Low rates of clinical recurrence after biopsy of benign to moderately dysplastic melanocytic nevi

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Background: Little is known about the recurrence/persistence rates of dysplastic nevi (DN) after biopsy, and whether incompletely removed DN should be re-excised to prevent recurrence.

Objective: Our purpose was to determine the recurrence rates of previously biopsied DN, and to assess whether biopsy method, margin involvement, congenital features, epidermal location, and degree of dysplasia are associated with recurrence.

Methods: Patients having a history of a “nevus biopsy” at least 2 years earlier were assessed for clinical recurrence. Slides of original lesions were re-reviewed by a dermatopathologist.

Results: A total of 271 nevus biopsy sites were assessed in 115 patients. Of 195 DN with greater than 2 years of follow-up, 7 (3.6%) demonstrated recurrence on clinical examination. In all, 98 DN had a follow-up period of at least 4 years with no clinical recurrence. Of 61 benign nevus biopsy sites examined, clinical recurrence was observed in two (3.3%). For all nevi, recurrence was significantly associated with shave biopsy technique but not with nevus dysplasia or subtype, or the presence of positive margin or congenital features.

Limitations: Most biopsies were performed in a pigmented lesion clinic at a single tertiary referral center. Determinations of nevus recurrence were made on clinical rather than histologic grounds, and follow-up times were limited in some cases.

Conclusion: In this cohort, rates of clinical recurrence after biopsy of DN and benign nevi were extremely low. Re-excision of nevi, including mildly to moderately DN with a positive margin, may not be necessary. (J Am Acad Dermatol 2010;62:591-6.)

Key words: biopsy; dysplastic; nevi; recurrence.

Management of dysplastic nevi (DN) after biopsy remains a controversial issue. Although most dermatologists would agree that DN demonstrating severe atypia should be re-excised because they may represent early melanoma or a lesion evolving into melanoma, there are no clear guidelines regarding whether an incompletely removed nevus with a mild or moderate degree of dysplasia should be re-excised. Discordance among dermatopathologists as to identifying dysplasia and differing degrees of atypia further complicate decision-making.1 Although a 1992 National Institutes of Health Consensus Conference established margin guidelines for re-excision of DN (0.2-0.5 cm), it did not specify indications for re-excision.2 In addition to potential risk of melanoma development, nevus recurrence may be associated with histologic “pseudomelanoma,” a benign process simulating melanoma that poses a diagnostic dilemma for the dermatopathologist.3

Most studies investigating recurrence of biopsied nevi examined benign nevi (BN) removed for
cosmetic purposes, and reported recurrence rates ranging from 6% to 41%.4-6 Gambichler et al7 prospectively evaluated the effectiveness of deep shave excision in removing macular melanocytic nevi and the cosmetic outcome. For 77 nevi biopsied in 45 patients, histologic evaluation revealed that 88% of lesions had clear margins, and 60% had atypical or dysplastic features. After 6 months 56 of 77 biopsy sites were reassessed, and 7 of 56 (13%) were found to have clinical recurrence.7

Given the limited data on recurrence rates of biopsied DN, and lack of clear guidelines for re-excision of DN, it is not surprising that there is significant variability in physician management. A survey of 145 fellows of the American Academy of Dermatology found that among 45% of responders who provided a reason for re-excising incompletely removed DN, the most common was a finding of moderate or severe cytologic atypia.8 In addition, 53% stated that they re-excise incompletely removed DN in the majority of cases.8 In this study, we sought to determine recurrence rates of previously biopsied DN, with the hope of providing some guidance as to whether incompletely removed DN should be re-excised.

