“Moderately dysplastic nevus, present at the margin”: now what?
A review of the literature

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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DISCLOSURES
I do not have any relevant relationships with industry.
Background

- Paucity of data regarding whether dysplastic nevi (DN) are premalignant lesions or markers of increased melanoma risk
- Histologically positive margins either at the peripheral edges or deep edges
- Absence of visible clinical residual pigmentation
- Decision to re-excise or observe
Concerns

1. The histological read of a biopsied DN assesses a small percentage of the total lesion allowing a potential focus of melanoma to be missed

2. Given pathologic interobserver variability, a moderately DN may represent an early “under-read” melanoma

3. Recurrent growth of atypical melanocytes at the biopsy site of incomplete may clinically and histologically demonstrate significant atypia/dysplasia (pseudomelanoma), which may be misinterpreted as melanoma

4. Residual cells can transform into melanoma
   concern that residual cells from biopsied DN have a higher risk of malignant transformation than do cells from similar-appearing, unbiopsied clinically atypical nevi
   Ability to monitor over time
Background

• “Sequentially removing numerous stable CAN results in discomfort, morbidity, and emotional and financial distress with no proven medical benefit for performing a “moleectomy.””

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Histologic read of DN may miss a potential focus of melanoma

• Majority of melanomas arise de novo and not from preexisting nevi

• Melanomas arising from preexisting nevi demonstrate similar rates of association with DN (21%-56%) vs common nevi (44%-79%)

• Rate of transformation of common nevi vs DN into melanoma is unknown as prevalence of common vs dysplastic nevus is unknown


- Risk of a nevus on a 20-year-old patient transforming into a melanoma by age 80 to be 0.03% to 0.009%
  - Systematic removal of benign-appearing nevi of little value

- Estimated risk of malignant transformation of single DN is ~1:10,000
  - The patient likely has multiple other nevi with the same degree of dysplasia that are not being removed

- Relatively low rate of transformation multiplied by likelihood of yielding residual melanocytes during re-excision may support clinical monitoring alone
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Smoller BR, Egbert BM. Dysplastic nevi can be diagnosed and graded reproducibly: a longitudinal study. JAAD 1992 Sep;27(3):399-402.

• **OBJECTIVE:** to examine the diagnostic profiles of melanocytic lesions of two dermatopathologists in a stable population base

• **METHODS:** 2600 melanocytic neoplasms diagnosed at Stanford over 4 years read by one dermatopathologist (1987-89) and a different dermatopathologist (1990-1). The two independently evaluated these lesions unaware of the other's criteria

• **RESULTS:** 8.8% versus 12.0% were diagnosed as mildly dysplastic, 7.0% versus 6.8% as moderately dysplastic, and 2.7% versus 1.6% as severely dysplastic

• **CONCLUSION:** two pathologists used reproducible criteria for diagnosing and grading dysplastic nevi
Elmore JG et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study.
BMJ. 2017 Jun 28;357

- **Objective** To quantify the accuracy and reproducibility of pathologists' diagnoses of melanocytic skin lesions
- **Participants** 240 skin biopsy cases, grouped into sets of 36 or 48 for interpretation by pathologists on two occasions at least eight months apart (same set)
- **Outcome measures**: Reproducibility assessed by intraobserver and interobserver concordance rates, and accuracy by concordance with three reference diagnoses
- **Results** 187 pathologists completed 8976 independent case interpretations
  - Same diagnosis given for the majority of benign or mild nevi or melanoma cases (76.7%-82.6%).
  - Lower reproducibility for cases interpreted as moderate (35.2%), severe or in situ (59.5%), and class IV early invasive melanoma (63.2%)
- Accuracy using a consensus diagnosis of experienced pathologists as reference varied similarly by class with benign, mild or melanoma having the greatest consensus and moderate, severe/MIS, and early melanoma having the least (25-43%)
- Population level estimate: 82.8% of melanocytic skin biopsy diagnoses would have their diagnosis verified if reviewed by a consensus reference panel of experienced pathologists, 8.0% of cases over-interpreted and 9.2% underinterpreted

• **OBJECTIVES**: investigate diagnostic drift among nine dermatopathologists re-evaluating pigmented lesion cases initially diagnosed 20 years ago

• **METHODS**: twenty nine cases of dysplastic nevi with severe atypia and 11 cases of thin radial growth-phase melanoma 1988 -1990 were retrieved from the pathology files of the MGH and re-reviewed by the same dermatopathologists 2008 -2009

