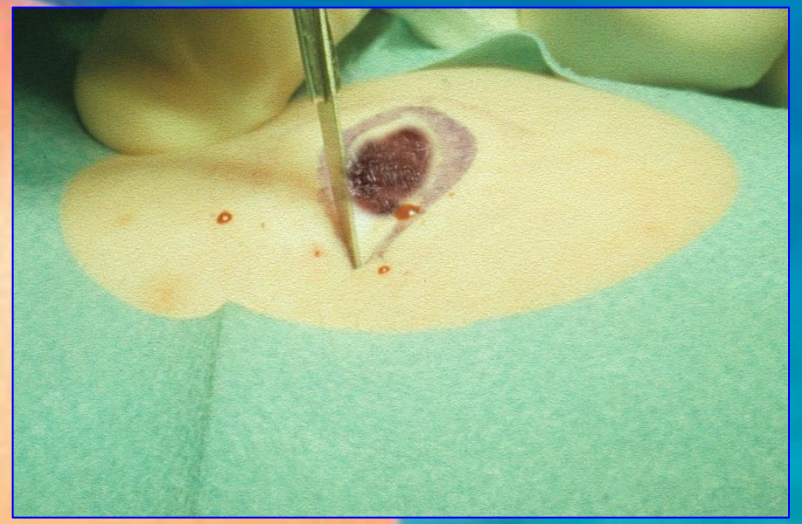
Overdiagnosis of Skin Cancer

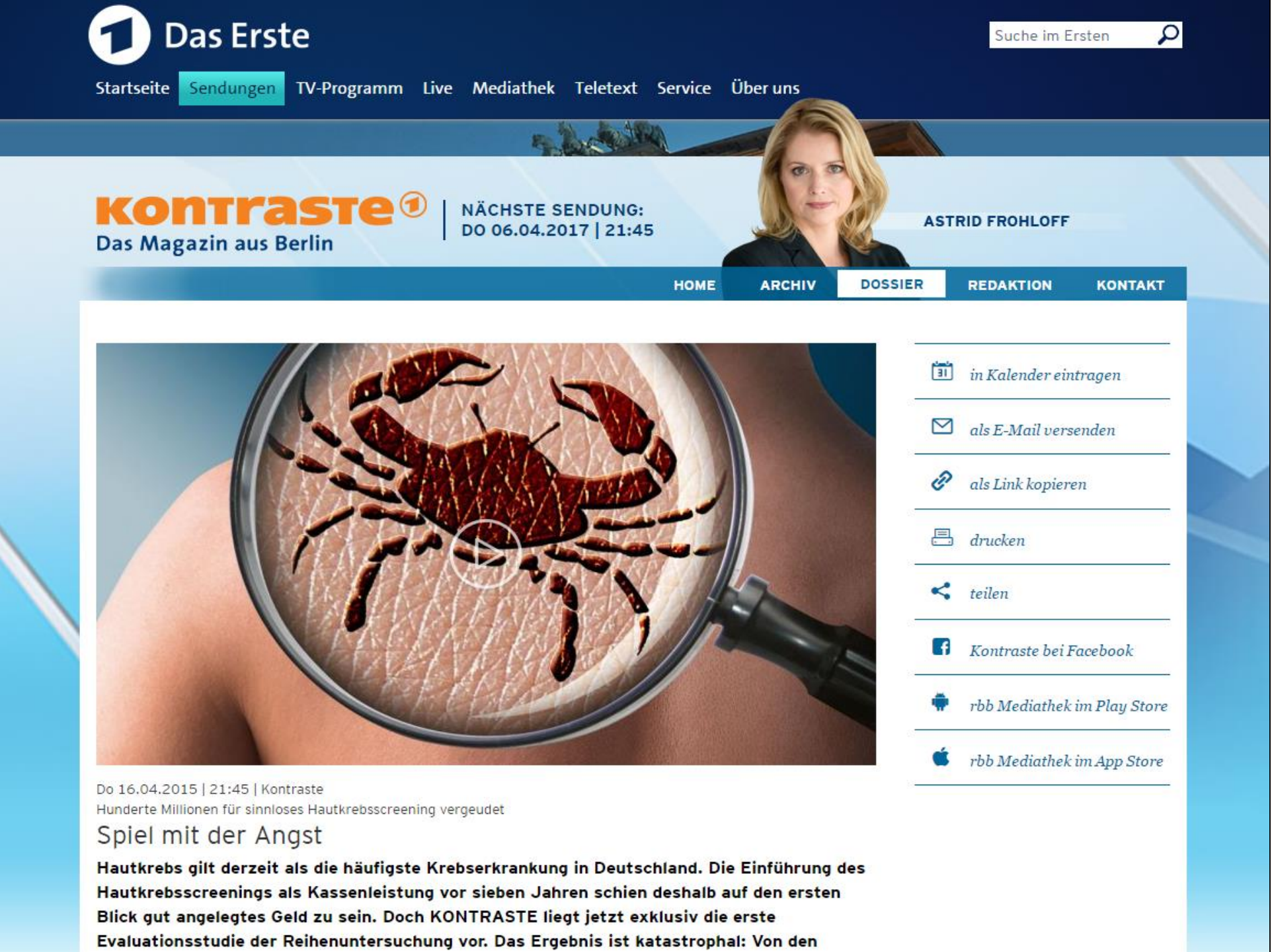
Key Note Lecture,
98th Annual Meeting of the British Association of Dermatologists,
Edinburgh, July 3rd, 2018

