Mohs Surgery for Melanoma In Situ

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Background and Epidemiology

Melanoma in situ (MIS) is a proliferation of malignant melanocytes within the epidermis, without invasion into the dermis. Typically, pigmented macules display the features of melanoma such as variegated color, asymmetry, and irregular border. However, presentation can be varied with some presenting similar to normal freckles or nevi, but distinguished by growth or change. The histologic features include a predominance of individual melanocytes over nests, confluent growth along the epidermis, and pagetoid spread of individual melanocytes into upper layers of the epidermis.

There are four subtypes of MIS: lentigo maligna, superficial spreading, acral lentiginous, and mucosal. Perhaps 75% of MIS can be further classified as lentigo maligna subtype, which has a confusing history. In 1890, it was described as "Hutchinson's melanotic freckle" [1]. Its slow growth led to the hypothesis that it was infectious in etiology. In 1912, Dubreuilh characterized the lesion as precancerous [2]. Some postulated there were two types of lentigo maligna, one that was benign photodamage and one that was malignant [3]. It is still misconstrued by some as a premalignant lesion [4].

Today, lentigo maligna is well established as a subtype of MIS on sun-exposed skin. As such, it occurs in older patients, with peak onset in the seventh and eighth decades of life. Histologically, it contains atypical melanocytes along the basal layer of the epidermis in solitary units or small nests and solar elastosis (abnormal elastin accumulation from excessive sun exposure). Extension of cytologic atypia down follicles and other adnexal structures is common. Though characterized by slow growth, sometimes taking years to diagnose, it is a malignant tumor.

Amelanotic extension is frequently described as an expected feature of lentigo maligna, but it is present in all MIS and invasive melanoma. At least 62% of melanomas contain an area of amelanotic or subclinical extension [5]. Amelanotic extension can be foreshadowed by the loss of freckling, but it is more commonly invisible to the eye. Due to the inability to visualize the border or margin of an MIS or melanoma, standard excision must be performed with an additional safety margin of normal-appearing skin. Discussion of excision guidelines follows.

Aside from subclinical extension, the presence of occult invasive components must be considered. Numerous studies have found that 5–67% of biopsy-proven MIS are later upgraded to invasive melanoma [3, 6–15]. The frequency with which MIS is upgraded depends upon the

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size of the lesion and how thoroughly one examines the specimen. Of note, the invasive area may be 5–10 mm away from the clinically evident lesion [16].

The single-most powerful risk factor for the development of a MIS and melanoma is long-term cumulative UV radiation. Risk factors include fair skin, history of sunburns, tanning bed use, atypical nevi, family history, and immune suppression. Smoking does not appear to be a risk factor [17].

MIS represents 40% of all melanomas diagnosed in the United States and the incidence is rising [18]. Some debate exists as to whether this is due to a true increase versus overdiagnosis. In part, it reflects more biopsies and better histologic criteria such that diagnosis occurs earlier and more accurately. However, studies conclude that increased screening and biopsy alone cannot account for the dramatic increase in incidence [19, 20]. Over 60,000 people in the United States are diagnosed with MIS each year.

Treatment

Given the initial belief that MIS, or at least lentigo maligna, was a premalignant process, plus the frequency with which it occurs, it is not surprising that many treatments have been attempted. Radiation is second-line treatment for patients who are not surgical candidates. It is associated with a 7% recurrence rate and delayed recurrences occurring around 4 years [21]. Topical imiquimod is an inferior option associated with clinical response, but with hidden histologic persistence in at least 25% [22]. Development of invasive disease with satellite metastases has also been reported [23].

MIS is a malignant skin cancer, with an associated risk for becoming a primary, invasive melanoma. Once invasive, it has the same prognosis as other melanomas. It is important to remove the entire lesion for three reasons. First, many MIS are actually invasive. Second, if it is not invasive now, it can be in the future. Twenty-three percent of MIS recur as an invasive melanoma, with a mean Breslow's depth of 0.9 mm [24]. Third, treatment of recurrent lesions is more difficult. Recurrent tumors can track stealthily along scars and be multifocal, lowering cure rates.

The goal of excision is to remove the entire primary lesion. Because it is not possible to visualize the edge of a melanoma with the naked eye, a safety margin must be excised. Guidelines for surgical margins refer to additional tissue that should be excised beyond the visible tumor edge. The guidelines only apply in instances where one is using visual inspection to determine the tumor edge, and they do not apply if instead one uses a microscope to determine the tumor boundary. It is important to understand that the guidelines are recommendations for the clinical surgical margin measured on the patient during excision, and do not refer to histologic margins that may later appear on pathology reports.