• **RESULTS**: mean number of melanoma diagnoses by the 9 study participants increased from 11 to 18, and a majority agreed with the original diagnosis of melanoma in all 11 cases

• A majority of current raters diagnosed melanoma in 4/29 cases originally reported as severely dysplastic. Interrater agreement over time was excellent (kappa 0.88) and fair (kappa 0.47) for cases originally diagnosed as melanoma and severely atypical dysplastic nevus, respectively

• **CONCLUSIONS**: dermatopathologists demonstrated a general trend toward the reclassification of prior nonmalignant diagnoses of severely atypical dysplastic nevi as malignant but did not tend to revise prior diagnoses of cutaneous melanoma as benign
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• **OBJECTIVE:** Evaluate the utility of re-excising margin-positive mildly and moderately DN

• **METHODS:** A retrospective chart review of all adult patients with a biopsy-proven DN from 2010 through 2011 assessing the presence of melanocytic residuum in re-excisional specimens and a clinically significant change in diagnosis

• **RESULTS:** 1809 mildly and moderately DN were diagnosed, 765 (42.3%) had positive margins, and 495 (64.7) of the 765 lesions were re-excised. 18.2% of re-excisional specimens had melanocytic residuum. Re-excision resulted in a clinically significant alteration of the diagnosis in only 1 case (to severe) (0.2%); 0.1% overall (1/765)

• **CONCLUSIONS:** Re-excising mildly and moderately DN results in a low histopathological yield, rarely a clinically significant change in diagnosis

• Clinical monitoring of margin-positive lesions may be warranted

**OBJECTIVE:** To evaluate the effect of surgical excision after biopsy of dysplastic nevus, on final diagnosis, melanoma prevention, and melanoma detection

**METHODS:** retrospective review of specimens from US community and academic practices of dysplastic nevi and cutaneous melanomas 9/1/1999 – 3/1/2011

**RESULTS:**
- 196/580 (34%) of DN had positive biopsy margin; 127/196 (65%) with positive biopsy margin received excision. 2/127 excisions (1.6%) had clinically significant diagnosis change after (moderately-to-severely DN → melanoma in situ)
- 216 melanomas: in situ and superficial spreading subtypes infrequently associated with DN (20% and 18%, respectively) (P = .002), most often of moderate-to-severe or severe grade
  - 10.97% of invasive melanomas were associated with a dysplastic nevus

**CONCLUSIONS:** Excision of biopsy-diagnosed mildly or moderately DN is unlikely to create clinically significant diagnosis change; very low transformation risk to melanoma
- Moderate-to-severely/severely dysplastic nevi more often associated with melanoma, and excision may be beneficial for melanoma detection or prevention

• **OBJECTIVE:** to determine recurrence rates of previously biopsied DN, to assess whether biopsy method, margin involvement, congenital features, epidermal location, and degree of dysplasia associate with recurrence

• **METHODS:** Patients w/ 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:** 271 biopsy sites assessed in 115 patients.
  • Of 195 DN with greater than 2 years of follow-up, 7 (3.6%) demonstrated recurrence on clinical examination
  • 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%).

• **CONCLUSION:** 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.

- **OBJECTIVE:** determine the recurrence rate of MDN with positive histologic margins

- **METHODS:** retrospective study on 147 MDN 2007-2013 with positive histologic margins that were not re-excised and for which at least 1 year of clinical follow-up was available

- **RESULTS:** Six (4%) MDN (5 compound and 1 junctional) recurred, with an average recurrence time of 1.7 years

- **CONCLUSION:** incompletely excised MDN do not require re-excision
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• **OBJECTIVE:** determine the rate of melanoma development in patients with DNs that approached a microscopic border but were not re-excised

• **METHODS:** retrospective study of 115 patients evaluated 1/1/1980- 12/31/1989, who had a DN that extended to within 0.2 mm of a punch, shave, or excision border and no re-excision

• **RESULTS:** average follow-up 17.4 years
  • 115 nevi: 66 mildly dysplastic, 42 moderately dysplastic, and 7 severe
  • No patient developed metastatic melanoma or melanoma at removal site of a DN

• **CONCLUSION:** routine re-excision of mildly or moderately DN may be unnecessary
Current Evidence Regarding Outcomes of DN With Positive Margins

• Kmetz et al: no melanomas arose in 26 previously biopsied DN with positive margins or in 29 DN with clear margins during a mean follow-up period of 6.12 years
  • No designation of histopathologic degree of atypia

• Goodson et al: no melanomas in 65 mildly and 4 moderately DN with positive margins and in 106 DN with clear margins (97 mild and 9 moderate) with at least 2 years of clinical follow-up

• **OBJECTIVE:** determine long-term risk of melanoma in biopsied mild or moderate DN with positive histologic margins that were clinically observed vs reexcised with negative margins

• **METHODS:** Retrospective cohort study of 590 cases in 498 patients from an academic pigmented lesion clinic and dermatology clinics with biopsy-confirmed DN with positive histologic margins 5/15/91-7/8/2015, and followed up through 5/30/2016.