Cancer screening is usually depicted in sunny colours: as a chance to save lives with simple measures.
And it is true:

Overdiagnosis of Skin Cancer



detection and excision at an early stage is still by far the best treatment for any malignant neoplasm. For many patients, early detection is a blessing, but it is also associated with problems



that have received considerable public attention in recent years. In German television, for example, cancer screening has been referred to as the *“game with the Angst,”*

and the New York Times posed the question whether *"cancer survivors"* are not, in reality, *"victims of overdiagnosis."*
Of course, the answer to that question depends on the definition of "overdiagnosis."

Overdiagnosis of Congenital Dislocation of the Hip

NIS FREDENSBORG AND BO E. NILSSON*

Gastrointestinal Radiology

JOURNAL OF THE AMERICAN GERIATRICS SOCIETY
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Overdiagnosis of Dementia

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Division of Chronic and Degenerative Disorders, Department of Neurology, and the Dementia Research Service, Cornell Medical College at the Burke Rehabilitation Center, White Plains, New York

Borderlands in the Diagnosis of Regional Enteritis

Trends in Overdiagnosis and Value of Therapeutic Trial

Stanley F. Chang, Morton I. Burrell, Norberto A. Belleza, a
Departments of Radiology and Medicine, Yale University School of Medic

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Key words: Small bowel — Crohn's disease, regional enteritis, endometriosis, carcinoid, metastatic carcinoma.

OVERDIAGNOSIS OF ENDOCRINE GUT TUMOURS

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A patient was referred to us from abroad with a diagnosis

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Case Reports

Overdiagnosis of left anterior hemiblock

To the Editor:

In the October, 1977, issue of THIS JOURNAL Dr. G. E. Burch cautions against overdiagnosing left anterior hemiblock (LAH). This caution is justified, but Rosenbaum, in his

In general, that term is used for misdiagnoses that suggest a more serious condition than the one extant.This has been the case since decades, and in all fields of medicine.

