Detection of Melanoma – The Earlier, the Better

At the outset, I have to declare a conflict of interest: It is in my economic interest as a dermatopathologist that as many biopsies are taken as possible. In the following, I shall violate my own interests by suggesting just the opposite.
Disclosure

☐ I have no potential conflict of interest to report
☒ I have the following potential conflict(s) of interest to report

Editorial

Acknowledgments

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Let me start with the famous quote by my close fatherly friend Bernard Ackerman: “No one should die of malignant melanoma.” That demand was made in 1985, at a time
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No one should die of malignant melanoma

Time was, not so many years ago, when tuberculosis, pneumoconiosis, and pulmonary tuberculosis were fatal diseases. Because of modern methods of accurate diagnosis and effective treatment, no one dies of those diseases nowadays. The same should also be true for malignant melanoma as of now. We have all the know-how, diagnostically and therapeutically, to eradicate curable lesions of malignant melanoma. An international effort should be undertaken immediately to achieve that desideratum.

In general, although it is a vast oversimplification, the thicker a malignant melanoma is, the worse the prognosis for the patient; the thinner, the better. Tumorous lesions of malignant melanoma carry a poor prognosis in general, whereas macules and patches of malignant melanomas are curable. In macules and patches, neoplastic melanocytes of malignant melanoma are confined wholly to epidermal and adnexal epithelium. In diagnostic features of malignant melanoma in situ, i.e., neoplastic melanocytes of malignant melanoma within the epidermis and epithelial structures of adnexa, not in the dermis. Histologically, macules of malignant melanoma are characterized by an increased number of melanocytes showing variable degrees of nuclear atypia and arranged both as solitary units and in nests at the dermoepidermal junction and above it. The lesions are usually poorly circumscribed with some single atypical melanocytes trailing off above the basal layer beyond the last, well-defined nest of melanocytes at both lateral margins. Such lesions are often asymmetric with more nests of melanocytes in one half than in the other or with more melanophages in the papillary dermis on one side than on the other. In some fact, single atypical melanocytes dominate over nests of melanocytes. The nests themselves vary in sizes and shapes, some have irregular shapes, and some tend...
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and can be distinguished reliably from nevi early-on in the vast majority of cases, both clinically...
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and histopathologically. Ackerman pointed out that most criteria for histopathologic diagnosis of melanoma pertain to changes in the epidermis so that diagnosis can be made at an in situ stage.
Because of easy recognition at an early stage and slow growth in the majority of cases, melanoma is an ideal candidate for cancer screening, and it is perplexing that the logic of cancer screening has been turned upside down by arguing that melanoma in situ is not a malignant disease because it cannot kill.
Cancer is an entity because its development and evolution are comparable from one neoplastic system to the next, regardless of the inductive mechanism and differences in clinical and histologic appearance due to origin from different kinds of cells and tissues. Cancer develops through a sequence of lesions; the lesions appearing serially are a manifestation of tumor progression. One lesion which is a part of the strict epidermal lesion is having cells entirely above the dermal-epidermal basement membrane zone with some structural features of invasive melanomas, have been termed melanoma in situ. In this report, the histology possessing the following features is discussed as a possible candidate for designation as melanoma in situ. The individual cells are large and epithelioid, and have an abundance of finely divided pigments, giving the cytoplasm a tan, dusty appearance. The nuclei are large and hyperchromatic, and usually about 1.5 to 2 times the diameter of the surrounding keratinocytes. The malignant melanoma in situ, malignancy in situ) is a contradiction in terms, the prototype of an oxymoron.

For example, Clark in 1990 spoke of melanoma in situ as “a contradiction in terms, the prototype of an oxymoron.”
and, more recently, Juan Rosai referred to it as an “obsolete, untenable concept.” Those notions have been coupled
Evaluation of Overdiagnosis of Breast Cancer in Screening with Mammography: Results of the Nijmegen Programme


After 12 years of screening for breast cancer in Nijmegen (1975–86), during which period six mammographic examination rounds were carried out, the extent of overdiagnosis was evaluated. Overdiagnosis is defined as a histologically established diagnosis of invasive or intraductal breast cancer that would never have developed into a clinically manifest tumour during the patient’s normal life expectancy if no screening examination had been carried out. The whole 12-year period shows an excess of 11% of breast cancer cases in Nijmegen, compared with the neighbouring city of Arnhem, where no mass screening was performed. The incidence of breast cancers in Nijmegen in the period 1975–78 is higher, compared with the incidence rates in Arnhem; the rate ratio is 1.30. For the time-intervals 1979–82 and 1983–86 the rate ratios are 1.03 and 1.01 respectively with (0.88; 1.18) and (0.86; 1.16) as 95% confidence intervals. This leads to the conclusion that there is no evidence that screening programmes using modern mammography constitute a significant risk for overdiagnosis of breast cancers.

