Management of Dysplastic Nevi: The Role of Complete Surgical Excision

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Atypical moles, also called dysplastic nevi (DN), are considered by many to reside in the grey portion of the spectrum between benign nevi and melanoma. Because of the difficulty of assessing the behavior of an individual DN, and the association with an increased overall risk of melanoma, physicians and patients have grappled with the choice between observation and surgical excision. In the absence of a reliable predictive test or formal management guidelines, many physicians elect complete surgical excision of DN. The prevalence of DN is believed to be at least 8-10 percent in susceptible populations, posing a large health burden. An improved understanding of their role in and relationship with melanoma thus remains an important objective.

In pursuit of this goal, our research team examined detailed outcomes of surgical excision of DN, as well as the association of DN with melanoma. This pivotal data was analyzed for clinically relevant measures and sorted by grade of atypia, forming the first published evidence of specific DN excision outcomes.

Diagnosis and Current Practices
Clinically, atypical moles exhibit border or color irregularity, have a variable and often larger size than ordinary moles (5-15 mm), and are often found in patients with numerous nevi (often >50-100). Clark, Lynch and Elder originally described the clinical and histologic characteristics of these distinctive-appearing nevi in a portion of melanoma-prone families and sporadically in individuals prone to melanoma. Biopsy of either normal-appearing nevi or clinically atypical nevi reveals a subset with histologic features of atypia, such as atypical melanocytic hyperplasia, lamellar or eosinophilic fibrosis, and lymphocytic inflammatory response; these are termed nevi with architectural disorder, or dysplastic nevi. Some prefer to name these Clark’s nevi, noting that the term “dysplastic” may imply that all DN have significant malignant potential. Unifying diagnostic criteria have not been established to date for atypical or dysplastic nevi, but a number of groups have suggested criteria.

The presence of clinically atypical nevi and/or histologic dysplasia in nevi is associated with increased overall melanoma risk. Due to this increased risk, management includes counseling on skin cancer prevention and detection, as well as regular full-body skin examinations. Further management of a biopsied DN having a positive histologic margin has remained variable. As our study and others have demonstrated, in the absence of significant guidance as to risk, there has been substantial inter-physician variability in recommendations for observation or excision, and a standard of care has not been established. In our study sample of 580 DN, after biopsies reporting DN with a positive histologic margin, those with mild histologic dysplasia were most often observed (only 12 percent received excision), those with moderate dysplasia were variably excised (63 percent), and the vast majority of those with severe dysplasia (62 percent) received excision. Not surprisingly, nevi reported to have moderate histologic dysplasia represent the most nebulous portion of the DN spectrum, and management has been correspondingly ambiguous.

Surgical Excision after Biopsy
In our study of 580 dysplastic nevi and 216 primary cutaneous melanomas, biopsied DN demonstrated a number of key characteristics. Positive histologic margins were more frequently reported as the grade of DN increased. In addition, biopsied DN with a positive histologic margin were treated with subsequent complete excision more frequently as the grade of DN increased. Changes in diagnosis upon excision of biopsied DN and rates of associated melanoma were examined. Primary cutaneous melanomas were also reviewed and analyzed to determine the type and depth of melanoma, rate of DN-associated melanoma, and grade of associated DN.

The study outcomes provide evidence suggesting that mildly and moderately dysplastic nevi may generally behave differently than...
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Moderately-to-severely and severely dysplastic nevi.1 Of biopsy-diagnosed DN, two were found to harbor melanoma upon re-excision; both were moderately-to-severely dysplastic nevi. A 3.1% percent rate of melanoma was diagnosed on excision of DN with moderate-to-severe dysplasia. In contrast, there was not any instance in the study of a biopsy-diagnosed mildly or moderately dysplastic nevus containing melanoma upon excision.

Of 216 primary melanomas evaluated, a significant association with moderately-to-severely or severely DN was also evident. In cases where a grade of DN was specified, 93% of DN-associated melanomas showed moderately-to-severely or severely DN. Mildly and moderately dysplastic nevi were found significantly less often (6% of the time when a grade was specified) in DN-associated melanoma.