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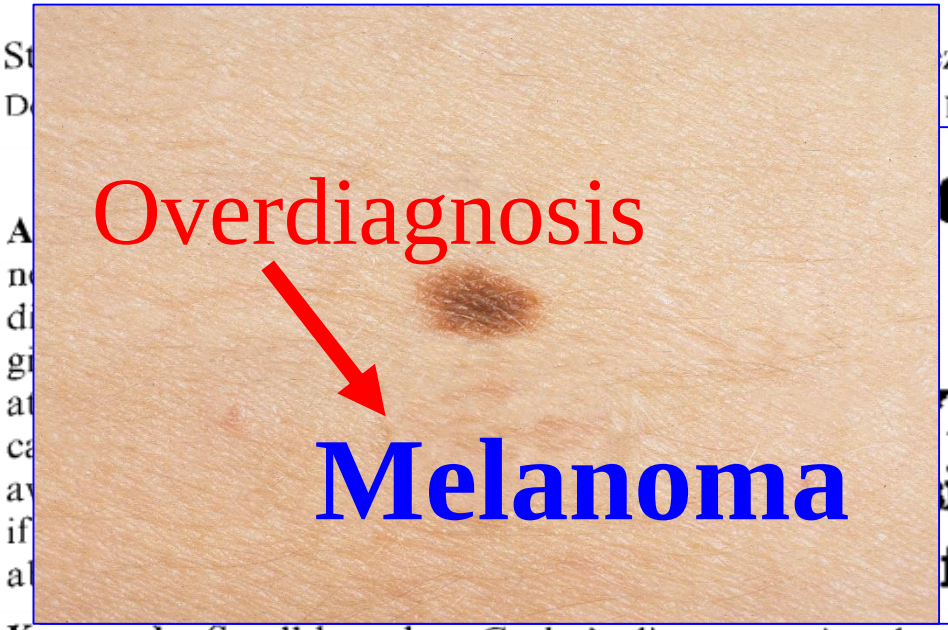

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In regard to melanocytic neoplasms, for example, "overdiagnosis" implies misdiagnosis of a nevus as melanoma,

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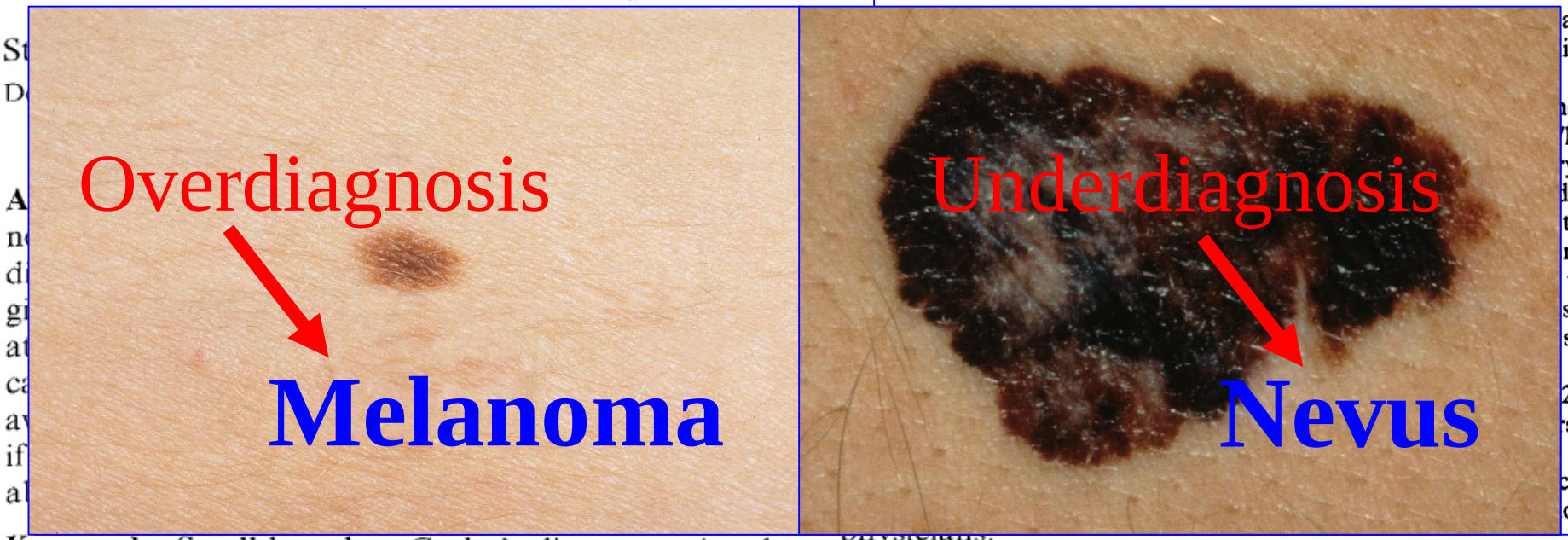

whereas misdiagnosis of a melanoma as nevus qualifies as "underdiagnosis."