with a new definition of “overdiagnosis” advanced by epidemiologists in regard to breast cancer, namely, a “histologically established diagnosis of invasive or intraductal breast cancer that would never have developed into a clinically manifest tumour during the patient’s normal life expectancy if no screening examination had been carried out.” But how should anybody know in advance whether or not a histopathologically established malignant neoplasm would develop into a clinically manifest tumour? And what if the patient exceeds his or her “normal life expectancy”? 
That definition is clearly untenable but, nonetheless, it has become accepted worldwide and has been applied to all types of malignant neoplasms, including melanoma. In 2005, Welch found a strong correlation between skin biopsy rates and the incidence of melanoma, noted that “the extra cases diagnosed were confined to early stage cancer,” and attributed that phenomenon to overdiagnosis. This conclusion was based on statistics.
Here we have a practical example: a melanoma in situ at the edge of a congenital nevus. In the terminology of epidemiologists, the melanoma in situ is “early stage cancer” or “inconsequential cancer,” and it has even been suggested to avoid the label of cancer for such lesions because it represents “overdiagnosis.” This may be the case, but only if the lesion is excised completely. Unfortunately, this melanoma in situ was present in only one of several sections, all the others showing the nevus exclusively, and the relevant section was overlooked.
Two years later, the diagnosis of melanoma was no “overdiagnosis” any more
because the lesion was no longer “inconsequential.” This example illustrates the purpose of cancer screening, namely, to prevent “inconsequential” cancer from becoming consequential. The diagnosis of melanoma should have been made
at the in-situ stage, and it could have been made at that stage because criteria for melanoma were fulfilled: predominance of single melanocytes, poorly confined nests, melanocytes in all reaches of the epidermis. Here it is really true:
“Detection of melanoma – the earlier, the better.”

However, it is true only if the melanoma can be recognized.
In general, detection is possible at an in-situ stage, but the earlier one wants to interfere, the more difficult detection becomes.
This lesion is an in-situ melanoma,
but how about this one that looks remarkably similar? One cannot be sure because it is simply too small; if it is another melanoma, it did not have enough time to develop features that make it recognizable.
just as one cannot recognize a human being at an early stage of embryogenesis. And if one tries to interfere at that stage, overdiagnoses are inevitable, not those fulfilling the definition of epidemiologists, but true overdiagnoses, i.e., melanocytic nevi misinterpreted as melanoma.
One problem is clinical overdiagnosis. The ratio of benign moles excised for each malignant melanoma, also known as the “number needed to treat,” varies considerably between different studies. I recently looked at our own figures, i.e., the ratio between nevi and melanomas at a laboratory of dermatopathology in Germany where regular skin cancer screening has been implemented nine years ago,
The number of benign moles excised for each malignant melanoma: the number needed to treat

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Summary

Background. The ratio of benign moles to malignant melanoma (MM) is a useful indicator of risk, and may have personal implications for the individual.

Aim. To assess the NNT of 600,000, and to compare our numbers with others.

Methods. This was a retrospective analysis of a 5-year period (2005–2010), including all melanoma patients who had at least one lesion excised; benign naevi were not counted. The NNT was calculated as the ratio of benign naevi (BN) to melanomas (MM), with 95% CI calculated. The NNT was 6.3, with 95% CI 5.0–8.5.

Results. In total, 4,691 patients were assessed, a range of 4.9–11.3 for the NNT, with 95% CI 7.6 for female and 4.8 for male, with 95% CI 8.0–7.5 (p < 0.001). This was similar in the DN and MM groups, but had a disproportionately female bias in the latter group. The NNT was 6.3, with 95% CI 5.0–8.5.

Figure 2: Comparison of number needed to treat published in various studies. Bars (left to right): Marks et al.; Wilkinson et al.; Hansen et al.; English et al.; Buade et al.; Marks et al.; present study; Chia et al.
too small to exhibit criteria for clinical diagnosis of melanoma such as an irregular border or irregular distribution of pigment. In the absence of such criteria, the vast majority of pigmented lesions are going to be melanocytic nevi, rather than melanomas.
and epidemiologists are right to deplore that “biopsy samples are taken from hundreds of thousands of benign lesions … In addition to needless morbidity, these interventions cost billions of dollars.”

