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Optimal management of common acquired melanocytic nevi (moles): current perspectives

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Abstract: Although common acquired melanocytic nevi are largely benign, they are probably one of the most common indications for cosmetic surgery encountered by dermatologists. With recent advances, noninvasive tools can largely determine the potential for malignancy, although they cannot supplant histology. Although surgical shave excision with its myriad modifications has been in vogue for decades, the lack of an adequate histological sample, the largely blind nature of the procedure, and the possibility of recurrence are persisting issues. Pigment-specific lasers were initially used in the Q-switched mode, which was based on the thermal relaxation time of the melanocyte (size 7 µm; 1 µsec), which is not the primary target in melanocytic nevus. The cluster of nevus cells (100 µm) probably lends itself to treatment with a millisecond laser rather than a nanosecond laser. Thus, normal mode pigment-specific lasers and pulsed ablative lasers (CO₂/erbium [Er]:yttrium aluminum garnet [YAG]) are more suited to treat acquired melanocytic nevi. The complexities of treating this disorder can be overcome by following a structured approach by using lasers that achieve the appropriate depth to treat the three subtypes of nevi: junctional, compound, and dermal. Thus, junctional nevi respond to Q-switched/normal mode pigment lasers, where for the compound and dermal nevi, pulsed ablative laser (CO₂/Er:YAG) may be needed. If surgical excision is employed, a wide margin and proper depth must be ensured, which is skill dependent. A lifelong follow-up for recurrence and melanoma is warranted in predisposed individuals, although melanoma is decidedly uncommon in most acquired melanocytic nevi, even though histological markers may be seen on evaluation.

Keywords: lasers, surgery, nevus, melanoma

Introduction
Common acquired melanocytic nevi (CAMN) is a common, largely acquired, condition resulting from benign proliferation of nevus cells. This disorder, also referred to as “signature nevi,” has been variably classified depending on the anatomic, architectural, and cellular histological pattern. Melanocytic nevi form a convenient head to classify the varied manifestations of both congenital and acquired nevi, of which our focus is largely on the common acquired nevi (Figure 1). The histological spectrum of the melanocytic nevi is bewildering and diverse, with a variety of histologic, anatomic, architectural, and cellular patterns. There are numerous other terms used, such as “ugly duckling” sign, Spitz’s nevi, dysplastic nevi, traumatized nevi, and eponym terms such as Unna, Clark, Reed, Miescher, Zitelli, Mark, Seab, and Ackerman which complicate the bewildering spectrum of lesions. Certain vague descriptive terms such as atypical nevus, dysplastic nevus with architectural disorder and moderate to severe cytologic atypia; may represent uncertainty and indecision by
the pathologist as to whether the melanocytic proliferation is benign or malignant.3

Our aim is not to arrive at a consensus on these bewildering and evocative names, as there is no unanimity or litmus test to distinguish between unusual and tricky clinical and histologic melanocytic nevi, or between melanocytic proliferations and subtle melanomas. A wide array of invasive and noninvasive tests has been able to classify most acquired nevi into three common clinical types: junctional, compound, and dermal. We will be using the classification proposed previously and given in Figure 1 to categorize acquired melanocytic nevi.4

In the routine evaluation of melanocytic lesions, one is continually faced with the decision as to whether a lesion is benign or malignant. In approaching this problem, one has to apply a number of criteria for this interpretation, since no single criterion is sufficient. At present, there is no universal consensus as to which criteria should be included in this exercise, or the relative importance or relative weight of each criterion. It is certain that this latter exercise should take into consideration clinical information, organizational, cytological, and cell proliferation-related properties of the individual lesion. It must be emphasized that there are exceptions to each criterion, and the failure to consider this may result in both over- and underdiagnosis of melanoma. The authors believe that additional research and substantial efforts are needed to standardize the terminology of benign (and malignant) melanocytic neoplasms.

Prevalence

Some factors have emerged from studies that can predict the development of melanocytic nevi, the most important being sun exposure in childhood.5 The emergence of nevi is under strong genetic control, whereas environmental exposures affect the mean number of nevi.6 Nevi are seen more in boys than in girls, in White children more than in other ethnic groups, and in children with fair skin and blond or red hair.6,7 This latter finding has been contradicted in a study where children with red hair had more freckles but fewer melanocytic nevi.7 The use of a sunscreen reduces the development of new nevi on intermittently sun-exposed body sites, particularly in freckled children.8 Neonatal phototherapy is
a strong risk factor for nevus development in childhood.\textsuperscript{11} Experimentally, ultraviolet radiation produces transient melanocytic activation.\textsuperscript{12}

The genetic control of nevi does not appear to be related to changes in the \textit{CDKN2A} gene, but a loss of heterozygosity is present, which may suggest that some are precursors of melanoma.\textsuperscript{13,14} Clinical confirmation of this transformation, however, can be seen only in those with a familial predisposition.