Our data suggest that excision of biopsy-diagnosed DN with moderate-to-severe and/or severe dysplasia may offer measurable benefits in the early detection and possible prevention of associated melanoma.1 The data also suggest that routine excision of biopsy-diagnosed DN with mild or moderate dysplasia may have significantly less benefit.1 As it is standard practice to remove the entire clinically visible nevus during biopsy, our findings are most generalizable to cases where the lesion has been clinically removed with the initial biopsy. The data further suggest that pathologist-issued recommendations for routine complete excision of clinically removed DN with mild or moderate dysplasia may be unnecessary. Based on these data, further examination is encouraged of the risks and benefits of excision in the management of these common skin lesions.1

Key Considerations

Investigation of outcomes of the excision of DN represents a milestone in our understanding of DN and raises important questions for discussion.1

DN generally receive more aggressive management by both pathologists and clinicians in cases of positive margins and with increasing grades of atypia.1,10 In our study, as the grade of DN increased, positive histologic margins were more frequently reported, and DN with a positive histologic margin were more often treated with complete excision.1 While the majority of dysplastic nevi are considered benign lesions, increasing concern about diagnostic accuracy and risk of transformation appears correlated with higher grade of atypia. Our study confirms the validity of these concerns in cases of DN with moderate-to-severe atypia and severe atypia, for which excision provides a measurable benefit in melanoma diagnosis and possible melanoma prevention.1 In addition, the data reveal that mildly and moderately dysplastic nevi appear to have a high degree of diagnostic accuracy on biopsy and a significantly lower association with melanoma, so excision offers fewer benefits.1

Many pathology reports routinely contain comments that DN with moderate or greater atypia and a positive histologic margin should be completely excised to confirm the diagnosis.11 It has been informally reported in the literature that many pathologists may increase the reported DN grade when a positive margin is found,1 suggesting pathologists’ desire to view a completely excised DN with negative histologic margins before feeling confident in the rendered diagnosis. Our study suggests that such diagnostic concerns may be appropriate in cases of biopsy-diagnosed DN with a severely atypical component, which show a significant rate of melanoma upon complete excision. However, greater confidence in the biopsy diagnosis of clinically removed mildly and moderately dysplastic nevi may be warranted, since in our study none revealed severe atypia or melanoma upon complete excision.1 Based on these data, pathologist-issued comments advising routine complete excision to confirm the diagnosis of biopsied mildly and moderately dysplastic nevi with negative clinical margins and a positive histologic margin may be unnecessary.

Recent studies have further examined rates of melanoma diagnosis upon excision of dysplastic nevi, supporting many of these findings. In a study of 77 histologically dysplastic acral nevi having mild to severe atypia, none revealed melanoma upon excision.12 A study of 134 cases of biopsied nevi with histologically moderate or severe dysplasia similarly did not find melanoma upon excision.14

Inter-observer diagnostic variability among pathologists remains a consideration.11 Uniform guidelines and improved diagnostic concordance should be a priority, with specimens optimally interpreted by a board-certified dermatopathologist. Potential inter-observer variability does not appear likely to justify routine re-excision of every biopsy-diagnosed moderately dysplastic nevus for fear of pathologic misdiagnosis. Diagnostic limitations in this regard should be improved through continued research and development of uniform guidelines of care.

In assessing the risk of transformation of a DN, Tsao and colleagues have estimated an overall rate of 1 in 10,000 for an “average” atypical nevus, based on rates of association.