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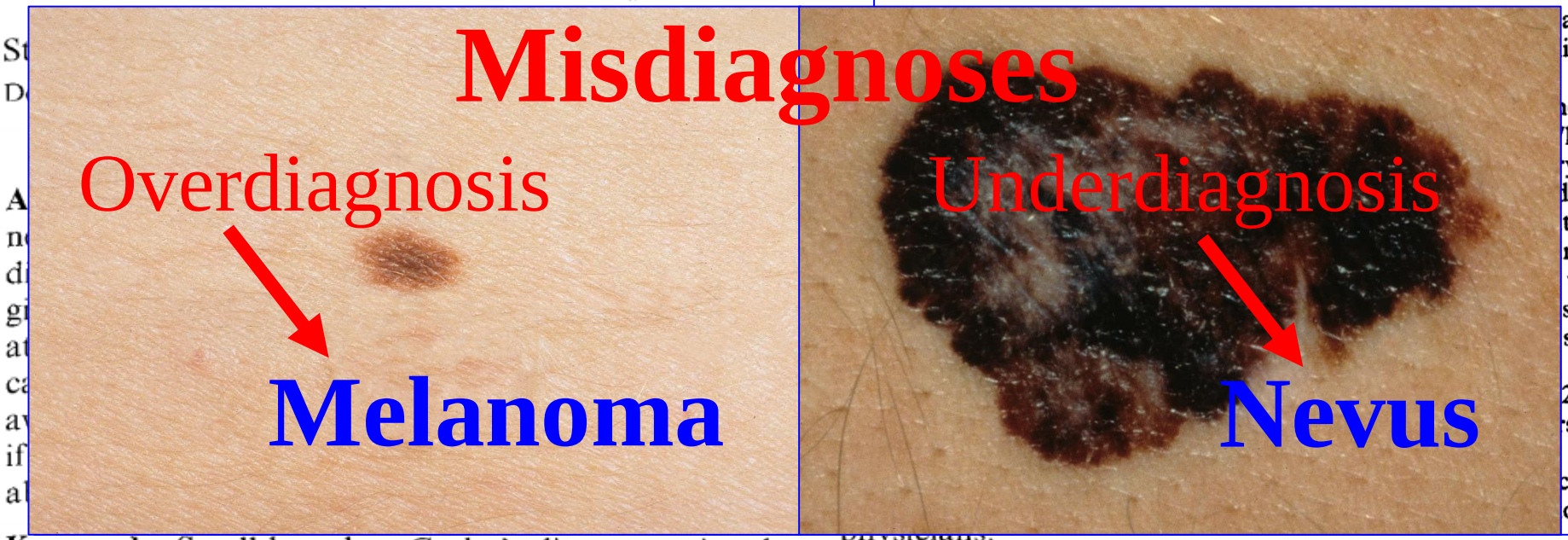

Irrespective from "over" or "under," both terms signify misdiagnoses and are perceived that way by most physicians and the laity.

In 1989, however, a very different definition of "overdiagnosis" has been introduced by epidemiologists in the context of screening for breast cancer,

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Evaluation of Overdiagnosis of Breast Cancer in Screening with Mammography: Results of the Nijmegen Programme

PETRA H M PEETERS*, A L M VERBEEK*, H STRAATMAN*, R HOLLAND**, J H C L HENDRIKS†, M MRAVUNAC‡, C ROTHENGATTER§, A VAN DIJK-MILATZ§ AND J M WERRE§

Peeters P H M (Department of Epidemiology, Institute of Social Medicine, Nijmegen University, Verlengde Groenestraat 75, 6525 EJ Nijmegen, The Netherlands), Verbeek A L M, Straatman H, Holland R, Hendriks J H C L, Mravunac M, Rothengatter C, Van Dijk-Milatz A and Werre J M. Evaluation of overdiagnosis of breast cancer in screening with mammography: results of the Nijmegen programme. *International Journal of Epidemiology* 1989, **18**: 295–299.

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 (0.89; 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.