**Pathogenesis and course of melanocytic nevus**

Melanocytes seem to originate from pluripotent cells that migrate from the neural crest to the skin via the paraspinal ganglia and their peripheral nerves and become terminally differentiated after migration to the local microenvironment of the dermis and basal layer of the epidermis. Beyond establishing the embryonic origin of melanocytic nevi from neural crest-derived cells, the histogenesis of these melanocytic proliferations has not been adequately elucidated. The conventional viewpoint is that nevi arise from proliferation of intraepidermal melanocytes within junctional nests or theques. According to this model, nevus cells are considered a morphological variant of melanocytes that have assumed a morphology that is more epithelioid and less dendritic. With evolution of the lesions, it is held that cells “drop off” (Abtropfung of Unna) into the dermis. The Abtropfung hypothesis derives from cross-sectional observations correlating histological findings in nevi with chronological aging.

Unna’s concept of Abtropfung (“dropping off”) has been challenged in recent times,\textsuperscript{15,16} although the higher reactivity of proliferating cell nuclear antigen in junctional and compound nevi than in intradermal nevi supports the epidermal origin of acquired melanocytic nevi.\textsuperscript{17} Another hypothesis is that of the melanocyte differentiation pathway, which is an attempt to explain the origin of melanocytes and their subsequent upward migration into the epidermis, the reverse of Abtropfung.\textsuperscript{18,19} Zalaudek et al have put forward another theory based on dermoscopy that involves neither of these theories of pathogenesis.\textsuperscript{20}

A reasonable hypothesis regarding the natural history of melanocytic nevi is that they arise as a lentigous (ie, lentigo-like) proliferation of single-cell units along the basal zone of elongated and hyperpigmented rete ridges. At some point thereafter, the melanocytes undergo a morphological transition into the epithelioid nevus cells, with their propensity to aggregate as junctional nests (junctional nevus). Following this stage of development as a junctional nevus, further cellular development and proliferation results in the migration or “dropping off” of nevus cells and their organization into nests within the papillary dermis (compound nevus). According to this generally accepted model, eventually all intraepidermal proliferation of melanocytes ceases, and the nevus becomes entirely intradermal (dermal nevus). Nevus cells residing within the dermis have reduced proliferative and metabolic activity, except for the formation of melanosomes. With the decline of replication, the nevus cell population is gradually replaced by mesenchymal elements, including fibrous matrix, glycosaminoglycans, and adipose tissue. Most dermal nevi are believed to undergo progressive involution, some eventuating as acrochordons, and others shedding. This is reflected in the course of the disease, as with advancing age, there is a progressive decrease in the number of nevi; thus, whereas the number of nevi in young adults varies from approximately 15 to 40, this decreases markedly over the age of 50 years.\textsuperscript{21}

**Clinical features**

Melanocytic nevi are well circumscribed, round to ovoid lesions, with regular and well defined borders. Although most are diagnosed clinically, a new classification system for nevi was proposed in 2007, based on dermoscopic features.\textsuperscript{22-25} The categories included in this are globular (congenital), reticular (acquired), starburst (Spitz/Reed), blue (homogeneous), and site-related nevi, and those with special features, such as halo, eczematous, combined,\textsuperscript{24} and recurrent nevi.\textsuperscript{22} A clinical and histological tabulation (Tables 1 and 2) is provided for the CAMN; although, in expert hands, dermoscopy may be equally effective in accurate diagnosis.

The junctional nevus is a macular lesion with slight accentuation of skin markings (Figure 2). The dermoscopic

| Table 1 | Clinical classification of common acquired melanocytic nevi |
| --- | --- | --- |
| **Junctional nevus** | **Compound nevus** | **Dermal nevus** |
| Size | 2–5 mm macule | 3 to 6 mm papule | 3–6 mm papule, dome-shaped or papillomatous |
| Onset | Childhood, adolescence | Childhood, adolescence, third decade | Onset first, second, third decades or later |
| Shape | Round, oval, symmetrical | Round, oval, symmetrical | Round, oval, symmetrical |
| Borders | Well defined, regular borders | Regular borders | Well defined, regular borders |
| Color | Homogeneous brown, dark brown | Homogeneous brown, dark brown | Light brown to flesh tones |

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\textsuperscript{91} For personal use only.
Table 2 Histopathologic features of common acquired melanocytic nevi

<table>
<thead>
<tr>
<th>Feature</th>
<th>Junctional nevus</th>
<th>Compound nevus</th>
<th>Dermal nevus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetry</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Borders</td>
<td>Well circumscribed</td>
<td>Well circumscribed</td>
<td>Well circumscribed</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junctional nesting</td>
<td>Regular</td>
<td>Regular</td>
<td>Dome-shaped or papillomatous</td>
</tr>
<tr>
<td>Morphology of nests</td>
<td>Uniform size, shape, and placement of nests</td>
<td>Uniform size, shape, and placement of nests</td>
<td>Orderly arrangement of nevus cells in the dermis</td>
</tr>
<tr>
<td>Degree of cohesion</td>
<td>Cohesive nests at tips of rete ridges</td>
<td>Cohesive nests at tips of rete ridges</td>
<td>Nevus cells often confined to papillary or superficial reticular dermis</td>
</tr>
<tr>
<td>Site of nevus cells</td>
<td>Basal layer</td>
<td>Nevus cells often confined to papillary or superficial reticular dermis</td>
<td>Transition from epithelioid to lymphocytoid to spindled cells with dermal descent</td>
</tr>
<tr>
<td>Type of cells</td>
<td>Epithelioid cells</td>
<td>Transition from epithelioid to lymphocytoid to spindled cells</td>
<td>Transition from epithelioid to lymphocytoid to spindled cells with dermal descent</td>
</tr>
</tbody>
</table>