Figure 1. Characteristics of biopsied dysplastic nevi
of atypical nevi with melanoma that are consistent with our data.1,15 Risk stratification by grade of atypical nevus appears prudent. Our study data provide evidence suggesting that if DN are in some cases precursor lesions to melanoma, moderately-to-severely and severely dysplastic nevi may be more likely to transform than mildly or moderately dysplastic nevi.1

Though concerns exist that the biologic behavior of any individual DN is not possible to predict, most agree that wholesale removal of DN is not warranted.12 Similarly, the routine re-excision of all incompletely excised DN in an individual or population of patients may not be necessary. Presumably, DN selected for biopsy may have appeared clinically more suspicious than the patient’s other nevi, but there is no evidence that clinical selection of a DN for biopsy correlates with an increased risk of future transformation.12,16 In our study, there were not any cases of melanoma arising at the site of a previously biopsied DN.1 Two studies have followed patients with incompletely excised DN for 5 and 17 years, respectively, and similarly failed to find melanoma at the site of a biopsied DN, suggesting that risk of melanoma development at the site of a biopsied DN is very low.17,18

Finally, the risk that a recurrent benign mole or recurrent DN may appear as a pseudo-melanoma, resulting in unnecessary surgery, appears low based on available literature.19 Further data would be valuable, as there are few published cases. Recurrence of DN after biopsy has been reported as 3.6 percent, similar to the 3.3 percent recurrence rate found for benign nevi.20 Biopsy margin positivity does not appear to influence the recurrence rate, indicating that to prevent recurrent nevi, re-excision of both typical and atypical nevi having either negative or positive biopsy margins would be considered.20 Shave removals are associated with a higher risk of recurrence, and punch excisions sampling the entire clinical lesion may be considered optimal when seeking to prevent recurrence.20

Continued evaluation of the primary characteristics of atypical nevi and their related clinical outcomes will assist physicians and patients in making appropriate treatment decisions about these challenging lesions, as well as aid in improving melanoma prevention and detection efforts.

Clinical Recommendations

In advising patients who have a biopsy diagnosis of dysplastic nevus with a positive margin, discussion about the generally benign nature of most DN, relevant concerns and uncertainties about the ultimate behavior of some nevi, especially high-grade DN, and review of treatment choices is encouraged (Figure 2). By explaining the association with an increased overall risk of melanoma at any site, physicians can help moderate excessive fears about a particular individual nevus, while encouraging appropriate monitoring of the entire skin surface for any suspicious or changing lesions and providing education on melanoma-preventive behaviors.

For patients with DN containing a severely atypical component (moderately-to-severely and severely dysplastic nevi), the increased association with melanoma and increased rate of melanoma diagnosis upon excision may be reviewed to support general management by excision. In cases of moderately dysplastic nevi, our study data suggest the possibility of generally benign behavior that may be similar to that of mildly dysplastic nevi. This evidence supports the commonly accepted management method of periodic observation for mildly dysplastic nevi with a positive margin, and suggests that observation represents a similarly reasonable option for moderately dysplastic nevi. Reliable evidence for most mildly or moderately dysplastic nevi behaving as true precursor lesions progressing to melanoma at a higher rate than typical benign nevi remains lacking or insufficient.4 However, until further evidence and diagnostic tests can be developed to improve our understanding of DN, each lesion should be considered in the context of the individual patient, with excision considered if deemed appropriate by the patient and treating physician.

While histologic classification into categories of mild, moderate, and severe atypia appears to provide some guidance as to melanoma risk, future improved classification by genetic or biologic characteristics may allow us to improve risk stratification and thereby improve the balance of risks and benefits of surgical excision. Ultimately, by collecting evidence to guide management of atypical nevi, we will improve our melanoma prevention and treatment efforts while also limiting unnecessary procedures and surgical complications.

References


Figure 2. Clinical management of dysplastic nevi.
Why Do Men Have Worse Melanoma Survival than Women? Is It Behavior, Biology, or Both?

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In 1969, melanoma pioneer Dr. Wallace Clark and colleagues proposed that melanoma behaves in a “somewhat less malignant” manner in women than in men.1 Over the ensuing four decades, worldwide data have confirmed higher melanoma mortality in men compared with women, particularly in older white males.2,3 However, it remains unclear whether these survival disparities are due to diagnostic delay, other related health behaviors in men, or gender differences in tumor biology. Recent published data support the notion that gender differences in melanoma biology may play a larger role in patient outcome than previously thought.

