Published in final edited form as:

J Am Acad Dermatol. 2010 April ; 62(4): 591–596. doi:10.1016/j.jaad.2009.06.080.

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

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Abstract

Background—Little is known about the recurrence/persistence rates of dysplastic nevi (DN) following 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 nevus biopsy at least two years prior 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 two years of follow-up, seven (3.6%) demonstrated recurrence on clinical exam. Ninety-eight DN had a follow-up period of at least four 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 following biopsy of dysplastic and benign nevi were extremely low. Re-excision of nevi, including moderately dysplastic nevi with a positive margin, may not be necessary.

Keywords

nevi; recurrence; biopsy; dysplastic

Introduction

Management of dysplastic nevi (DN) following biopsy remains a controversial issue. Although most dermatologists would agree that DN demonstrating severe atypia should be re-excised

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Conflicts of interest: None declared.

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 NIH 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 al.⁷ prospectively evaluated the effectiveness of deep shave excision in removing macular melanocytic nevi as well as 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.⁷ After six months 56/77 biopsy sites were reassessed, and 7/56 (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 the Institutional Review Board of the University of Utah. Patients were recruited from our pigmented lesion clinic, in which approximately seven new patients are seen each week and over 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 prior to their visit to determine whether any previously biopsied melanocytic nevi were appropriate for the study. Prior biopsies had been performed between 1998 and 2007 predominantly by physicians at our institution as well as 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%). Biopsies from most anatomic areas were included, with the majority (55%) from the trunk. Lesions that were non-melanocytic, had demonstrated recurrent nevus on initial biopsy, were biopsied less than two years prior to 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 five other nevi, Table 1) following 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 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’s Exact tests were used for all comparisons. Statistical analysis was performed using R 2.8.0 (The R Foundation for Statistical Computing, Copyright 2008, Vienna, Austria). P values ≤ 0.05 were considered statistically significant.

Results

Rates of nevus recurrence

Over an eight-month period, 271 sites of previously biopsied melanocytic nevi were assessed for clinical recurrence in 115 patients (Table 1). In most cases, nevi at the follow-up visit presented as a well-healed hypopigmented scar (Figure 1A). In some cases on the other hand, pigmentation was seen within the scar (Figure 1B), and interpreted as nevus recurrence. After histologic re-evaluation of original biopsies, 195 lesions were classified as DN, 61 were classified as BN, and 15 were classified as “other” (which included six blue nevi, eight Spitz nevi or spindle cell nevi, and one combined Spitz/blue nevus). The majority (179/195) of DN in this study were mildly dysplastic, while 16/195 lesions were moderately dysplastic (Table 1). There were no DN with severe dysplasia. None of the 25 lesions (9.2% of total) that had been re-excised following biopsy were found to have recurred. After excluding these lesions that had been previously re-excised, only seven of 175 (4.0%) DN showed clinical recurrence at least two years following biopsy (Table 2). Of the 175 DN, 93 lesions showed no evidence of recurrence four years or more following biopsy. Of the 61 BN, only two (3.3%) had clinical evidence of recurrence greater than two years after initial biopsy (Table 2). 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.

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 vs. non-recurrent nevi, excluding the lesions that had been re-excised following biopsy. The breakdown by lesion type, subtype, biopsy method, margin involvement, and presence of congenital features is detailed in Table 2. 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) vs. moderate (0/13) dysplasia were not statistically

significant ($P=1.00$). Of the seven recurrent DN, five had a positive margin and three had congenital features. Of 168 non-recurrent DN, 53 (32%) were junctional and 115 (68%) were compound. These non-recurrent DN represented lesions biopsied by shave (48%), punch (34%) and excisional (18%) technique, and 64/168 (38%) had a positive margin while 42/168 (25%) had congenital features. For all DN, there was not a statistically significant association of recurrence with nevus subtype (junctional or compound, $P=0.44$), presence of positive margin ($P=0.11$), or congenital features ($P=0.38$). On the other hand, for all DN, shave biopsy technique was significantly ($P=0.033$) associated with recurrence.