features of a junctional nevus shows a uniform pigment network thinning out towards the periphery. Compound nevi show variable degrees of elevation and have a general somewhat lighter shade of brown than do junctional nevi (Figure 3). Dermoscopically, they are characterized by a globular architecture with multiple round to ovoid globules, sometimes forming a cobblestone pattern. Dermal nevi are usually more elevated and are a lighter shade of brown or even skin-colored compared with compound nevi (Figure 4). The dermoscopic features of an intradermal nevus predominantly consist of focal globules or globular-like structures. In addition, there may be pale to whitish structureless areas and fine linear or comma vessels. Occasionally a patient may have lesions of all three types which typify the theory (Figure 4). In addition to clinical and dermoscopic overlap amongst all three types of nevi, dermal nevi may be papillomatous with pseudo-horn cysts. Some nevi, especially acquired “congenital-appearing” nevi, contain hairs that are coarse and dark compared with those in the surrounding skin (Figure 5).

The recurrent (persistent) nevus is defined as the appearance of macular pigmentation within the confines of the clinical scar of a previously biopsied (usually by shave technique) melanocytic nevus, usually after about 6 weeks to 6 months (Figure 6).

Pathology

It is generally accepted that all nevi should be submitted for histological examination for medicolegal reasons. In a recent study, 2.3% of clinically diagnosed benign nevi were microscopically diagnosed as malignant tumors, either melanomas or basal or squamous cell carcinomas. Although the BRAF mutation is common in melanomas, it is also found in a significant number of benign nevi. This finding raises doubts about its relevance in melanoma development. Thus, melanoma development in melanocytic nevi is probably not as common as it is believed.

It has been customary to refer to the cells comprising a melanocytic nevus as “nevus cells” or “nevomelanocytes.” Nevus cells are melanocytes which have lost their long dendritic processes due to an adaptive response associated with the formation of nests of cells. As this change cannot usually be appreciated in hematoxylin and eosin-stained

Figure 2 Macular junctional melanocytic nevi showing increased skin markings.

Figure 3 Raised pigmented papular lesion pathognomonic of a compound melanocytic nevus.
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Acquired melanocytic nevi

preparations, it has been suggested that all cells in melanocytic nevi (epidermal and dermal) should be referred to as melanocytes.28

Melanocytic nevi contain intraepidermal or dermal collections of nevus cells or both. The cells within the junc- tional nests have round, ovoid, or fusiform shapes and are arranged in cohesive nests.4 With the notable exception of the unusual amelanotic variants, these cells contain melanin.4 In the superficial dermis, the cells have an epithelioid cell topography and contain amphophilic cytoplasm with granular melanin. The nuclei have uniform chromatin with a slightly clumped texture. Deeper in the dermis, there is a diminished content of cytoplasm, and the cells resemble lymphocytes and are arranged in linear cords. There may be a further transition to cells separated by fine connective tissue and assuming a spindled configuration, similar to fibroblasts or Schwann cells.

The “maturation” of melanocytes is accompanied by an alteration in the antigens they express. Cells in the junctional layer contain S100 protein and sometimes one or more of the melanoma-associated antigens (including NKI/C3 and HMB-45), but usually only S100 protein is expressed by dermal nevus cells.29

Treatment

The treatment of CAMN is in most scenarios dictated by cosmetic necessity,30 and thus before embarking on such a procedure, the clinician should be sure about the possibility of melanoma or dysplasia. Although dermoscopy23,24 in trained hands is a good noninvasive choice, it must be remembered that in doubtful cases, a biopsy is probably the only certain way of confirming dysplasia. With greater emphasis being given to cosmetic results and because of an ever increasing workload, a number of “faster and less traumatizing” tech- niques have been introduced in the treatment and diagnosis of atypical nevi, including punch, shave, and “scoop shave” biopsies. However, it must be remembered that only a complete scalpel excision of all clinically atypical nevi permits the histological assessment of the entire lesion, while the aim of cosmetic surgery is largely removal of the visible lesion and is thus largely incomplete.31