Mortality by Gender

In 2013, an estimated 9,480 persons died from melanoma in the US, nearly two-thirds men.4 Almost 60 percent of melanoma deaths occur in white men aged 50 years and older,5 and the American Association for Cancer Research (AACR) Cancer Progress Report in 2013 noted that melanoma is one of only three malignancies in men whose death rates from 1990 to 2009 increased (by 10.5 percent).6 In contrast, melanoma death rates in women declined by 9.6 percent over the same period.7 National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registry data similarly show that white men > age 65 have the highest melanoma mortality (Figure 1),8 and this has mainly been attributed to health behaviors and practices in men that result in reduced skin screening and later detection of thicker, more lethal melanoma.

Role of Health Behaviors and Practices

In a study of 227 men older than or equal to age 40 with newly diagnosed melanoma, factors related to thicker melanoma at diagnosis included nodular histologic subtype, lack of atypical nevi, education level below high school, and patient (vs. physician) detection of melanoma.9 Physician-detected melanomas on the back of the body were significantly thinner compared to patient-detected tumors.10 Nearly one-third of melanomas in men occur on the back, are likely to be thicker, and are often missed by patients. Therefore, promoting regular examination of the back by older men, their spouses, and their health providers may prove beneficial in reducing melanoma mortality in this age group.

Female partners may play a critical role in increasing melanoma awareness in the older male population by encouraging routine skin checks during primary medical care exams and assisting with skin self-examination practices.11 Multiple studies have demonstrated that thinner lesions are found by health providers during routine professional examination (i.e., opportunistic screening) than lesions found when patients notice a symptomatic or bleeding pigmented lesion then bring it to medical attention.12,13 In a survey study of 566 recently diagnosed adults with cutaneous melanoma, the odds of older men (>60 years) presenting with a thin (T1, ≤1mm) melanoma were four times higher if they had received a physician skin examination for skin cancer in the year before diagnosis (OR 4.09, 95 percent confidence interval (CI) 1.88-8.89), even though most melanomas (81 percent) were not reported to be physician-detected.14 It was also demonstrated in the study that use of a melanoma picture aid and routine self-examination of some/all of the body prior to diagnosis were more beneficial for older men than younger men in detecting thinner tumors.

Role of Biological Differences

These studies show that delays in diagnosis due to health behaviors may account for gender disparities in melanoma survival. However, several recent publications suggest that biologic differences may play an equally, if not more important, role. In 2011, Joosse et al.15 assessed gender differences in survival and disease progression in the Munich Cancer Registry (Germany) between 1978 and 2007, finding that in over 11,000 melanoma cases, women had a 38 percent survival advantage compared to men (adjusted Hazard Ratio (HR) 0.62; 95% CI 0.56-0.70), and were significantly less likely to progress to lymph node and visceral metastasis (42 percent and 44

Figure 1. Age-Adjusted Melanoma Mortality Rates for non-Hispanic white men and women by age group (<65 years of age, >65 years of age), Surveillance, Epidemiology, and End Results (SEER) Program, 1990-2010
percent less likely, respectively). In addition, women retained an approximate 20 percent survival advantage even after disease progression, including in-transit and lymph node but not visceral metastasis. Cutaneous melanomas in women appeared to have a lower propensity to metastasize, and the authors postulated that differences in tumor-host interaction were evident by gender.

A subsequent study by Joosse, et al suggested an even stronger role for gender differences in tumor biology. In a pooled analysis of 2,672 patients with cutaneous melanoma (stage I/II) enrolled in four European Organisation for Research and Treatment of Cancer (EORTC) prospective clinical trials, women demonstrated a 30 percent overall and melanoma-specific survival advantage, as well as a longer time before developing lymph node and distant metastasis. As in other studies, men were more likely than women to have thicker, ulcerated melanomas and tumors on the head, neck, and trunk – all well-established adverse prognostic factors. Men and women were matched for age (mean 52.5 years for men, 50.1 years for women), tumor characteristics (thickness, ulceration, histologic subtype), anatomic location of the primary, and trial-associated treatment and surveillance, so these confounding variables (including differences in patient follow-up or compliance with therapy) were unlikely to explain the findings. Female melanoma patients demonstrated not only a longer delay before relapse but a higher cure rate compared with males, and this was true across individual trials, prognostic parameters, and countries.