METHODS
Patients and nevus biopsies
This study was approved by our university institutional review board. Patients were recruited from our pigmented lesion clinic, in which approximately 7 new patients are seen each week and more than 1000 patients with history of numerous or atypical nevi and/or personal or family history of melanoma are monitored. The charts of patients scheduled for examination were reviewed before their visit to determine whether any previously biopsied melanocytic nevi were appropriate for the study. Earlier biopsies had been performed between 1998 and 2007, predominantly by physicians at our institution and some from the surrounding area. Of the 271 biopsies studied (Table 1), shave technique was used in 163 (60%), punch technique was used in 74 (27%), and elliptical excision was used in 34 (13%). Biopsy specimens from most anatomic areas were included, with the majority (55%) from the trunk. Lesions that were nonmelanocytic, had demonstrated recurrent nevus on initial biopsy specimen, or were biopsied less than 2 years before the visit; those without a pathology report; and those for which a biopsy scar could not be identified on the patient or the original slide could not be obtained for review were excluded. During the visit, sites of previously biopsied melanocytic nevi that met inclusion criteria were assessed for clinical recurrence. No lesions that had been re-excised (20 DN and 5 other nevi) (Table 1) after initial biopsy recurred, and these were not further analyzed for histologic features.

Histologic examination
Hematoxylin and eosin-stained slides were obtained, and re-reviewed by a dermatopathologist (S. R. F.) to determine whether nevi were benign or dysplastic, nevus subtype (junctional, compound, intradermal), degree of dysplasia, margin involvement, and presence of congenital features. Diagnosis of common (BN) and DN was based on well-established architectural and cytologic criteria. The DN exhibited architectural disorder manifested by irregular placement of variably sized melanocytic theques at the tips and sides of elongated and sometimes bridged rete. Patterned fibroplasia of the papillary dermis was present. In some specimens, “mild” cytologic atypia of melanocytes was characterized by nuclear enlargement similar to the size of a keratinocyte nucleus with finely granular pigmented cytoplasm. Dermal melanocytes were arrayed in theques that showed nuclear and cytoplasmic maturation with progressive descent. “Moderately” atypical DN demonstrated prominent fibroplasia of the dermis with entrapment of dermal melanocytic theques and a host response of lymphocytes. Significant pagetoid scatter of melanocytes was not observed in any of the nevi. Nevi with congenital features demonstrated dermal melanocytes arrayed in theques, sheets, or cords that splayed reticular dermal collagen bundles with close association of nevus cells with adnexal structures. Positive margins were defined as melanocytic theques, either in the epidermis or dermis, that were identified in inked specimen margins. Negative

CAPSULE SUMMARY
- It is unclear whether incompletely removed dysplastic nevi should be re-excised to prevent recurrence.
- For 175 dysplastic nevi and 61 benign nevi without earlier re-excision and with greater than 2 years of follow-up, recurrence on clinical examination was found in 4.0% and 3.3% of lesions, respectively.
- Nevus recurrence was significantly associated with shave biopsy technique.
- The low rates of recurrence after biopsy suggest that re-excision of nevi, including dysplastic nevi with a positive margin, may not be necessary.
margins were defined as lack of melanocytic theques in inked margins. Close extension (≤0.2 mm) of either the junctional or dermal component to an inked margin was considered to be a positive margin.

Statistical analysis
Two-sided Fisher exact tests were used for all comparisons. Statistical analysis was performed using R 2.8.0 (The R Foundation for Statistical Computing, Vienna, Austria). P values of ≤0.05 or less were considered statistically significant.

RESULTS

Rates of nevus recurrence
During an 8-month period, 271 sites of previously biopsied melanocytic nevi were assessed for clinical recurrence in 115 patients (Table I). In most cases, nevi at the follow-up visit presented as a well-healed hypopigmented scar (Fig 1, A). In some cases, on the other hand, pigmentation was seen within the scar (Fig 1, B), and interpreted as nevus recurrence. After histologic re-evaluation of original biopsy specimens, 195 lesions were classified as DN, 61 were classified as BN, and 15 were classified as “other” (which included 6 blue nevi, 8 Spitz nevi or spindle cell nevi, and one combined Spitz/blue nevus). The majority (179/195) of DN in this study were mildly dysplastic, whereas 16 of 195 lesions were moderately dysplastic (Table I). There were no DN with severe dysplasia. None of the 25 lesions (9.2% of total) that had been re-excised after biopsy were found to have recurred. After excluding these lesions that had been previously re-excised, only 7 of 175 (4.0%) DN showed clinical recurrence at least 2 years after biopsy (Table II). Of the 175 DN, 93 lesions showed no evidence of recurrence 4 years or more after biopsy. Of the 61 BN, only two (3.3%) had clinical evidence of recurrence greater than 2 years after initial biopsy (Table II). Thus, our observed rates of recurrence for both types of nevi were very low, and without statistical difference (P = 1.00) between the two groups. None of the blue nevi or Spitz/spindle nevi demonstrated recurrence.