Laser removal of CAMN is itself controversial since no specimen is submitted for tissue diagnosis and margin assessment.30,32 Conversely, the gold standard technique for removal of melanocytic nevi, which is excision followed by histological examination, results in a scar that is an undesired cosmetic outcome. The issue of melanoma arising as a con- sequence of laser therapy is debatable.30,32 Although some
believe that selective destruction of abnormal melanocytes is a means for reducing the number of cells at risk for malignant transformation, it is also possible that laser or other treatments may inadvertently stimulate transformation to melanoma. There have been reports of histological atypia (pseudomelanoma) in patients with melanocytic nevi that were treated by CO₂ lasers as well as lasers for hair removal. 33 Racial differences probably also need to be taken into consideration, as in Asians, the incidence of melanoma has been reported to be between 0.2 and 2.2 per 100,000, much lower than among Whites. 34 Furthermore, the most common sites for the development of melanoma among people with skin of color are areas not directly exposed to the sun, such as palmar, plantar, subungual, and mucosal surfaces. 34 This may account for the liberal use of lasers for the treatment of melanocytic nevi in Asian countries on the facial skin. However, it must be pointed out that malignant transformation takes time, and if the patient goes to an oncosurgeon or oncologist, it may not always reflect as long-term complications in dermatological practice. This is exemplified by the development of carcinoma bladder in patients of pemphigus on cyclophosphamide, wherein it takes 15 years to develop the complication 35 and rarely presents to the treating dermatologist.

There are other issues regarding the use of pigment-specific lasers for CAMN. The smaller and thinner lesions (junctional nevus) are typically more treatment-sensitive. 30,32 With deeper lesions (compound and dermal nevus), complete eradication is much more difficult, and recurrence is common. 30,32 Laser therapy decreases the number of the pigmented nevomelanocytic cells in the papillary dermis, but is unlikely to treat deep-seated non-pigmented cells that are closely associated with adnexal structures. This has been demonstrated histologically as persistent nevomelanocytic nests in the mid papillary and deeper dermis at depths of 0.16–0.44 mm. 30,32

Although radiofrequency and electrocautery are commonly used for removing CAMN, the nonspecific thermal damage induced by these techniques and the consequent cosmetic results do not justify their use in CAMN, removal of which is largely a cosmetic concern. Thus, our focus will be on surgical removal and the use of lasers.

**Surgical excision**

The technique of surgical excision is probably the oldest and involves various techniques like shave excision, round excision, deep excision, and razor-blade excision. 36–39 The most common technique used is the razor-blade shave technique. 36 This entails the use of a slightly curved classic razor blade to shave and remove the exophytic part of a skin lesion and part of the intradermal structure down to the papillary dermis. 36,39

The existing data suggest that although it may have a favorable cosmetic outcome, issues of recurrence and histological confirmation have not been adequately addressed. This is more so as the deeper nevus cells can never be reliably removed. 30,31

There are certain prerequisites while using the aforesaid techniques, the most important being the depth achieved via a vis the type of nevi. For junctional nevi, a shave excision may suffice, 36 but for the deeper compound and intradermal nevus, 37 a modification may be required to enable a deeper excision. 37

Another modification that has been suggested involves excision with a number 15 scalpel blade, 2 mm beyond the limits, with incision to the full depth of the dermis. 38 In spite of all these modifications, the recurrence rate is high, and it is not unreasonable to believe that a longer follow-up would lead to more recurrences (Table 3). Immediate patient satisfaction, however, is good, even though there is a scar that is perceptible. 36 The high recurrence rate (13%–26%) of this largely “blind” procedure is the reason to use the technique with caution.

It is important to consider the histopathological perspective 31 in the technique of shave excisions in melanocytic nevi. The use of the various methods (punch, shave, and “scoop shave” biopsies) 36–40 have a major limitation as only a part of the lesion is available for histological assessment. 31 Cohen et al 41 found residual nevus in 24.9% of re-excisions of atypical melanocytic nevi that were initially biopsied with either the shave or punch technique. As shave and punch biopsies contain only the central portion of the lesion, the area of interface between the melanocytic lesion and normal skin

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Number</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrandiz et al 36</td>
<td>Shave excision</td>
<td>204 nevi</td>
<td>Recurrence seen in 19.6% of cases at 3 months</td>
</tr>
<tr>
<td>Tursen et al 37</td>
<td>Round excision technique</td>
<td>36 papular nevi</td>
<td>Complete removal in all cases</td>
</tr>
<tr>
<td>Gambichler et al 37</td>
<td>Deep shave excision of macular nevus</td>
<td>77 macular melanocytic nevi</td>
<td>12% were incompletely excised</td>
</tr>
<tr>
<td>Breuninger et al 37</td>
<td>Conventional excisions (intracutaneous butterfly sutures) and shave excisions</td>
<td>268 nevi versus 403 nevi</td>
<td>Recurrence seen in 13% at 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shave excisions resulted in fewer complications (7.9% versus 15%), but recurrences were more frequent (18.1% versus 6.0%)</td>
</tr>
</tbody>
</table>
is absent. Thus, the evaluation of architecture is not possible. Shave biopsies that sample only the superficial aspect of the lesion do not allow for evaluation of maturation.

In compound dysplastic nevi, the junctional component often extends beyond the underlying dermal component (the “shoulder”), and trails off several rete ridges. This corresponds to the clinical appearance of a central papule with fading edges that merge with the normal skin. To ensure complete removal, these lesions should be excised with a 2 mm clinically clear margin to ensure that the tapering junctional component is completely excised. In the study by Cohen et al,41 residual nevus was more often associated with punch than with shave biopsies, probably because the “shoulder” is more efficiently excised by shave biopsies. A recent study by Barr et al42 documented that 35.9% of atypical nevi show variations in the degree of atypia from one area to another.