**Survival Differences in Younger Men and Women**

As most of the published data demonstrating a survival difference between men and women pertain to middle-aged and older study populations, our team examined survival differences and prognostic factors among male and female adolescents and young adults (AYAs), aged 15-39 years at melanoma diagnosis. This collaboration involved investigators from the Stanford Cancer Institute and the Cancer Prevention Institute of California (CPIC), which is responsible for SEER cancer reporting in the Greater San Francisco Bay Area. From 1989-2009, there were 26,107 invasive melanoma cases among non-Hispanic white AYAs in the SEER analysis of 18 cancer registries nationwide, and 1,561 melanoma-specific deaths, with an overall mean follow-up of 7.5 years over the 20-year study period assessed.

Males accounted for only 40 percent of melanoma cases but comprised over 63 percent of melanoma-specific deaths. AYA males were 55 percent more likely to die from melanoma compared with women (HR 1.55; 95% CI 1.39-1.73), even after adjusting for age at diagnosis, other primary cancers, body site, tumor thickness, regional lymph node metastasis, distant metastasis, and histologic subtype. Males had significantly poorer survival across all age ranges <40 years, across all thickness ranges (with the exception of T2 melanoma, 1.01-2 mm), irrespective of superficial spreading or nodular melanoma subtype, and regardless of the presence or extent of metastasis. Men with cutaneous melanoma were 52 percent more likely to die than women, and those with regional nodal disease were 74 percent more likely to die than women. As in other studies, there were no significant survival differences between men and women with distant metastasis. Surprisingly, even men with the thinnest (T1) melanoma were nearly twice as likely to die as women (HR 1.95; 95% CI 1.57-2.42), although it should be emphasized that both men and women with thin melanoma have a high overall likelihood of cure.

Because younger men and women are more likely to self-detect their melanomas and less likely to rely on physician detection, our study suggests that biology may play a larger role in the observed gender disparity in survival in the AYA population. While we cannot exclude the possibility that increased health provider visits by AYA females during...
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their reproductive years may contribute to survival differences, physician discovery and skin self-examination practices are less likely to play a role in thinner melanoma detection in this age group compared with older individuals. Furthermore, we performed a subset analysis of patients diagnosed in California to adjust for health insurance and socioeconomic status (factors that correlate with skin examination), and found no difference in the gender survival disparity among AYAs.

Male Biologic Factors Potentially Behind Lower Survival

Differences in melanoma biology and/or immune surveillance between men and women have been proposed, including a possible “protective factor” in females or a “stimulating factor” in males.\(^15,16\) Theories include gender differences in sex hormones, vitamin D metabolism, immune homeostasis and regulation, oxidative stress, epigenetic factors such as methylation, and ultraviolet radiation-induced gene mutations and exposure patterns.\(^17,18\) Differences in sex hormones, especially estrogens, would appear to be the most plausible explanation. However, in the EORTC analysis,\(^19\) sex differences in survival were similar in pre- and post-menopausal-aged women, and other studies have reported a persistent female advantage in older, post-menopausal groups.\(^15,20,21\) Furthermore, no gender differences in the expression of estrogen receptor beta (associated with increased melanoma mortality) have been noted in melanocytic nevi or melanoma. Nor has a gender difference been seen in the incidence of BRAF, NRAS, or KIT mutations.

Perhaps a more compelling argument can be made for the potential deleterious effect of androgen expression, based on the elevated risks of melanoma among prostate cancer survivors and prostate cancer as a second primary malignancy in cutaneous melanoma patients. In a prior CPIC/Stanford Cancer Institute collaboration,\(^22\) we demonstrated an increased risk of prostate cancer following cutaneous melanoma diagnosis (between 1973 and 2003), which was not explained by surveillance bias or shared risk factors in older men. This risk was bidirectional, with a greater risk of cutaneous melanoma also observed following the diagnosis of prostate cancer.

