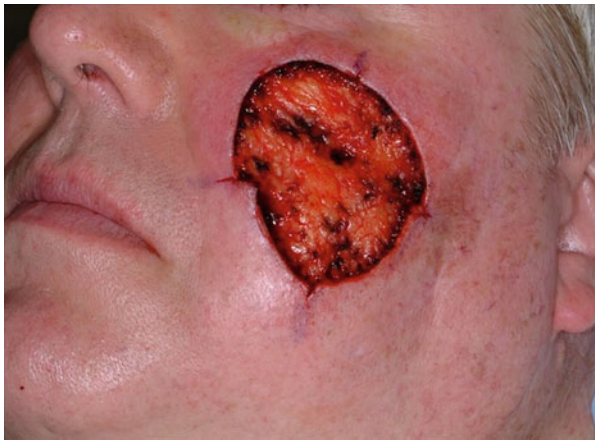

Fig. 17.5 5 cm surgical defect on left cheek following staged excision

nodes were positive for melanoma with extranodal extension. Post-operative adjuvant radiotherapy was performed, and the patient continued clinical followup with medical oncology with interval scans. One year later, an enlarging pulmonary nodule was noted on CT scan and biopsy confirmed metastatic melanoma. He underwent radiofrequency ablation of the pulmonary nodules but ultimately succumbed to metastatic melanoma 2 years later.

Discussion

This case demonstrates the multiple challenges in treating LM/LMM. This patient had a very subtle pigmented lesion with poorly defined visual borders making it clinically difficult to differentiate from the surrounding benign solar lentigines, seborrheic keratosis, and sun damaged skin. When a change in a pigmented lesion is noted on the face, frequently only small partial biopsies can be performed within the concerning portion of the large pigmented lesion in anatomically sensitive areas of the head and neck. In this case, a complete excisional biopsy was not feasible. Once a diagnosis of melanoma is confirmed histologically, further mapping biopsies are often needed to establish extent of the melanoma to guide management [2]. Dermoscopy and reflectance confocal microscopy can help guide mapping of the peripheral margins but cannot determine melanoma depth of invasion.

Surgical excision is the recommended treatment for LM/LMM. Multiple studies have shown that standard 5 mm margins typically recommended for melanoma in situ are often inadequate for the LM subtype [3, 4]. Given the tendency of LM to be ill-defined, wide excision with immediate repair of the defect can often lead to the need for re-excision which can be problematic if a complex flap has already been performed. Therefore, a margin controlled surgical technique is recommended to allow all margins to be evaluated histologically prior to reconstruction of a defect

[3–7]. Recurrence rates with a margin controlled staged excision method are 0–7 %, superior to the reported recurrence rates of up to 20 % for wide local excision [4].

In this case, a staged excision was performed using rush 24-hour paraffin-embedded permanent sections [3]. The pigmented lesion was excised to the deep subcutaneous plane and sent for permanent sections as tumor debulking for melanoma prognostic information. The final pathologic staging showed a melanoma with Breslow thickness of 2.2 mm with perineural invasion. Even mapping biopsies are subject to sampling error. As seen in this case, the deeper involvement of the melanoma was not diagnosed until the complete excision was performed despite 4 partial biopsies. The peripheral margins were divided into four quadrants labeled 12 to 3 o'clock, 3 to 6 o'clock, 6 to 9 o'clock, 9 to 12 o'clock with sutures placed to maintain orientation. These margins were excised to the deep subcutis and processed into radial sections to enhance margin evaluation and determine peripheral margin of clearance.

Although the peripheral margins were completely clear in this case, in other cases it can be difficult to define the clear margins if there is trailing melanocytic atypia. A control biopsy of normal appearing but sun-damaged skin may provide a reference for normal melanocyte density for an individual and help determine the often challenging demarcation between background of severely sun-damaged skin and LMM on histopathology [8].

This LMM case also represents an uncommon case of upstaging associated with a worse prognosis [9, 10]. While unsuspected invasion is noted in 4–16 % of LM cases [4], upstaging to an intermediate or thick melanoma is not typically found. Most cases of unsuspected invasion involve a thin LMM diagnosed histologically during complete excision following an initial diagnosis of in situ melanoma on biopsy. Often the invasive melanoma when noted on excision is limited to the radial growth phase and does not change the prognosis significantly [3]. The other uncommon finding in this case was presence of perineural invasion. Invasion of nerve twigs is more common with desmoplastic melanoma. Desmoplastic melanoma may be associated with LM or atypical intraepidermal melanocytic proliferations [8]. In this case however, the finding of perineural invasion was seen without associated desmoplastic melanoma.