Another issue is that when the pathologists receive partial biopsies of dysplastic nevi, there is a recommendation for a complete and adequate re-excision, with a specification of the precise margin in millimeters. This may be an issue for the dermatologists, as it can expose them to a litigious situation in the case of an unfavorable outcome.

Thus, although a structured approach with deep excision in compound and dermal nevus is proposed, the skills of the operator cannot predict the chance of recurrence36–39,43 and the inadequate histological opinion can lead to medicolegal issues.31,41,42

Lasers

The lasers used for CAMN range from pigment-selective lasers to ablative lasers (Figure 7). The use of lasers in CAMN (moles) is complicated by many practical issues and scenarios which have to be properly understood before attempting this mode of therapy.29,44–46

Principles of therapy

Like any other indication, the use of lasers in pigmented lesions begins at the helm of laser physics and depends on the absorption spectra of the target chromophore, which is believed to be the melanocyte (melanosomes).29,46 The spectrum of lasers used ranges from the green lasers (pulsed dye, Q-switched [Qsw], and neodymium [Nd];yttrium aluminum garnet [YAG] 532) to the far-infrared lasers (CO₂ 10,600 nm and erbium [Er]:YAG 2,940 nm) (Figure 7).

Mid-infrared lasers (1,300–1,600 nm) such as some diode, Er, thallium, and the 1,320 nm emission line of Nd:YAG are moderately absorbed by water. These produce thermal damage in the epidermis, upper dermis, and/or mid-dermis but do not specifically target melanin.32 In general, the best wavelength region for treating pigmented lesions is red and near-infrared (approximately 600–1,100 nm).32,44,45 This wave band combines the most selective absorption by melanin, with the deepest skin penetration.

The second important proviso is to minimize heat damage, which requires optimal setting of the pulse duration of the laser. A laser with a pulse duration less or equal to the thermal relaxation time (TRT) of the target tissue should be employed. This, in turn, depends on the size of the target tissue which dictates TRT. This ranges from 0.25 to 1.00 µsec for the melanosome to 0.1 msec (100 µsec) for the melanocyte.32 Although the nanosecond lasers (Qsw) have been conventionally used to treat pigmented lesions such as lentigines, freckles, and “nevus of Ota,” the same principle cannot apply to CAMN. The geometry (and therefore the microscopic characteristics) of the lesion is important, and as the nevus is composed of melanocytes in aggregates (collectively of a size of 100 µm in diameter) this corresponds to a TRT of about 10 msec,32 thus accounting for the use of normal mode (msec) and far-infrared lasers to treat CAMN.

The third requirement is to achieve an adequate depth to target the chromophore for which the red (ruby 694 nm, alexandrite 755 nm) and near-infrared (QswNd:YAG 1,064 nm) lasers (approximately 600–1,100 nm) are ideal.

Based on these three principles, the devices useful for treating melanocytic lesions are of two basic classes: far-infrared skin resurfacing lasers and pulsed lasers/intense pulsed light (IPL) lasers. The pulsed lasers are further divided into long-pulse (msec) devices, which tend to target relatively large pigmented structures such as hair follicles and “nests” of nevus cells, and short-pulse (Qsw nsec lasers) devices, which are capable of targeting individual pigmented cells.32 Histologically, CAMN have both isolated nevo-melanocyte cells, and “nests,” or clusters, of cells.32,44–46 Thus, a mixture of lasers targeting both should ideally be used, with the use of short (nsec) pulses and long (msec) pulses. This is the reason why melanocytic nevi are better treated with a combination of lasers.

Recent studies47 have used pulsed CO₂, ostensibly to ensure ablation of the epidermis, followed by a Qsw frequency-doubled Nd:YAG, Qsw Nd:YAG, or a Qsw alexandrite laser. The logic employed in the use of combination lasers (normal mode and Qsw ruby laser, CO₂ and Qsw alexandrite, CO₂ and Qsw frequency-doubled Nd:YAG laser, CO₂ and Qsw ruby laser) is to expose the otherwise unaffected, deep-sited
nevomelanocytes to the pigment-specific laser. Nevus cells in the superficial dermis are additionally removed by the CO$_2$ laser. Alternatively, for a smaller “mole” (<1.5 cm), a short-pulsed Er:YAG would be an ideal tool, as apart from the pulse duration (300–1,000 µsec) the Er:YAG laser has a predictable depth (5 µm/J/cm$^2$), minimal thermal damage (20–30 µm), and a high absorption coefficient of water (Er:YAG 12,800 cm$^{-1}$; CO$_2$ 800 cm$^{-1}$), and is thus capable of a far finer and safer superficial ablation, with minimal sequelae. A comparison of various modalities at our center revealed that the combined or pulsed ablative method is better than using the Qsw lasers for CAMN.