Excision guidelines have changed over the past decade to reflect the current best evidence. In 1992, a consensus conference recommended 5 mm excision margins for MIS [25]. This was based on expert opinion at the time, not on high-level studies. Since then, multiple studies have shown that a 5 mm excision margin is inadequate (Table 18.1). A margin of 5 mm will only clear 23–86% of all MIS lesions [3, 8, 9, 12, 26, 27, 29–38].

To determine the surgical margin required to completely excise 97% of MIS, Kunishige et al. prospectively collected data on the treatment of 1,120 MIS lesions. In order to obtain a 97% clearance rate, a 9 mm margin of excision was required [26]. A closer look at this patient population suggested that some lesions on the head and neck actually required a 1.2 cm margin (Author's Unpublished Data). Others have also reported that a 1–1.5 cm margin is necessary [8, 12, 27, 32, 35]. The surgical margin necessary for MIS mirroring that of invasive melanoma makes sense for two reasons: First, studies have not found a correlation between Breslow's depth and the amount of subclinical extension. Second, up to 67% of MIS are actually invasive [3, 6–15].

Clinicians who treat MIS inherently understand that 5 mm margins are not adequate. However, because of the dogma that lentigo

Table 18.1 Melanoma in situ clearance rate with 5 or 6 mm is low

Study	No. of MIS lesions	Follow-up time (month)	Clearance rate with 5- or 6-mm margins
Biernet et al. [29]	76	33	0%
Clayton et al. [30]	81	22	23%
Albertini et al. [31]	42	Unknown	24% if 5 mm
			41% if 6 mm
Moyer et al. [32]	232	101	41%
Agarwal-Antal et al. [33]	92	48	42%
Zalla et al. [12]	46	16	50%
Felton et al. [27]	343	29	65%
Malhotra et al. [50]	109	32	69%
deVries et al. [34]	100	60	~69%
Huilgol et al. [8]	125	38	70%
Hilari et al. [35]	62	Unknown	73.5% if primary
			30.8% if recurrent
Bricca et al. [36]	331	58	84%
Bub et al. [9]	55	57	85%
Kunishige et al. [26]	1120	56	86%
Cohen [3]	45	58	Unknown
Bene et al. [37]	167	63	Unknown

maligna subtype has wide extensions, many question the need for a wider resection margin for other subtypes of MIS. A comparison of 1506 lentigo malignas to 849 other subtypes of MIS found no difference in margin requirements based upon subtype. Both LM and other MIS on the trunk and extremities achieved a 97% clearance with 1 cm margins. Both LM and other MIS on the head and neck achieved 97% clearance with 1.2 cm margins (Author's Unpublished Data).

Indeed, 1 or 1.2 cm margins are not always doable or desirable. In these cases, Mohs surgery should be considered. The Mohs technique is described below, noting that any technique that enables visualization of the entire peripheral margin can be used, such as staged excision or "slow Mohs," and the square technique. The more one sees, the more one can be confident the margin is clear, and thus reduce recurrence rates. In contrast, wide local excision specimens are processed by "breadloaf" technique (Fig. 18.1). The excised ellipse is cut vertically from skin to adipose. A few cross sections are viewed under the microscope. In total, less than 1% of the peripheral margin is examined [39]. Thus, residual MIS is unlikely to be detected and is often missed [40]. If there is 5 mm between each vertical cross section, then there will be a < 20% chance of finding residual tumor. This explains the exasperating tendency of MIS to recur, even when the final pathology report declares "clear" margins: recurrence rate for standard excision of MIS with a 5-mm margin is 8–20% [11, 41, 42].

Mohs surgery for melanoma is safe, effective, and validated (Table 18.2) [3, 7–9, 26–30, 32–34, 37, 40, 43–48, 50–52]. It consistently boasts low recurrence rates that approach zero. It is also associated with improved cure rates for tumors that are recurrent or located on the head and neck [27, 28, 32, 36, 37, 51].