The head and neck region has a rich and complex lymphatic drainage creating challenges for nodal staging in melanoma in these areas. Given the overlapping lymphatic drainage, head and neck melanomas do not always follow predictable metastatic patterns. Some authors feel sentinel lymph node biopsies may have a higher false negative rate for the head and neck in comparison to melanomas on the trunk or extremity [11]. In this case, our patient had a large defect after staged excision and unsuspected intermediate thickness melanoma. A sentinel lymph node biopsy was not performed given the size of the defect but others may have considered it for staging purposes.

There are as yet no longitudinal studies that have definitely determined the risk or rate of progression from LM to LMM; however, extrapolated data from melanoma registries estimate a lifetime risk of 4.7 % in a patient diagnosed with LM at age 45 [12]. LMM are detected and diagnosed at an early stage are often curable through surgical resection with meticulous evaluation of margins. However, as this

case demonstrates, it is important to be aware of the many subtleties and pitfalls in the management of LMM. Furthermore, when a LMM is upstaged to a higher risk melanoma, the management of the melanoma then follows melanoma clinical practice guidelines as outlined by the National Comprehensive Cancer Network and requires a multidisciplinary approach [7].

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Chapter 18
Case C: Topical Treatment of Lentigo Maligna: A Case Comparison

Emily C. Newsom and Steven Q. Wang

Surgery is the treatment of choice for lentigo maligna (LM) and lentigo maligna melanoma (LMM). However, not all patients are good surgical candidates for reasons such as large lesion size, anatomically sensitive location, medical comorbidities, or patient preference. Non-surgical treatment options include topical imiquimod, topical retinoids, cryotherapy, elecrodessication and curettage, ablative CO2 laser, and radiation therapy. Off-label use of topical imiquimod for lentigo maligna has been reported in the literature since 2000 [1]. Studies are limited to small series with short follow up [1–5]. Two LM cases are presented to illustrate treatment challenges with topical imiquimod and variability of treatment response.

Case 1: Lentigo Maligna with Durable Response to Imiquimod

An 86 year old Caucasian female presented with a biopsy-proven lentigo maligna on the left cheek. Examination revealed a 3.5 cm pigmented patch on the left cheek with no palpable head and neck lymphadenopathy. Given her advanced age, lesion

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3_18

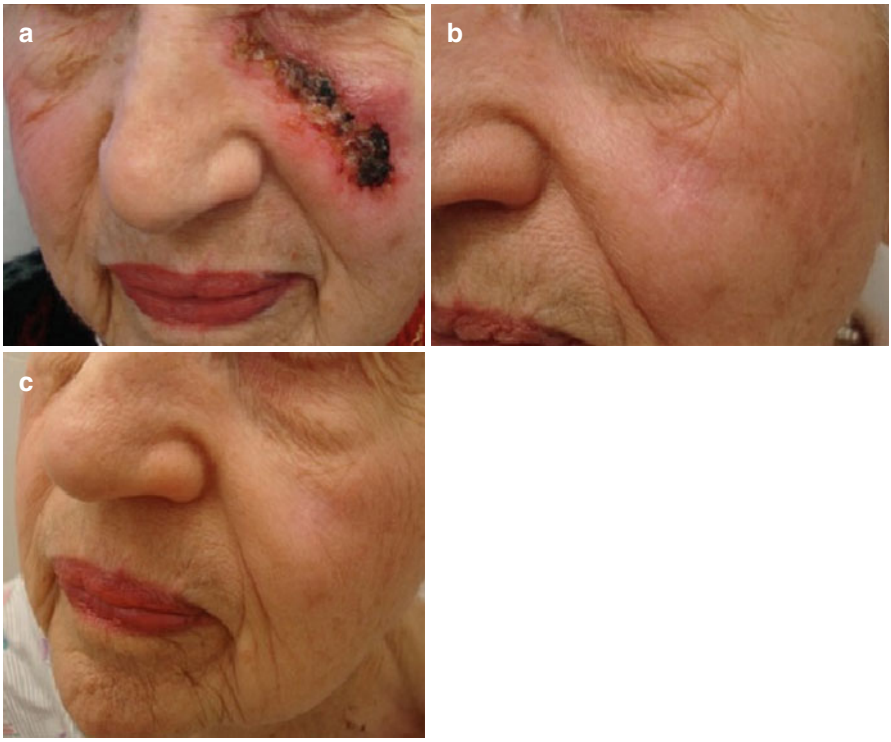

Fig. 18.1 (**a**) Lentigo maligna on left cheek with brisk inflammatory response after a 12-week course of imiquimod. (**b**) Clinical clearance of lentigo maligna 4 months after completion of imiquimod course. (**c**) Durable clinical response 5 years after treatment