Similar findings were reported in a recent study by Li, et al.\(^23\) which tracked over 42,000 male participants in the Health Professional Follow-Up Study from 1986 to 2010. During this time frame, 5,091 prostate cancers were documented in white male health professionals, along with 539 melanomas. Personal history of prostate cancer was significantly associated with an increased risk of subsequent melanoma (HR 1.83, 95% CI 1.32-2.54), even after adjusting for mole counts, sun exposure, and other characteristics in the study population. While both cancers tend to occur in older males and while chronic sun exposure could be a confounder, nonmelanoma skin cancer risk was only weakly associated with personal history of prostate cancer. The authors postulated a potential link between testosterone and increased melanoma cell proliferation or an androgenic effect on suppression of host immune response.

Evidence of sexual dimorphism in immune responses to melanoma is yet another competitive hypothesis. Mouse models have shown functional differences in regulatory T cells by gender in the absence of PD-L1, as well as differential responses to anti-PD-L1 therapy in males vs. females with murine B16 melanomas.\(^24\) Potential gender differences in immune cell subset profiles and function in humans have yet to be explored. Given the published data in the last few years suggesting a biological basis for gender disparities in melanoma survival, further research is warranted.

What Does This Mean for Patients?

Regardless of whether the cause of observed differences in melanoma survival between men and women is predominantly behavioral, biological, or a combination of factors, several key public health messages can be gleaned. Young men must be educated regarding the dangers of skin cancer. Most of the recent public health messages regarding tanning bed and suntan avoidance have focused on women. A similar message to AYA men emphasizing their poorer survival with melanoma may help to promote early detection and enhance the likelihood of cure. Men of all ages should seek prompt medical attention for any changing moles or skin lesions that look different from the rest. While these may end up being harmless skin findings, early detection of melanoma can be lifesaving.

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From the Editors

Since they were first described, the melanocytic neoplasms called dysplastic nevi, aka atypical moles, have been shrouded in controversy. It is clear, nonetheless, that certain groups of acquired nevi have features in the gray zone between benign nevi and melanoma. Histologically, these nevi display at least some degree of architectural disorder and cytologic atypia. Many also manifest an atypical clinical morphology.

Given the nebulous complexity of these lesions, it should come as no surprise that management recommendations vary widely. Fortunately, controversy spaws research, which in turn slowly peels away the shroud of uncertainty. In their lead story in this issue of The Melanoma Letter, Drs. Reddy and Rogers discuss the key factors involved in choosing between watchful waiting and complete surgical excision of biopsied DN. In their recent research, dysplastic nevi with mild to moderate atypia were rarely associated with melanoma, while those with moderate-to-severe or severe atypia were not uncommonly associated with melanoma. Specifically, when positive margins were found after initial biopsy, only a few moderate-to-severe or severe DN, and no mild to moderate DN, were found to have an associated melanoma. The authors suggest that the former may have a higher propensity for transformation or for harboring a focus of melanoma, with patients benefiting from complete re-excision, while the latter might safely be followed over time.

The second article in this issue, by Drs. Swetter, Clarke, and Keegan, explores the reasons behind the gender differences in melanoma survival. It has been known for some time that the prognosis for men with melanoma is worse than that of women. Much of this has been attributed to men’s lower awareness of and attentiveness to melanoma’s early warning signs. While this lack of awareness in men may contribute to later discovery and thicker tumors, recent work by Swetter and colleagues has suggested that the answer may be much more complex. The authors explore the possibility that female hormones may be protective and/or male hormones deleterious in melanoma biology. They even provide evidence that there may be gender differences in the immune response to melanoma. Their insights and hypotheses are intriguing and clearly warrant further research.

At the very least, the findings of the authors of our stories help to expand our

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