Procedure

Mohs Technique

The biopsy scar and any residual pigment, plus 3 mm of normal-appearing skin, is excised down to the superficial adipose tissue. This debulking specimen is evaluated by routine breadloaf processing (vertical sections) to determine if there is an upgrade in Breslow's

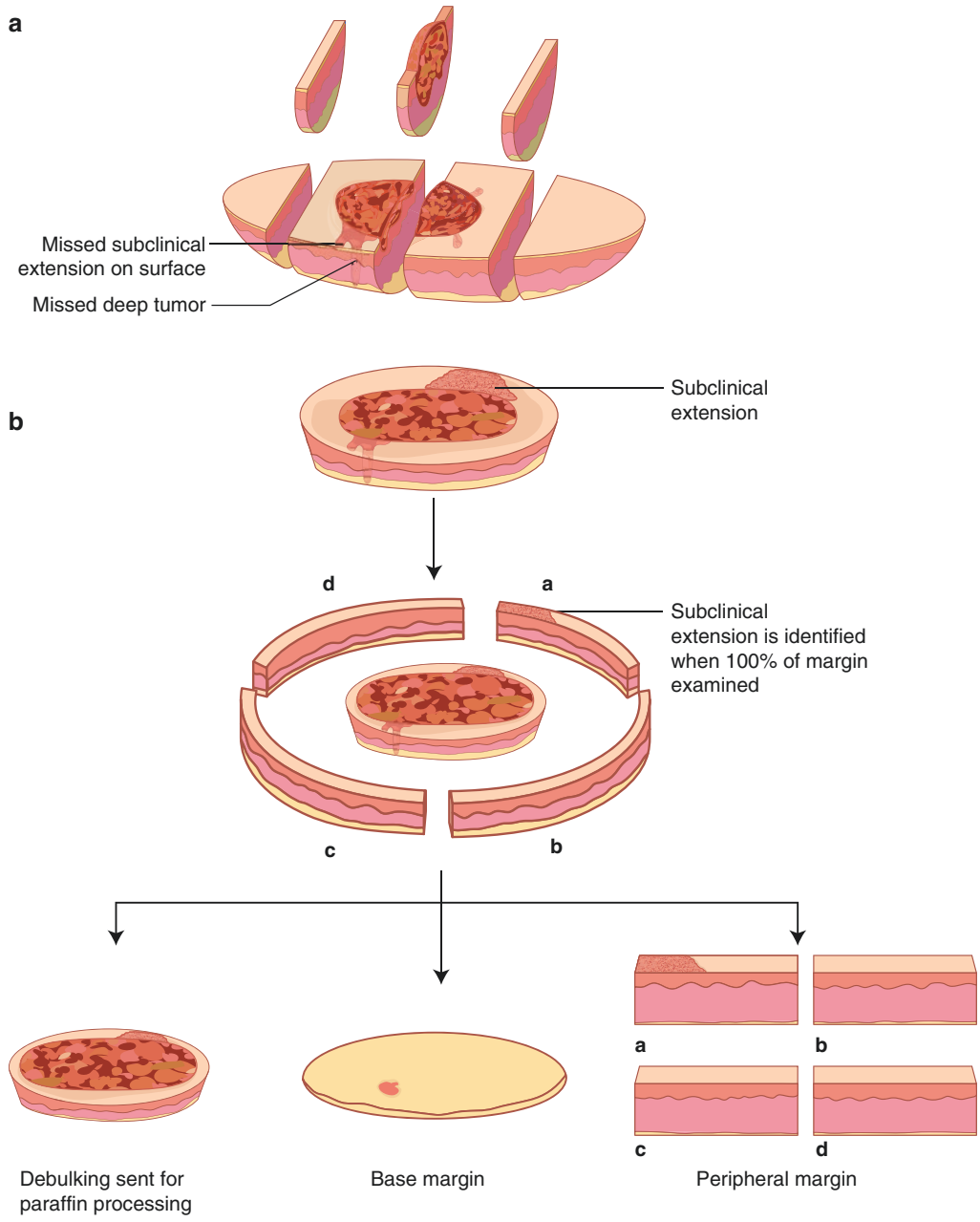

Fig. 18.1 Breadloaf technique enables visualization of less than 1% of the peripheral and deep margin, which is indicated in blue (**a**). Mohs micrographic surgery employs beveled excision and relaxing techniques to flatten the specimen, so that 100% of the peripheral and deep margin can be examined in one plane (**b**)

thickness. This can be done via permanent sections or frozen sections. Immediately after debulking, an additional 3 mm margin is taken laterally and excised as a single piece down to the deep adipose for frozen-section examination by Mohs technique. The peripheral tissue is cut into 1–2 cm strips, then stained with various colors to facilitate orientation and