size in an anatomically sensitive area, and patient preference, decision was made to use off-label topical imiquimod and avoid extensive surgery and complex reconstruction. Patient completed a 12-week course of topical imiquimod 5 times per week applied to the lesion and 2 cm of surrounding tissue. During the treatment course, she developed a brisk inflammatory response (Fig. 18.1a) followed by complete clinical resolution of the pigmented lesion (Fig. 18.1b). At 4 months post-treatment, there was no clinical evidence of persistent or recurrent melanoma aside from focal areas of faint pigmentation on dermoscopy. Punch biopsies at these pigmented areas confirmed histologic clearance of melanoma. The patient was followed clinically at regular 6 month intervals. At 5 years post topical treatment, she had maintained a durable response with no clinical evidence of recurrence (Fig. 18.1c). It is also worthy to mention that the treated side had a significant improvement in rhytides and photoaging compared to the surrounding untreated area and contralateral cheek.

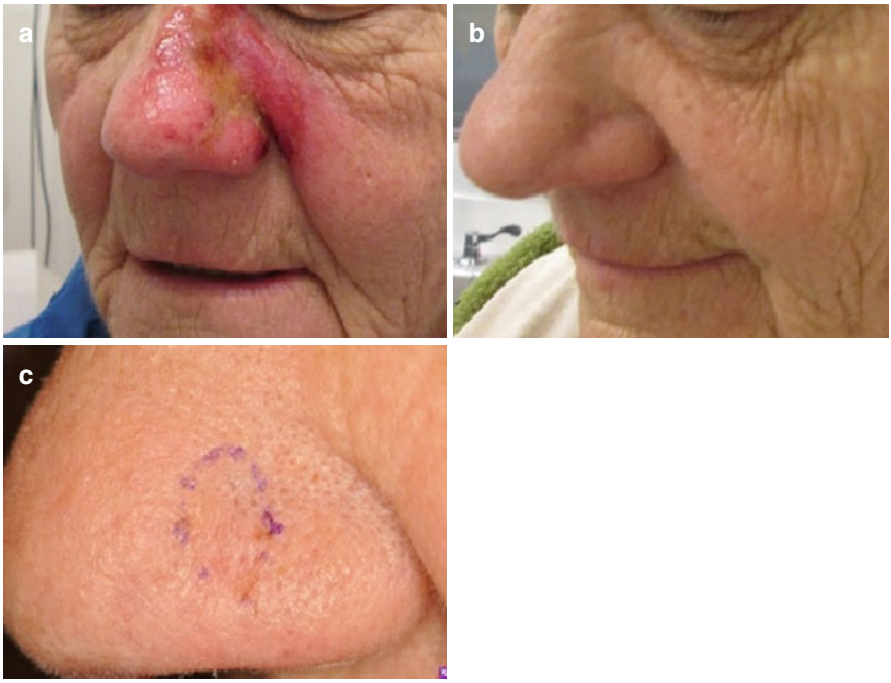

Fig. 18.2 (**a**) Lentigo maligna on left nose with an exuberant inflammatory response after a 12-week course of topical imiquimod. (**b**) 3 months post-treatment with clinical resolution of pigmented lesion. (**c**) Re-pigmentation at inferior aspect of lesion 1.5 years post-treatment that showed melanoma in situ on biopsy

Case 2: Recurrent Lentigo Maligna After 12-Week Imiquimod Course

A 75 year-old Caucasian female presented with a pigmented lesion on the left nose and the initial biopsy showed a melanoma in situ. Woods light exam showed an asymmetric ill defined 2.6 cm pigmented patch in a background of extensive sun damage. After discussing the rationale, risks and benefits of staged excision versus nonsurgical options such as off-label use of topical imiquimod, the patient elected treatment with imiquimod. Patient began a 12-week course of topical imiquimod applied 5 times a week to the lesion plus 2 cm overlap area. She developed an exuberant inflammatory response to treatment (Fig. 18.2) with complete clinical resolution of the pigmented lesion. This clinical response was maintained until 1.5 years after treatment when she noticed repigmentation at the inferior aspect of the lesion. Two repeat biopsies both confirmed persistent melanoma in situ.