Lasers and melanoma

The controversy of laser treatment of melanocytic nevi emanates from the concept that laser irradiation may have the potential to induce malignant change in nevus cells. In-vitro studies of melanoma cells treated with Qsw lasers have found changes in cell surface integrin expression, with subsequent alteration of cell migration. A significant increase in p16INK4a in p16 positive cell lines following irradiation with Qsw laser light suggests that sub-lethal laser damage may increase DNA damage, leading to an increase in p16 expression. In clinical practice, benign appearing nevi that tend to recur following laser treatment...
may show newfound clinical and histologic atypia, referred to as pseudomelanoma. There has never been a report, however, of true malignant transformation of a benign pigmented lesion following laser treatment, which is epidemiologically low in the Asian skin type even without an intervention. Conversely, laser treatment of melanocytic lesions may decrease the risk of malignant transformation of a benign pigmented lesion simply by reducing the population of existing potentially premalignant cells. This is supported by a study where no significant malignant markers (such as proliferation cell nuclear antigen, pyrimidine dimers, 8-OHdG [8-hydroxy-2′-deoxyguanosine], and p53) were found following treatment of nevi with Qsw lasers.

Pigment-specific lasers (Table 4)
The Qsw ruby, alexandrite, and 1,064 nm Nd:YAG lasers all have some efficacy in removing flat or slightly raised acquired nevi. As a rule of thumb, lighter nevi respond best to shorter wavelengths that maximize melanin absorption, while darker nevi typically respond to any wavelength within the melanin absorption spectrum. Also, the deeper intradermal and compound nevi do not respond to conventional dose settings of the Qsw lasers. Multiple treatments are frequently necessary for optimal lightening.

It is often not feasible to hope for complete resolution of nevi, and recurrence after laser treatment is common. This is because there is persistence of nevus cells containing little pigment located in the deeper dermis that are shielded from laser radiation by the more pigmented superficial cells. Also, Qsw laser radiation does not penetrate sufficiently to effectively treat thicker papillated or dome-shaped dermal nevi.

This led to the use of microsecond and millisecond pigment-specific lasers for CAMN. Although the results were better than the nanosecond lasers, issues of recurrence have not been adequately addressed. So, while it makes sense to use a laser with a millisecond pulse duration to match

<table>
<thead>
<tr>
<th>Laser</th>
<th>Pulse duration</th>
<th>Number</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al</td>
<td>755 nm alexandrite</td>
<td>100 µsec long-pulsed mode</td>
<td>53 lesions</td>
<td>38.9% of patients had “excellent” results. At 4 weeks post-treatment, 92.5% were totally cleared, with 26.4% reporting mild atrophy, and 20.8% reporting mild post-inflammatory hypopigmentation. No follow-up or histological evaluation was done.</td>
</tr>
<tr>
<td>Alshami</td>
<td>Long-pulsed 532 nm Nd:YAG</td>
<td>20 msec</td>
<td>350</td>
<td>All nevi were completely removed, with good to excellent cosmetic results after only one session. Recurrence was seen within 2–6 months of laser treatment in 25 patients. Long pulse is a preferred laser mode for melanocytic nevi.</td>
</tr>
<tr>
<td>Sardana</td>
<td>Qsw Nd:YAG</td>
<td>nsec</td>
<td>20</td>
<td>75% improvement. Most lesions lightened but were not removed.</td>
</tr>
<tr>
<td>Kim et al</td>
<td>Qsw Nd:YAG</td>
<td>nsec</td>
<td>2,064 patients</td>
<td>70% removed in one session. The lesions were small. No follow-up or histological evaluation was performed.</td>
</tr>
<tr>
<td>Duke et al</td>
<td>Normal-mode and Qsw ruby laser light (694 nm)</td>
<td>Variable</td>
<td>Benign, atypical, and congenital nevi (31)</td>
<td>Sixteen (52%) of the nevi improved. Complete histologic removal of all nevomelanocytes was not seen in any case.</td>
</tr>
<tr>
<td>Westerhof and Gamei</td>
<td>Qsw and normal mode ruby laser</td>
<td>nsec vs msec</td>
<td>Qsw f/b normal mode</td>
<td>1–3 sessions. Junctional nevus responded the best to Qsw lasers.</td>
</tr>
<tr>
<td>Reda et al</td>
<td>Alexandrite laser (755 nm)</td>
<td>Normal mode (3 msec)</td>
<td>40 lesions</td>
<td>At the end of 4 months, 76.92% nevi attained moderate to significant lightening of color, 19% nevi had their color matching that of the surrounding skin. Complete removal was not seen.</td>
</tr>
<tr>
<td>Rosenbach et al</td>
<td>Qsw alexandrite (755 nm) and Nd:YAG (1,064 nm)</td>
<td>Comparison of two nsec lasers</td>
<td>NA</td>
<td>Significant reduction after 3 sessions. Qsw alexandrite laser produced slightly better results using the parameters outlined. Objective evaluation with reflectance spectrometry and histology was performed.</td>
</tr>
<tr>
<td>Vibhagool et al</td>
<td>Qsw ruby laser (694 nm, 28 nsec)</td>
<td>nsec</td>
<td>18 small melanocytic nevi</td>
<td>Twelve lesions (67%) showed a complete response and six lesions (33%) had a partial response. The Qsw ruby laser is effective in removing small melanocytic nevi, but recurrence was seen.</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; Nd:YAG, neodymium yttrium aluminum garnet; Qsw, Q-switched; f/b, followed by.
Table 5 Studies on ablative lasers for treating acquired common acquired melanocytic nevi