Table 18.2 Low recurrence rates associated with Mohs technique

Study	# of MIS	Procedure	Follow-up (month)	Recurrence
Bienert et al. [29]	76	Mohs	33	0%
Agarwal-Antal et al. [33]	92	Mohs	48	0%
Johnson et al. [40]	35	SE	Unknown	0%
Jejurikar et al. [43]	42	SE	31	0%
Mahoney et al. [7]	11	SE	4.7	0%
Moller et al. [44]	49	SE	14	0%
Kunishige et al. [26]	2335	Mohs	56	0.3%
Felton et al. [27]	343	Mohs	29	0.3%
Etzkorn et al. [28]	436	Mohs	34	0.5%
Anderson et al. [45]	150	SE	<60	0.7%
Clayton et al. [30]	77	Mohs	22	1%
Bosbous et al. [46]	49	SE	26	1.7%
Bene et al. [37]	116	Mohs	63	1.8%
Nasrati et al. [47]	277	Mohs	103	1.8%
Hou et al. [48]	407	Mohs	95	1.9%
Huilgol et al. [8]	125	Modified SE	38	2%
Moyer et al. [32]	834	SE	10	2%
Cohen et al. [3]	26	Mohs and SE	58	2.2%
Hill et al. [49]	38	Modified SE	25	2.6%
Bub et al. [9]	55	Modified SE	57	3.6%
Malhotra et al. [50]	109	Modified SE	32	3.7%
deVries et al. [34]	100	SE	60	4%
Walling et al. [51]	50	Modified SE	95	6%
Lee et al. [52]	31	Modified SE	42	9.6%
Total	5863	Mohs or SE	45 (mean)	2% (mean)

SE staged excision, *Modified SE* vertical sections were used and entire margin not examined

localization. Frozen sections with and without MART-1 immunostain are reviewed (Fig. 18.2). Any remaining tumor is marked on a map representing the surgical wound. Additional 3 mm margins are excised in exact areas where residual tumor is noted.

Positive margins are defined as those containing at least one of the following: (1) nests of at least 3 atypical melanocytes, (2) melanocytes above the dermoepidermal junction, and (3) nonuniform crowding of cells along the basement membrane. Other histologic findings raising suspicion include: (1) extension of atypical, crowded melanocytes far down adnexal structures, (2) nonuniform distribution of pigment, (3) excessive number of melanophages, and (4) brisk inflammatory response. Increased melanocyte density and mild to moderate confluence alone are typical of melanocytic hyperplasia in sun-damaged skin, and should not be interpreted as melanoma [54, 55]. Using these criteria, the interpretation of frozen sections is comparable to that of paraffin sections [56].

Some Mohs centers utilize additional or alternate immunostains. MITF is a nuclear stain and therefore will only stain melanocytes, whereas MART-1 stains an antigen found on the surface of melanocytes that can sometimes be found in keratinocytes and pseudonests. Though MITF is more specific, the nuclear stain creates faint and tiny dots. MART-1 is sensitive and brightly positive. The rapid 1-hour protocol makes it the most practical and efficient method for Mohs surgeons to judge the presence or absence of melanoma at the margin [54, 57].

The evaluation of melanoma by frozen section requires meticulous lab processing. The immunostain must be applied exactly and without contact with agents that can bind the immunostain and render it useless. Most importantly, the sections of tissue must be very thin. Thicker sections result in viewing a stack of cells, which results in