Table I. Nevi assessed for recurrence in this study

<table>
<thead>
<tr>
<th>Nevus type</th>
<th>Total No.</th>
<th>Subtype</th>
<th>Biopsy method</th>
<th>Re-excised</th>
</tr>
</thead>
<tbody>
<tr>
<td>DN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild atypia</td>
<td>179</td>
<td>56/179 Junctional</td>
<td>96/179 Shave</td>
<td>17/179</td>
</tr>
<tr>
<td></td>
<td></td>
<td>123/179 Compound</td>
<td>57/179 Punch</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>26/179 Excision</td>
<td></td>
</tr>
<tr>
<td>Moderate atypia</td>
<td>16</td>
<td>3/16 Junctional</td>
<td>8/16 Shave</td>
<td>3/16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13/16 Compound</td>
<td>3/16 Punch</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5/16 Excision</td>
<td></td>
</tr>
<tr>
<td>Severe atypia</td>
<td>0</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BN</td>
<td>61</td>
<td>35/61 Compound</td>
<td>50/61 Shave</td>
<td>0/61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26/61 Intradermal</td>
<td>8/61 Punch</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3/61 Excision</td>
<td></td>
</tr>
<tr>
<td>Other nevi (Spitz, blue)</td>
<td>15</td>
<td>8/15 Compound</td>
<td>9/15 Shave</td>
<td>5/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/15 Intradermal</td>
<td>6/15 Punch</td>
<td></td>
</tr>
</tbody>
</table>

BN, Benign nevi; DN, dysplastic nevi.

Fig 1. Nevus biopsy sites demonstrating clinical lack (A) or presence (B) of nevus recurrence.
We next analyzed whether particular nevus features and biopsy method were associated with recurrent versus nonrecurrent nevi, excluding the lesions that had been re-excised after biopsy. The breakdown by lesion type, subtype, biopsy method, margin involvement, and presence of congenital features is detailed in Table II. Most DN that recurred (6/7) were of compound type and one was junctional, and all (7/7) had mild dysplasia and had been biopsied by shave technique. None of 13 DN with moderate dysplasia recurred. The different recurrence rates between DN with mild (7/162) versus moderate (0/13) dysplasia were not statistically significant (P = 1.00). Of the 7 recurrent DN, 5 had a positive margin and 3 had congenital features. Of 168 nonrecurrent DN, 53 (32%) were junctional and 115 (68%) were compound. These nonrecurrent DN represented lesions biopsied by shave (81%), punch (14%), and excisional (5%) technique, and 53 of 59 (90%) had a positive margin whereas 58 of 59 (98%) had congenital features. For all DN, there was not a statistically significant association of recurrence with nevus subtype (compound or intradermal, P = .50), presence of positive margin (P = 1.00), or congenital features (P = .38). In contrast to the DN, shave biopsy technique was not significantly (P = 1.00) associated with recurrence of BN. Considering all the nevi (DN and BN combined), shave biopsy technique was significantly (P = .045) associated with recurrence; for lesions biopsied only by shave or punch technique, the association between shave and recurrence was of even greater significance (P = .032).

### DISCUSSION

It is clear from the literature that patients with DN are at increased risk for developing melanoma.\(^9\)\(^{11}\) Although 20% to 50% of melanomas appear to arise from a pre-existing nevus,\(^9\)\(^{12}\)\(^{-14}\) the annual risk of individual nevi transforming into a melanoma is extremely low—estimated to be only 1 in 200,000.\(^15\) The annual risk is higher for DN (estimated 1 in