• **RESULTS:** 590 positive-margin DN: 191 reexcised, 399 clinically observed; 170 reexcised and 304 observed DN with follow-up data, mean follow-up of 5.5y. Observation recurrence 3.3%
  
  • 6/304 (2.0%) observed DN developed melanoma at the same site, compared with 1/170 (0.06%) that were reexcised (P = .43).
  
  • 5/6 observed patients who developed melanoma initially underwent partial biopsy with grossly positive margins
  
  • 1 melanoma in situ evolved from an excisionally biopsied moderately dysplastic nevus 5 years later
  
  • No deaths from melanoma arising from biopsy-proven DN occurred.
  
  • New primary melanoma developed at other sites in 9.9% of excised and 9.4% of resected DN

• **CONCLUSIONS:** In mild and moderate DN with microscopically positive margins and no concerning clinical residual lesion, observation is a reasonable management option.
Delphi Guidelines:

• Clinically and dermatoscopically suspicious lesions for melanoma: excisional biopsy with 1- to 3-mm clinical margins and depth below any anticipated dermal component (usually reticular dermis) to clear histologic margins
  • Via saucerization/shave, punch, or elliptical biopsy

• Clinically monitor stable, banal-appearing CAN with the possible aid of imaging

• If a partial or incisional biopsy demonstrates a DN with positive margins and the remaining clinical pigmentation is not reexcised, the clinician and patient should be aware that the level of histopathologic dysplasia in the remaining lesion may not be identical to that in the biopsy specimen; monitor and reexcise if unusual clinical changes

Delphi Guidelines:

• Mildly DN and moderately DN biopsied with clear histologic margins following initial biopsy do not need to be reexcised

• Mildly DN with positive histologic margins following biopsy, without evidence of clinical residual pigmentation do not need to be reexcised

• Observation may be a reasonable option for management of moderate DN with positive histologic margins without clinical residual pigmentation

• Patients should be educated about examining scars for warning signs of melanoma and when to notify the clinician for reevaluation


- Recurrent nevi tend to develop within 8 months with pigmentation confined within the scar

- Melanomas tend to recur more than 20 months after the biopsy, in patients older than 30 years, and with pigmentation crossing into normal skin
Avoid the controversy

• Identify the signature nevus patterns of CAN to minimize need to biopsy

• Monitor stable CAN without concerning features for melanoma with regular exams
  • Size tracking
  • Clinical morphologic and dermoscopic feature evaluation
  • Comparison with prior appearance using individual or total body photographs


• “The histopathology of melanocytic proliferations in human skin can be defined in a way which allows a rational approach to their management. Mildly and moderately dysplastic nevus need only be narrowly removed. Severe dysplasia and melanoma in situ may recur locally as invasive melanoma, and consideration for conservative reexcision is warranted. Dysplastic nevi should be considered to be markers of patients who may develop melanoma. Patients with dysplastic nevi or a family history of unusual moles or melanoma should have continued follow-up, preferably with standardized clinical photographs.”
Heymann WR. Should Moderately Atypical Dysplastic Nevi Be Re-excised? Follow the Yellow Brick Road! Skinmed. 2015 Dec 1;13(6):475-6.
Brains, Heart, Courage, & Home

• Brains to review the data
• Heart to appreciate that biopsy and re-excision create anxiety, scars, economic burden
• Courage to not recommend reexcision of moderately atypical nevi that extend to the margin of the specimen
  • “Reexcision puts the clinician in a precarious position of having to perform another procedure that realistically only protects the dermatopathologist from potential litigation for the small possibility that a melanoma might develop at that site”
• Recommend reexcisions of severely atypical nevi that extend to the margin due to documented interpreter variability in categorizing lesions as severely atypical nevi vs melanoma in situ rather than moderately dysplastic nevi as melanoma in situ