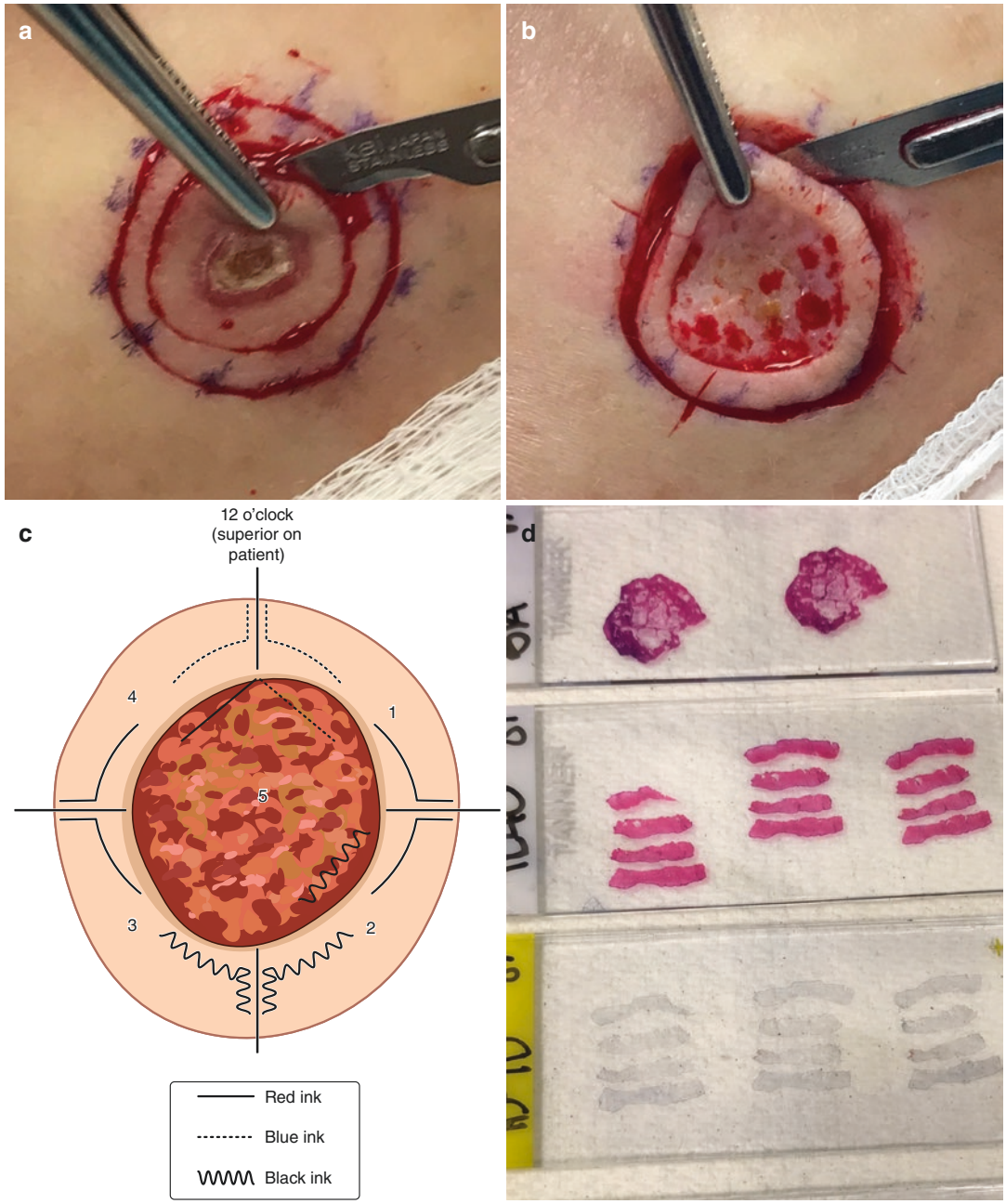

Fig. 18.2 Mohs technique for melanoma. First, the visible tumor is excised and examined with vertical sections (breadloaf technique) to confirm Breslow's thickness (**a**). Next, a peripheral and deep margin of normal-appearing skin is excised down to deep adipose (**b**). The peripheral margin is separated into thin strips to enable en face examination. All sections are inked and mapped (**c**). Frozen sections with and without MART-1 immunostain are reviewed (**d**). Any residual tumor at the margin is mapped then excised

increased stain and false positives. Tangential sections will also cause false positives, because the diagonal stack of melanocytes in the basal layer looks like pagetoid spread. When thin sections with crisp staining cannot be obtained, specimens can be sent out for formalin-fixed

permanent sections. Staged excision (slow Mohs) and the square technique are two procedures that utilize permanent sections to visualize the entire peripheral margin.

Staged Excision and Square Procedure

Often called "slow Mohs," staged excision mimics the procedure above, except all tissue is sent out for formalin-fixed permanent processing instead of frozen sections. After excising the central tumor to deep adipose, the first perimeter of tissue is taken. A map is drawn and sent out with the tissue. The resulting wound is dressed with petrolatum ointment and a bandage, and the patient returns in 2–3 days. If additional tissue is needed, this is excised and the patient returns in another 2–3 days. This continues until a tumor-free plane is reached. Then, the patient returns for reconstruction of the defect.

A variant of staged excision is the "square procedure." Here, the desired surgical margin is outlined with geometric angled corners of the lines, such as a square or rectangle. Geometric configuration may facilitate tissue processing. A double-bladed hair transplant scalpel is used to remove a 2–4 mm wide strip of tissue around the tumor. This circumferential band is sent out for permanent section margin evaluation. Additional stages are performed as necessary. Once a tumor-free peripheral plane has been reached, the remaining central "island" of tissue is excised to deep adipose and sent out. With melanoma in situ, it is reasonable to assume the deep margin will be clear and to repair the wound. Of course, if the deep margin proves to contain invasive tumor transected at the base, then additional excision will be necessary [43].