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.*"
However, nobody knows in advance whether or not a histopathologically established malignant neoplasm would ever develop into a *"clinically manifest tumour"*? And what if the patient exceeds his or her *"normal life expectancy"*? Evidently, this definition is untenable, being based on of post-hoc reasoning,

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REVIEW

Overdiagnosis in Cancer

H. Gilbert Welch, William C. Black

Manuscript received September 3, 2009; revised March 1, 2010; accepted March 5, 2010.

Correspondence to: H. Gilbert Welch, MD, MPH, Veterans Affairs Outcomes Group (111B), Department of Veterans Affairs Medical Center, White River Junction, VT 05009 (e-mail: h.gilbert.welch@dartmouth.edu).

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J Natl Cancer Inst 2010;102:605–613

The conundrum in overdiagnosis is that clinicians can never know who is overdiagnosed at the time of cancer diagnosis. Instead, overdiagnosis can only be identified in an individual if that individual 1) is never treated and 2) goes on to die from some other cause. Because clinicians do not know which patients have been overdiagnosed at the time of diagnosis, we tend to treat all of them. Thus, overdiagnosis contributes to the problem of escalating health-care costs. But even where there no money involved, overdiagnosis would be a major concern: Although such patients cannot benefit from unnecessary treatment, they can be harmed.

and even epidemiologists acknowledge that *"the conundrum in overdiagnosis is that clinicians can never know who is overdiagnosed at the time of cancer diagnosis. Instead, overdiagnosis can only be identified in an individual if that individual 1) is never treated and 2) goes on to die from some other cause."*

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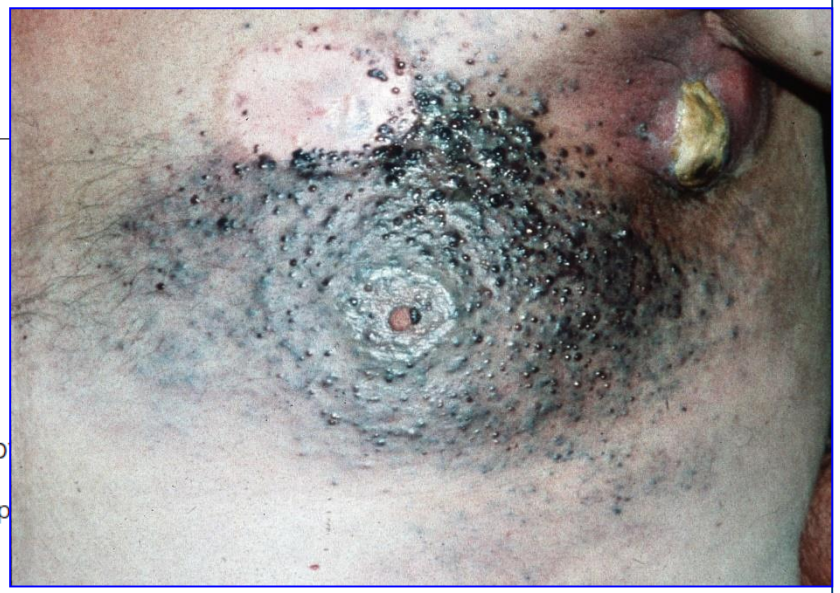

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In other words, according to the definition by epidemiologists, the diagnosis of metastatic melanoma in a case such as this one is an overdiagnosis if the patient is killed in a car crash five minutes later.

Despite its digressiveness, this caricature of a definition has been embraced worldwide and has come to bear on the management of patients.

VIEWPOINT

Overdiagnosis and Overtreatment in Cancer
An Opportunity for Improvement

Laura J. Esserman, MD, MBA
University of California, San Francisco.

Ian M. Thompson Jr, MD
University of Texas Health Science Center at San Antonio.

Brian Reid, MD, PhD
Fred Hutchinson Cancer Research Center, Seattle, Washington.