<table>
<thead>
<tr>
<th>Nevi type</th>
<th>No.</th>
<th>Subtype</th>
<th>Biopsy method</th>
<th>Positive margin</th>
<th>Congenital features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DN, mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>7/162</td>
<td>1/7 Junctional</td>
<td>7/7 Shave</td>
<td>5/7</td>
<td>3/7</td>
</tr>
<tr>
<td>Nonrecurrent</td>
<td>155/162</td>
<td>51/155 Junctional</td>
<td>76/155 Shave</td>
<td>60/155</td>
<td>38/155</td>
</tr>
<tr>
<td>DN, moderate</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>0/13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonrecurrent</td>
<td>13/13</td>
<td>2/13 Junctional</td>
<td>5/13 Shave</td>
<td>4/13</td>
<td>4/13</td>
</tr>
<tr>
<td>BN</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>2/61</td>
<td>2/2 Compound</td>
<td>2/2 Shave</td>
<td>2/2</td>
<td>2/2</td>
</tr>
<tr>
<td>Nonrecurrent</td>
<td>59/61</td>
<td>33/59 Compound</td>
<td>48/59 Shave</td>
<td>53/59</td>
<td>58/59</td>
</tr>
<tr>
<td>Other nevi</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>0/10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonrecurrent</td>
<td>10/10</td>
<td>6/10 Compound</td>
<td>5/10 Shave</td>
<td>4/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>

BN, Benign nevi; DN, dysplastic nevi.
Nevi that were re-excised after original biopsy (Table I) are excluded here.

**Role of degree of dysplasia, lesion subtype, biopsy method, margin involvement, and congenital features**

We next analyzed whether particular nevus features and biopsy method were associated with recurrent versus nonrecurrent nevi, excluding the lesions that had been re-excised after biopsy. The breakdown by lesion type, subtype, biopsy method, margin involvement, and presence of congenital features is detailed in Table II. Most DN that recurred (6/7) were of compound type and one was junctional, and all (7/7) had mild dysplasia and had been biopsied by shave technique. None of 13 DN with moderate dysplasia recurred. The different recurrence rates between DN with mild (7/162) versus moderate (0/13) dysplasia were not statistically significant (P = 1.00). Of the 7 recurrent DN, 5 had a positive margin and 3 had congenital features. Of 168 nonrecurrent DN, 53 (32%) were junctional and 115 (68%) were compound. These nonrecurrent DN represented lesions biopsied by shave (81%), punch (14%), and excisional (5%) technique, and 53 of 59 (90%) had a positive margin whereas 58 of 59 (98%) had congenital features. For all DN, there was not a statistically significant association of recurrence with nevus subtype (compound or intradermal, P = .50), presence of positive margin (P = 1.00), or congenital features (P = 1.00). In contrast to the DN, shave biopsy technique was not significantly (P = 1.00) associated with recurrence of BN. Considering all the nevi (DN and BN combined), shave biopsy technique was significantly (P = .045) associated with recurrence; for lesions biopsied only by shave or punch technique, the association between shave and recurrence was of even greater significance (P = .032).
raising the question of whether incompletely removed DN should be re-excised with clear margins to prevent potential evolution into melanoma. Although most dermatologists would agree that DN demonstrating severe dysplasia should be re-excised given the risk of early or evolving melanoma, management of incompletely excised DN demonstrating mild or moderate dysplasia remains an open question. A key factor to consider is the likelihood of recurrence, which must be balanced against the cost of re-excision and risk associated with a surgical procedure, including a larger scar. To our knowledge, the current study of DN recurrence after biopsy involves the largest number of lesions and longest follow-up period reported in the literature.

We found very low (3%-4%) recurrence rates for both BN and DN after biopsy, regardless of margin involvement, nevus subtype (junctional, compound, intradermal), or the presence of congenital features. We might have expected the recurrence rate of incompletely excised DN to be significantly higher than that of BN, given that DN are associated with increased proliferation and decreased senescence. In addition, we might have expected the recurrence rate to be higher for compound than intradermal lesions because nevus cells are more likely to be proliferative and less differentiated in a compound nevus. The recurrence rates we observed were much lower than those seen in previous studies. Our lower recurrence rates are unlikely a result of differences in follow-up times, because our follow-up period was greater than that in most of the other studies. A more likely explanation is that we may perform deeper and broader shave biopsies of clinically atypical nevi in our patients at high risk in an attempt to remove nevi completely, whereas earlier studies primarily examined recurrence of BN removed for cosmetic purposes, where a more superficial shave biopsy may have been done to minimize scarring.