With either of these procedures, the surgeon and pathologist must work together to ensure the entire peripheral margin is evaluated. The circumference of the excision should be embedded *en face*. Modified staged excision refers to the use of vertical, radial, or breadloaf sections to examine part, or all, of the peripheral margin. This will result in higher recurrence rates (Table 18.2).

Clinical Scenarios

Patient referred for lentigo maligna on the right nasal sidewall. This was excised with 6 mm margin. The peripheral and deep margins were examined by standard Mohs technique. No additional stages were needed. The final defect measured 2 cm and was able to be repaired with a local flap (Fig. 18.3). Note that margins narrower than 6 mm may be attempted, with the understanding that there will be a higher probability that additional stages will be needed. The authors routinely use narrower margins of 2 or 3 mm when working near the eye or nasal tip, or when it would allow for simpler reconstruction options.

Patient presented with multiply recurrent MIS on the left cheek. The areas of tumor were delineated via the Mohs procedure, with sparing of some scarred tissue on the lower lid. The wound was repaired with linear repair and graft (Fig. 18.4).

Patient referred for recurrent desmoplastic melanoma arising in an old forehead flap, with the desire to avoid total rhinectomy. He presented with an 8 mm nodule with surrounding induration. The tumor was excised using Mohs technique in four stages. This resulted in a hemi-rhinectomy. The patient returned to his country with plans to pursue reconstruction after one year. If delayed repair is desired to enable monitoring for recurrence, then a skin graft can be applied to prevent wound contraction (Fig. 18.5). Patients may be referred to specialists for reconstruction, or rarely, for additional excision should the tumor invade the skull or nerve foramina.

Controversies and Future Areas of Research

There is no question that complete histologic margin control results in higher cure rates. Looking is better than not looking. However, controversy exists on how to look. Some feel permanent sections are superior to frozen sections for melanoma interpretation. Indeed, frozen sec-