The problem of trying to detect melanomas at the earliest possible stage, however, is not only overdiagnosis clinical, but also histopathological.
Of course, histopathologic diagnosis is usually possible at an earlier stage, but in principle, histopathologists are confronted with the same dilemma as clinicians:
If an incipient melanoma is not given the time for characteristics to develop that are crucial for diagnosis, the latter remains equivocal. For example, a few cells in the dermis may be extremely helpful for distinction between nevus and melanoma.
Were it not for those nests in the dermis, one might be tempted to invoke the diagnosis of melanoma in situ in this lesion because of some melanocytes above the junction.
Another example removed at an earlier stage. There is no dermal component. Single melanocytes predominate over nests because there are no discrete nests – they were not given the time to form –,
and there are some melanocytes above the junction. This is probably a nevus, but a melanoma in situ cannot be excluded, and because nobody wants to overlook a melanoma, overdiagnoses are common. Because what happens in the event of error?
If a benign lesion is classified as malignant, one gets a medical laurel wreath because patients believe they have been saved;
if a malignant lesion is classified as benign, it may recur and one may be taken to court. This is a strong incentive to err on the malignant side.
The so-called “melanoma epidemic” is probably caused, in part,
I believe that the overdiagnosis of melanoma is arguably the most difficult problem that we face in dermatopathology today.
That problem is aggravated by poor biopsy technique. Incomplete biopsies are becoming increasingly common, and they impede interpretation of findings tremendously. The flippant way with which biopsies are being performed is enhanced by a low degree of clinical suspicion. It is my experience that, the smaller the lesion is,
the more inadequate is the biopsy specimen, the consequence being that a definite diagnosis of melanoma is substituted by vague suspicion,
until a histopathologic diagnosis can no longer be made.
Those small lesions are probably nevi, but one simply cannot be sure, and a re-excision usually does not clarify the situation because most re-excision specimens contain either no or only small remnants of the lesion that defy interpretation.
Predictive value of biopsy specimens suspicious for melanoma: Support for 6-mm criterion in the ABCD rule

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Objective: Clinical detection of melanoma can be challenging. The number of biopsy specimens performed to diagnose 1 melanoma is a measure of efficiency of skin cancer detection, but few data are available to describe this measure from US health care. We studied the diagnosis of melanoma among biopsy specimens of clinically concerning pigmented lesions at an academic dermatology department.

Methods: We searched for all biopsy specimens that were performed because of clinical suspicion of melanoma in 2013. Characteristics of the patient, lesion, and clinician performing the biopsy, and the final pathology diagnosis were recorded.

Results: A total of 2643 biopsy specimens from 2213 patients submitted by 43 providers were included. Melanoma was diagnosed in 165 cases (positive predictive value 6.4%, 95% confidence interval 5.5%-7.4%). Older age (P < .001), male gender (P = .045), and nontrunk location (P < .001) were predictors of higher probability of melanoma detection. Lesions larger than 6 mm in size had higher positive predictive value 11.5% (8.8%-14.1%) than smaller lesions 2.6% (1.6%-3.6%).

Limitations: Factors influencing the decision to biopsy a lesion may be difficult to evaluate retrospectively.

Conclusion: At an academic medical center, 16 clinically concerning lesions were biopsied to diagnose 1 melanoma. Biopsy specimens of clinically concerning pigmented lesions larger than 6 mm on older men had the highest yield. (J Am Acad Dermatol 2015;72:412-8.)
Of course, there are exceptions, namely, melanomas of small diameter that acquire considerable depth early-on, but those lesions are usually not spotted by cancer screening anyhow because they tend to be domed and scarcely pigmented.
Most melanomas grow slowly and need not be biopsied until they have unfolded their true nature.
I acknowledge that clinical diagnosis can be accelerated by techniques such as dermatoscopy and confocal microscopy. Obviously, if clear-cut criteria for malignancy are detectable in smaller lesions, the latter should be excised. However, the reliability of adjunctive techniques is also hampered by an early stage of development, and those techniques are either not generally available or not generally applied with sufficient expertise. The wide spectrum of diagnostic avenues demonstrated at this meeting
reminds of an ivory tower; the reality of current practice is probably reflected better.
by some of the pictures just shown. For the time being,
I believe that, in general, patients would be served by a shift in management to later, fewer, but better biopsies.