<table>
<thead>
<tr>
<th>Laser</th>
<th>Pulse duration</th>
<th>Number</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sardana\textsuperscript{30}</td>
<td>Er:YAG</td>
<td>300 µsec</td>
<td>20 nevi</td>
</tr>
<tr>
<td>Hammes et al\textsuperscript{41}</td>
<td>CO\textsubscript{2}, Er:YAG, and ruby</td>
<td>Variable</td>
<td>130 intradermal nevi</td>
</tr>
<tr>
<td>Baba and Bal\textsuperscript{60}</td>
<td>Er:YAG</td>
<td>300 µsec</td>
<td>28 lesions</td>
</tr>
</tbody>
</table>

Abbreviations: Er:YAG, erbium yttrium aluminum garnet; Nd:YAG, neodymium yttrium aluminum garnet; Qsw, Q-switched; Up, ultrapulse; f/b, followed by.

Pigment selective lasers
Partial disintegration of nevus cells
Recurrent nevus
Junctional nevus
Dermal nevus
Ablative laser (pulsed)*
Zone of ablation
Zone of coagulation
Complete removal of nevus cells
Persistent nevus cells

Figure 8 A diagrammatic comparison of the effect of pigment-specific lasers and ablative lasers in common acquired melanocytic nevi. The lack of persistent nevus cells with ablative lasers leads to less chance of recurrent nevus, which is a distinct possibility with pigment-specific lasers.

Note: *Er:YAG (200–300 msec, pulse duration)/ultrapulse CO\textsubscript{2} (<1 msec, pulse duration).

Abbreviations: Er:YAG, erbium yttrium aluminum garnet.
the TRT of nevus cells, the increased energy may lead to a high thermal confinement, and the rise in peak temperature may result in scarring.

Ablative lasers (Table 5)
Although the traditional ablative lasers (Er:YAG and CO₂) had issues due to increased coagulation attributable to high thermal damage, the newer pulsed lasers have been programmed to achieve a pulse duration less than the TRT of skin (<1 msec).

Studies using the short-pulsed Er:YAG lasers (µsec pulse) have been reported to be quite effective in removing flat or slightly palpable melanocytic nevi.30,60,61

Which lasers should be used for acquired melanocytic nevi?
The histological variables of a CAMN are such that any laser has to factor in the depth, size of individual nests, and the variability of pigment in the nevus cells, especially in dermal

Figure 9 An algorithm for management of common acquired melanocytic nevi with lasers.
Note: *For most nevi, ablative lasers can remove the lesions without the use pigment-specific lasers.
Abbreviations: alex, alexandrite; Er:YAG, erbium yttrium aluminum garnet; fd, frequency-doubled; Nd:YAG, neodymium yttrium aluminum garnet; Qsw, Q-switched; Sp, shortpulsed.
nevi. Most of the present data are derived from the experience gained while using lasers for congenital melanocytic nevi.\textsuperscript{32,50,62,63} The effectiveness of lasers was believed to be due to the formation of superficial dermal fibrosis that hides the residual deep layer of nevus cells.\textsuperscript{62}

With pigment-specific lasers, there is a thermal acoustic effect with partial disintegration of pigment, and due to the variable depth achieved, some nevus cells may not be targeted (Figure 8). On the contrary, ablative lasers remove the target cells effectively, and the depth can be achieved by adjusting the dose.\textsuperscript{36,64} The Er:YAG laser ablates approximately 5–50 μm of tissue with each joule per square centimeter, the thermal injury per pass is 15–50 μm, and there is a predictable depth achieved with ablation of the nevi.\textsuperscript{46,64} The pulsed CO\textsubscript{2} laser has a higher ablation depth of 20–60 μm per pass and causes thermal coagulation ranging from 75 to 150 μm per pass.\textsuperscript{46,64} This high thermal coagulation may be advantageous in achieving complete destruction of nevus cells and preventing recurrence. Thus, both these lasers, if modulated correctly, can be used for removing CAMN with controlled thermal damage (Figure 8).

Combining various lasers\textsuperscript{30,47,55,56,61} has been shown to achieve better results while treating CAMN. One approach was suggested by Kono et al.,\textsuperscript{61} where a combination of Qsw and long-pulse laser passes was used in each treatment session. Kono’s technique can be pursued using ruby, alexandrite, and/or Nd:YAG lasers, all of which selectively target dermal pigmented cells and are available in both long-pulse and Qsw versions.\textsuperscript{61} A high-power 810 nm pulsed diode laser, delivered with cold sapphire contact cooling, or a red-NIR filtered IPL can also be used for the long-pulse device.\textsuperscript{32}

The basic principle that should guide the clinician is that, due to the variable histology of CAMN, a combination of lasers are used. An approach that we routinely follow is using the Qsw lasers for junctional nevi, Er:YAG/ultrapulse CO\textsubscript{2} followed by Qsw Nd:YAG for compound nevi, and ablative lasers for dermal nevi (Figure 9). A basic principle that should dictate therapy is to remove the epidermis, especially in compound and dermal nevi. This can be achieved either by a high-fluence Qsw laser or using Er:YAG or pulsed CO\textsubscript{2} lasers prior to the use of long-pulse laser and Qsw laser passes.\textsuperscript{47} As the longer wavelengths and longer pulse widths tend to require higher fluence for efficacy, there is a risk of thermal damage, and thus “pulse stacking” (repeating pulses in the same site) should be avoided.