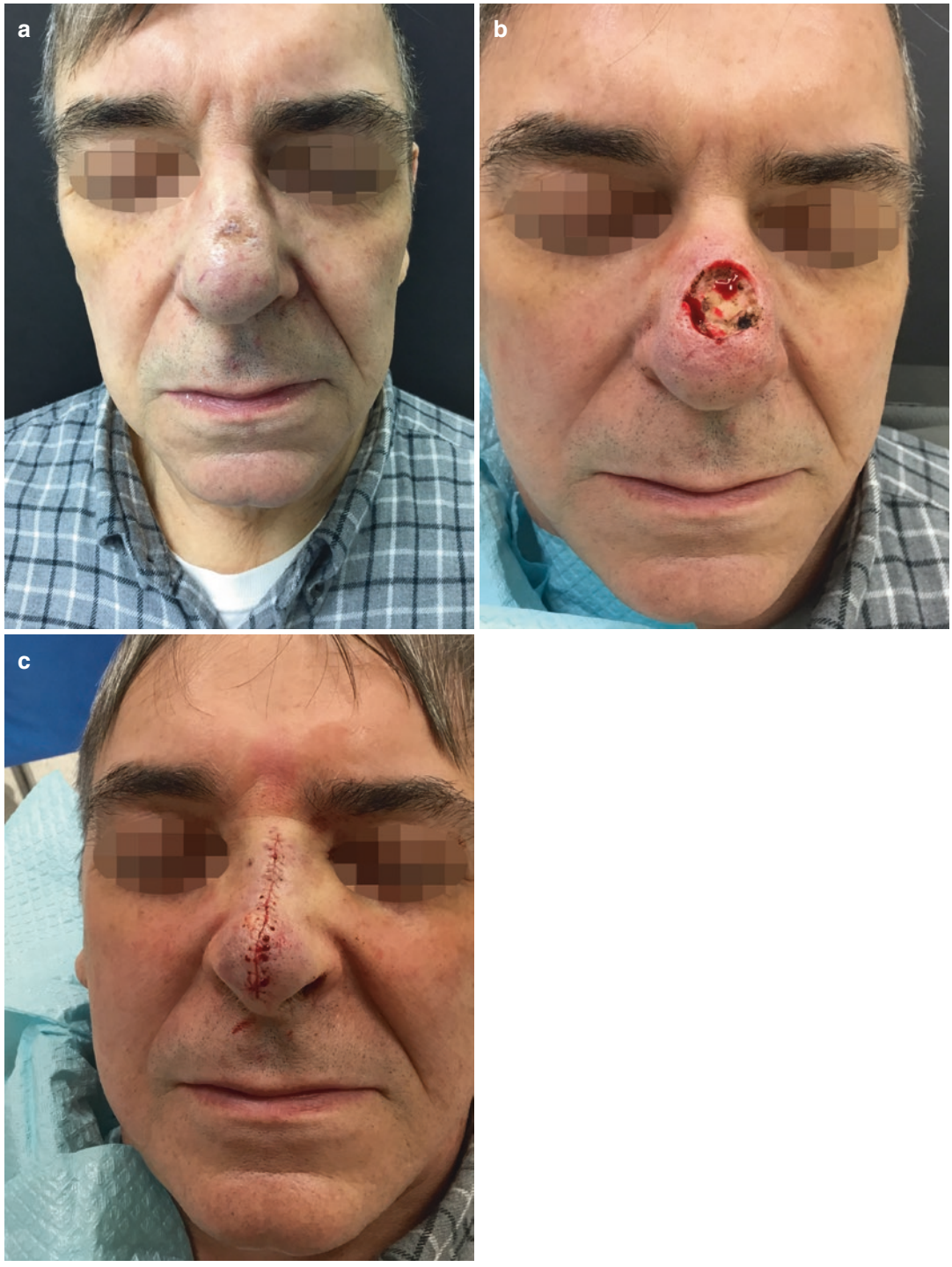

Fig. 18.3 Mohs technique simultaneously offers guaranteed clear margins (**a**, **b**) and tissue conservation enabling repair with local flap (**c**)

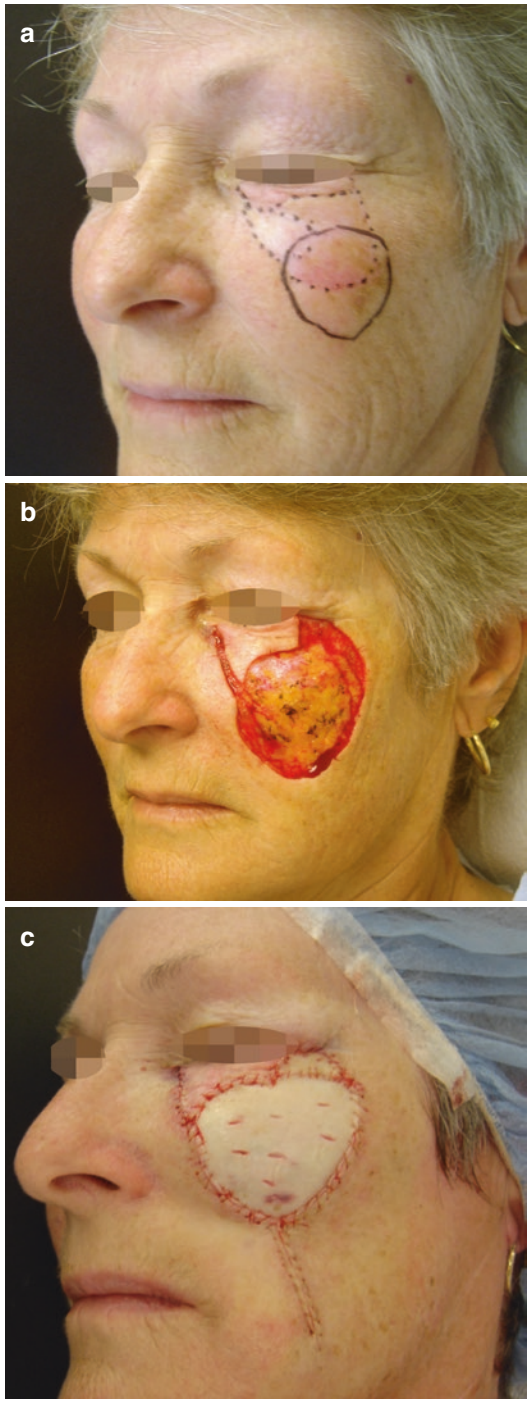

Fig. 18.4 Multiply recurrent melanoma excised with Mohs technique (**a**, **b**), then linear repair and graft (**c**). Checking 100% of the peripheral and deep margin enables the surgeon to excise less tissue than with wide local excision

tions for melanoma are technically difficult. Without an experienced technician and reliably thin sections, the stain will always appear positive, and overcalling will occur. More stages will seem required and large defects will result. The fact that most melanomas can be excised with one stage, in combination with recurrence rates of 0–2%, prove that frozen section analysis is a valid technique.