Discussion

The objective of this case discussion is to highlight clinical pearls and practical considerations for selecting this treatment modality for select non-surgical cases.

These two cases illustrate the clinical application of topical imiquimod for off-label treatment of lentigo maligna and the variability of clinical response. In both cases, a 12 week treatment course (5 times weekly regimen) resulted in a brisk inflammatory response with subsequent clinical resolution of the pigmented lesion. However, similar initial clinical responses resulted in two different long-term outcomes. One patient had a favorable outcome with a durable response with greater than 5 years of follow-up while the other patient developed a recurrence of the lentigo maligna after 1.5 years.

This unpredictable variability in clinical response emphasizes the importance of close clinical follow up after topical imiquimod treatment. According to a review of 44 studies evaluating 327 tumors [1], lentigo maligna primarily treated with topical imiquimod has an average histologic clearance rate of 71.5 % (64.7–78.3 %) and average clinical clearance rate of 78.6 % (72.3–84.9 %) with a mean follow up of 34±11.8 months. The treatment regimens ranged from 3 to 5 days a week for 1–6 months. In general, the studies show a positive inflammatory response correlates with clinical and histologic clearance [1–5]. More rigorous treatment regimens (>5× a week or >60 applications) correlated with better outcomes as well [1].

The decision to start topical imiquimod as compared to surgery for facial lentigo maligna requires careful case-by-case evaluation of individual patient situations. Factors affecting treatment decision include age, co-morbidities, size and location of the LM, psychological and emotional state, and family and social support. Aside from the biological behavior of the lesion and host immune system, treatment success also depends on the patient's willingness to complete the treatment course. Although the treatment duration varies from 6 to 12 weeks, longer treatment cycles may improve overall success.

To increase patient compliance, the expected extent and severity of inflammation must be communicated to the patient prior to initiating treatment. It is essential to manage patient expectations regarding facial appearance for the full 3 months of treatment. Frequent clinical follow up every 3–6 weeks during the treatment course is helpful. These "hand-holding" visits provide reassurance and motivation for the patient to complete the treatment cycle. In addition, these interval visits also allow the treating physicians to taper down or increase the frequency of application. At times, topical antibiotic ointment such as mupirocin or dilute vinegar soaks may be needed to treat impetiginization. The patient should be reassured and reminded that their skin will return to a normal texture and appearance once the inflammation resolves. The added anti-aging benefit of treatment can be a motivating factor for some patients.

Frequent post-treatment follow up, particularly within the first 6 months, is advised with exam consisting of palpation and visual and dermoscopic inspection. Confocal laser microscopy is also a useful to monitor the LM treatment site as it provides in vivo imaging of the skin at high resolution similar to histologic sections [6, 7]. The clini-

cian must be aware of pitfalls of treating lentigo maligna with topical treatment, and there should be a low threshold for repeat biopsies. For instance, a desmoplastic melanoma may be misdiagnosed as melanoma in situ if the initial biopsy was too superficial. Also, it is important to keep in mind that 5–50 % of lentigo maligna have a focus of invasion at initial presentation [8, 9], which could be missed due to sampling error with initial partial biopsy. Post-inflammatory pigmentary alteration may make follow up difficult, and amelanotic recurrence is particularly difficult to diagnose. Therefore, any suspicious changes should be biopsied at follow up.

Further investigation with randomized controlled trials and long-term follow up is needed to determine efficacy, recurrence risk, and optimal treatment parameters. A further understanding of which patients develop invasive melanoma is needed to better guide which patients are good candidates for topical therapy. Adjuvant imiquimod also requires further study for efficacy and to determine advantage of pre- vs. post-surgical imiquimod. In summary, imiquimod may be considered in select patients who are not good candidates for surgery, but are highly motivated to complete the treatment course.

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K.S. Nehal, K. Busam (eds.), *Lentigo Maligna Melanoma*,
DOI 10.1007/978-3-319-43787-3