Of the two recurrent BN, both were compound type, were biopsied by shave technique, and demonstrated a positive margin as well as congenital features. Of the other 59 BN that did not recur, 33 (56%) were compound and 26 (44%) were intradermal. These non-recurrent BN represented lesions biopsied by shave (81%), punch (14%) and excisional (5%) technique, and 53/59 (90%) had a positive margin while 58/59 (98%) had congenital features. For all BN, there was not a statistically significant association of recurrence with nevus subtype (compound or intradermal, $P=0.50$), 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 ($P=0.045$) associated with recurrence; for lesions biopsied only by shave or punch technique, the association between shave and recurrence was of even greater significance ($P=0.032$).

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,^{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 10,000),¹⁶ raising the question of whether incompletely removed DN should be re-excised with clear margins to prevent potential evolution into melanoma. While 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 present study of DN recurrence following 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 following 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.^{17,18} In addition, we might have expected the recurrence rate to be higher for compound than intradermal lesions since 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.^{4–7} Our lower recurrence rates are unlikely to be due to differences in follow-up times, since 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 high-risk patients in an attempt to remove nevi completely, while 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, since we did not re-biopsy 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 upon 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 ($P=0.17$ for all DN and BN combined, $P=0.11$ for DN), perhaps due to 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.⁸ 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 to 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 (Figure 1B). Since 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.¹⁹ Conversely, lesions originally diagnosed as thin or *in situ* melanomas were re-read as DN in 12% of the cases.¹⁹ 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 biopsies 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.²⁰ 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.²¹ 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 over a 5-year period following 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 In order 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 potentially later interpreted as melanoma given the possibility of interobserver variation among pathologists¹⁹ as noted above. However, our data suggest that lesions which 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.

Acknowledgments

We thank Glen Bowen for helpful discussions in the planning phase of this study.

D.G. is supported by the Department of Dermatology, the Huntsman Cancer Foundation, and the National Institutes of Health.

Abbreviations

BN	benign nevi
DN	dysplastic nevi

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Fig 1.
Nevus biopsy sites demonstrating clinical (A) lack or (B) presence of nevus recurrence.

Table 1

Nevi assessed for recurrence in this study

Nevus type	Total #	Subtype	Biopsy method	Re-excised
Dysplastic nevi (DN)				
Mild atypia	179	56/179 junctional 123/179 compound	96/179 shave 57/179 punch 26/179 excision	17/179
Moderate atypia	16	3/16 junctional 13/16 compound	8/16 shave 3/16 punch 5/16 excision	3/16
Severe atypia	0	–	–	–
Benign nevi (BN)	61	35/61 compound 26/61 intradermal	50/61 shave 8/61 punch 3/61 excision	0/61
Other nevi (Spitz, blue)	15	8/15 compound 7/15 intradermal	9/15 shave 6/15 punch	5/15

Table 2

Features of clinically recurrent and non-recurrent nevi.*

Nevus type	Number	Subtype	Biopsy method	Positive margin	Congenital features
DN, mild	162				
recurrent	7/162	1/7 junctional 6/7 compound	7/7 shave	5/7	3/7
non-recurrent	155/162	51/155 junctional 104/155 compound	76/155 shave 54/155 punch 25/155 excision	60/155	38/155
DN, moderate	13				
recurrent	0/13	–	–	–	–
non-recurrent	13/13	2/13 junctional 11/13 compound	5/13 shave 3/13 punch 5/13 excision	4/13	4/13
BN	61				
recurrent	2/61	2/2 compound	2/2 shave	2/2	2/2
non-recurrent	59/61	33/59 compound 26/59 intradermal	48/59 shave 8/59 punch 3/59 excision	53/59	58/59
Other nevi	10				
recurrent	0/10	–	–	–	–
non-recurrent	10/10	6/10 compound 4/10 intradermal	5/10 shave 5/10 punch	4/10	1/10

* Nevi that were re-excised following original biopsy (Table 1) are excluded here.