We also might have expected the presence of congenital features to be associated with nevus recurrence, given that nevus cells in congenital nevi tend to extend deeper into the skin through their involvement with vascular and follicular structures. However, because we did not rebiopsy the nevus sites in this study, it is possible that some cases lacking clinical evidence of recurrence might demonstrate residual nevus cells beneath the scar. Even if we did find nevus persistence in some sites on histologic examination, however, the lack of visibly apparent change over time would suggest limited clinical significance. It is also possible that clinically apparent nevus in the biopsy scar may represent pigmentation in keratinocytes or melanophages rather than persistent or recurrent nevus cells.

Although there was an association between positive margin and recurrence, it was not statistically significant (P = .17 for all DN and BN combined, P = .11 for DN), perhaps because of the low numbers of recurrences. Lack of greater association of recurrence with margin involvement was somewhat surprising, given that positive margin is the justification often used for re-excision of DN. Failure of nevi with positive margins to recur suggests that in most cases, residual nevus cells in the biopsy wound are not of sufficient number (or do not have the capacity) for regeneration and pigment production.

The only statistically significant association found with nevus recurrence was biopsy method, with shave technique being significantly associated with recurrence. One potential explanation for a higher recurrence rate with shave biopsies compared with punch biopsies is that nevus recurrence may be more likely to originate from a deep rather than lateral margin—which indeed we observed in most recurrent nevi in this study (Fig 1, B). Because shave biopsies are generally more superficial than punch biopsies, they would be more likely to have a positive deep margin. Another explanation for the association between shave technique and recurrence is that lesions that are shaved tend to be much larger than those selected for punch biopsy, where the diameter of the punch tool (usually ≤ 6 mm) necessarily limits application of punch biopsies to small lesions. Larger lesions may contain more proliferative cells or be more likely to recur from residual cells for other reasons that are presently unclear.

One of the factors complicating management of DN is potential variability in histologic interpretation. In one study addressing interobserver variation in histologic diagnosis of atypical nevi, lesions interpreted as DN by an expert panel were diagnosed as melanoma by other pathologists in 21% of cases. Conversely, lesions originally diagnosed as thin or in situ melanomas were re-read as DN in 12% of the cases. In our study, all of the histologic slides were re-reviewed by the same dermatopathologist to limit interobserver variation. In addition, routine histologic evaluation of punch or shave biopsy specimens typically involves examination of only a fraction of the lesion to determine degree of atypia and margin involvement, leading some to propose that all DN should undergo excisional biopsy to obtain the most accurate diagnosis. A recent study from our institution, however, found that in a majority of biopsied nevi the histologic findings were homogeneous such that the diagnostic information in one section could be extrapolated to the remainder of the specimen.
We recognize the possibility that some lesions may have had unrecognized margin involvement, and that the degree of dysplasia may have been underestimated. However, this information would not have affected the low rate of clinical recurrence that was observed.

Our results are consistent with those of Kmetz et al.\(^22\) who found that no melanomas developed during a 5-year period after biopsy of 55 atypical nevi (26 lesions with at least one positive margin and 29 with clear margins) that were not re-excised. Based on these findings, the authors recommended observation as a safe alternative to re-excision for incompletely removed atypical nevi.\(^22\) To fully answer the question of whether incompletely removed DN with mild or moderate dysplasia should be re-excised, longer follow-up of more lesions is required. We still believe that nevi with severe dysplasia should be re-excised to ensure complete removal, given that such lesions may represent evolving melanoma or could later be reinterpreted as melanoma given the possibility of interobserver variation among pathologists\(^19\) as noted above. However, our data suggest that lesions that demonstrate only mild or moderate dysplasia may not need to be re-excised given their low likelihood of recurrence, and can be followed clinically for evidence of recurrence or development of any concerning features.

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REFERENCES

17. Tuthill RJ, Reed RJ. Failure of senescence in the dysplasia-melanoma sequence: demonstration using a tissue microarray and a revised paradigm for melanoma. Semin Oncol 2007;34:467-75.