**Conclusion**

Recent studies have suggested that significant increases in melanocytic nevi counts in preschool children call for improved ultraviolet protection, but knowledge does not automatically change behavior.\textsuperscript{65} The use of any management decision in children with familial melanoma should be tempered by the findings of a recent study, where atypical nevi in childhood, the nevus count of atypical nevi on the buttocks, and most importantly, the number of excisions during follow-up correlated with the risk of melanoma.\textsuperscript{56} In Caucasian skin, it is believed that the total number of CAMN on the whole body is the most important independent risk factor for melanoma, and the risk of melanoma development increases almost linearly with rising numbers of melanocytic nevi.\textsuperscript{67}

The histological morphology of the acquired melanocytic nevi largely dictates the method of removal. The use of lasers is dependent on various factors, including the wavelength and the pulse duration of the laser (Table S1). Thus, in most CAMN, a millisecond pulse duration would be better than the conventional nanosecond lasers (Tables 4 and 5).

It has been the experience of some authors\textsuperscript{50,60,61} that a pulsed ablative laser (ultrapulse CO\textsubscript{2} or Er:YAG) can provide an equally effective method of removal of CAMN if a proper dose depth correlation can be ensured. A combination of pigment-specific and ablative lasers can also be used to treat acquired melanocytic nevi (Figure 9).

It has been our experience that subsets of CAMN are hairy and have a propensity for recurrence. This is because the nevus cells tend to extend along hair follicles deeply into skin. The hair follicles therefore harbor nevus cells beyond the depth for effective laser treatment. Techniques of hair removal, whether by laser devices, IPL, or electrolysis may be needed for these lesions.

It must be emphasized that the issue of recurrence and possible dysplasia being missed or melanoma appearing has never been adequately studied, as different techniques have been used in the studies on CAMN.\textsuperscript{36–40,52–61} Needless to say, although most of the excisional techniques\textsuperscript{36–40} may be clinically effective, this cannot absolve the clinician of the consequences of dysplasia or recurrence, as histological confirmation is usually difficult with most excisional techniques.\textsuperscript{31}

When using lasers, most clinicians do not biopsy a benign melanocytic nevus or consider a post-treatment biopsy. In such cases, it is advisable to ensure a follow-up and biopsy a recurrent “mole.”

Our approach to diagnosis\textsuperscript{30,31} and therapy using lasers\textsuperscript{47,52–64} on CAMN is based on the available evidence and can help in effectively removing most melanocytic nevi (Figure 9). However, as enshrined in the protocol (Figure 9), even after a biopsy, in populations where a risk of melanoma
is high, the patient should be asked to report back if there is any recurrence, to eliminate the chance of melanoma. Also it should be emphasized that the cosmetic procedure is not a “guarantee” against development of melanoma. There is still inadequate data on recurrence due to the lack of post-treatment biopsy or adequate follow-up. Also, comparative studies using pigment-specific lasers and ablative lasers are lacking, but at present, it can be safely assumed that in most cases, benign melanocytic nevi do not have any significant malignant potential after laser removal.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

34. Chan HH. Laser treatment of nevomelanocytic nevi – can results from an Asian study be applicable to the white population? *Arch Dermatol*. 2002;138:1535.


Supplementary material

Table S1 Summary of the use of lasers in common acquired melanocytic nevi

1. Q-switched lasers are inappropriate to treat the nevus clusters as the pulse duration (nanosecond) does not match with the size of the melanocytic nevus, which requires a millisecond laser.
2. The use of lasers is hampered by issues of recurrence, and thus the dose and pulse duration should be “tweaked” depending on the type of common acquired melanocytic nevi.
3. Both pre-laser histological classification of the common acquired melanocytic nevi and post-laser biopsy should be done to assess the depth of tissue damage and to identify the remnant nevus cells which in turn predicts recurrence.
4. Persistence of nevus cells in the deeper layers of the dermis has been observed in all treated nevi except in junctional nevus. Melanin pigmentation tends to decrease in the deep portion of these lesions, for unknown reasons. Treatment with lasers (ruby and alexandrite) that preferentially target the pigmented cells tends to affect only the superficial (approximately 2 mm deep) portion, because there is more melanin and more laser light impacting near the skin surface.
5. Lighter nevi respond best to shorter wavelengths that maximize melanin absorption, while darker nevi typically respond to any wavelength within the melanin absorption spectrum. It is often unfeasible to attain complete resolution of nevi, and recurrence after laser treatment is common.1

Note: Data from Sardana,2 Suzuki and Anderson,3 Chan,4 Graber and Dover,5 Sardana et al,6 and Westerhof and Gamei.7

References