One study comparing interpretation of frozen section to that of permanent sections found no difference [56]. Another study suggested frozen sections with immunostains may actually be superior to permanent sections: staged excision with permanent sections resulted in a wider margin of resection compared to that of Mohs surgery. The average margin excised was 9.3 mm compared to 6.8 mm for Mohs surgery [26, 32]. This raises the possibility that it is more difficult to distinguish actinic-induced melanocyte proliferation from true malignancy on permanent sections than on frozen sections with MART-1 immunostain. In summary, true Mohs surgery with 100% margin examination, excision and histologic evaluation performed by the same individual, and use of immunostains will yield the lowest recurrence of any method (Table 18.2). However, if thin frozen sections with immunostain cannot reliably be achieved, then staged excision with *en face* processing and permanent sections are a good alternative.

Randomized data may never be available to support Mohs for invasive melanoma. A study by Mayo et al. reported that Mohs surgery and wide local excision had similar recurrence rates [48]. However, the two treatment arms were not randomized. Larger and recurrent lesions, as well as those on the head and neck, were referred for Mohs surgery [48]. A truly randomized study is unlikely, because it is frequently impossible to excise the full 1 cm needed on the head and neck.

Accordingly, the six prospective, randomized, controlled trials behind the guidelines for melanoma excision excluded MIS and virtually

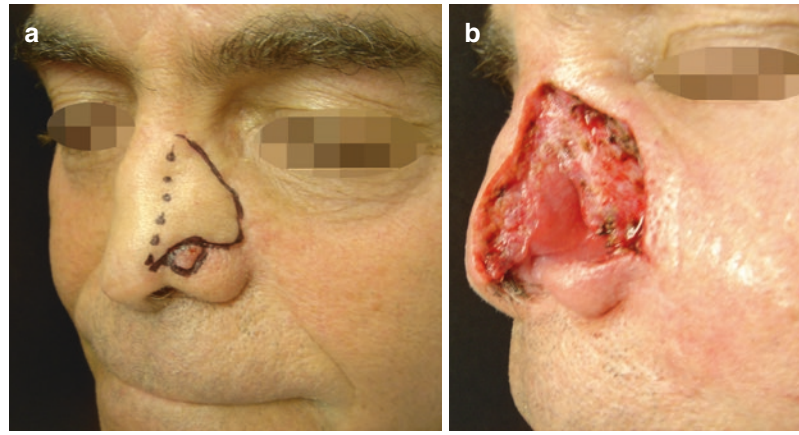

Fig. 18.5 Multiply recurrent desmoplastic melanoma excised, then patient referred to Plastic Surgery for repair (**a**, **b**). This can be done immediately post-operatively or 1–2 weeks later. If delayed repair is desired to enable monitoring for recurrence, then a skin graft can be applied to prevent wound contraction. Repair can be done with confidence that the margin is clear

excluded the head and neck location. Only 16 of 4231 randomized melanomas were on the head and neck [58–63]. Non-randomized studies of head and neck MIS and melanoma suggest that a 1 cm is inadequate for some lesions, clearing as few as 50% [27, 32, 64]. More telling, guideline margins were unable to be executed on 33% of head and neck melanomas [61].

An area of huge impact would be to increase the specificity of melanoma diagnosis. The separation of biologically important MIS from severely atypical photodamage has plagued dermatopathologists for decades, and the answer may lie in gene expression. Gene expression profiling tests already look at a battery of genes within excised melanoma tissue and accurately predict recurrence [65]. And, fluorescence in situ hybridization (FISH) analysis is frequently used to distinguish between benign Spitz nevi and malignant melanoma [66].

Another area of controversy in melanoma management is sentinel lymph node biopsy. The discussion of this is not relevant to a chapter on melanoma in situ. However, there are instances where a MIS is excised, and more thorough examination of the excised tissue results in an upgrade of Breslow's thickness whereby consideration of sentinel lymph node biopsy is warranted. In these cases, sentinel lymph node biopsy can still be performed after repair [67]. However, if this remains a concern of the multidisciplinary team, then frozen sections can be used on the debulking specimen to evaluate for the true Breslow's thickness. An upgrade in thickness would then be determined prior to starting repair, with final repair delayed until after sentinel lymph node biopsy [28].

Finally, the cost of Mohs surgery versus wide local excision is a valid concern. The cost of Mohs surgery (which includes cost of slide preparation and examination) is actually less than the cost of wide local excision plus permanent section evaluation. In a study of 406 tumors that cleared, on average, in 1.6 stages, Mohs surgery cost $805 per tumor compared to $1026 for standard excision with permanent margins [68]. Repair costs are also reduced, because Mohs typically results in smaller wounds that do not need repair or can be closed in a linear fashion. The cost of excision with positive margins and recurrent tumors should also be considered. Knowing that the margin is truly negative before embarking on a complicated reconstruction is invaluable.

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