Over the past 30 years, awareness and screening have led to an emphasis on early diagnosis of cancer. Although the goals of these efforts were to reduce the rate of late-stage disease and decrease cancer mortality, secular trends and clinical trials suggest that these goals have not been met; national data demonstrate significant increases in early-stage disease, without a proportional decline in later-stage disease. What has emerged has been an appreciation of the complexity of the pathologic condition called cancer. The word "cancer" often invokes the specter of an inexorably lethal process; however, cancers are heterogeneous and can follow multiple paths, not all of which progress to metastases and death, and include indolent disease that causes no harm during the patient's lifetime. Better biology alone can explain better outcomes. Although this complexity complicates the goal of early diagnosis, its recognition provides an opportunity to adapt cancer screening with a focus on identifying and treating those conditions most likely associated with morbidity and mortality.

Changes in cancer incidence and mortality[1] reveal 3 patterns that emerged after inception of screening (**Table**). Screening for breast cancer and prostate cancer appears to detect more cancers that are potentially clinically insignificant.[4] Lung cancer may follow this pattern if high-risk screening is adopted.[5] Barrett esophagus and ductal carcinoma of the breast are examples for

Change cancer terminology based on companion diagnostics. Use of the term "cancer" should be reserved for describing lesions with a reasonable likelihood of lethal progression if left untreated. There are 2 opportu-

Optimal screening frequency depends on the cancer's growth rate. If a cancer is fast growing, screening is rarely effective. If a cancer is slow growing but progressive, with a long latency and a precancerous lesion (eg, colonic polyps or cervical intraepithelial neoplasia), screening is ideal and less frequent screening (eg, 10 years for colonoscopy) may be effective. In the case of an indolent tumor, detection is potentially harmful because it can result in overtreatment. These observations provide an opportunity to refocus screening on reducing disease morbidity and mortality and lower the burden of cancer screening and treatments.

In March 2012, the National Cancer Institute convened a meeting to evaluate the problem of "overdiagnosis," which occurs when tumors are detected that, if left unattended, would not become clinically apparent or cause death. Overdiagnosis, if not recognized, generally leads to overtreatment. This Viewpoint summarizes the recommendations from a working group formed to develop a strategy to improve the current approach to cancer screening and prevention.

Periodic screening programs have the potential to identify a reservoir of indolent tumors.[4] However, cancer is still perceived as a diagnosis with lethal consequences if left untreated.

An ideal screening intervention focuses on detection of disease that will ultimately cause harm, that is more likely to be cured if detected early, and for which curative treatments are more effective in early-stage disease. Going forward, the ability to design better screening programs will depend on the ability to better characterize the biology of the disease detected and to use disease dynamics (behavior over time) and molecular diagnostics that determine whether cancer will be aggressive or indolent to avoid overtreatment. Understanding the biology of individual cancers is necessary to optimize early detection programs and tailor treatments accordingly. The following recommendations were made to the National Cancer Institute for consideration and dissemination.

Physicians, patients, and the general public must recognize that overdiagnosis is common and occurs more frequently with cancer screening. Overdiagnosis, or identification of indolent cancer, is common in breast, lung, prostate, and thyroid cancer. Whenever screening is used, the fraction of tumors in this category increases. By acknowledging this consequence of screening, approaches that mitigate the problem can be tested.

Change cancer terminology based on companion diagnostics. Use of the term "cancer" should be reserved for describing lesions with a reasonable likelihood of lethal progression if left untreated. There are 2 opportunities for change. First, premalignant conditions (eg, ductal carcinoma in situ or high-grade prostatic intraepithelial neoplasia) should not be labeled as cancers or neoplasia, nor should the word "cancer" be in the name. Second, molecular diagnostic tools that identify indolent or low-risk lesions need to be adopted and validated. Another step is to reclassify such cancers as IDLE (indolent lesions of epithelial origin) conditions.[4] An example is the reclassification of grade 1 papilloma to urothelial neoplasia of low malignant potential.[6] Presciently, the rationale for reclassifying papilloma and grade 1 carcinoma as "papillary urothelial neoplasia of low malignant potential" was "to take the lowest grades of tumor, the most benign-appearing lesions, and remove the word carcinoma."[6] A multidisciplinary effort across the pathology, imaging, surgical, advocate, and medical communities could be convened by an independent group (eg, the Institute of Medicine) to revise the

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Based on the claim that *"overdiagnosis, if not recognized, generally leads to overtreatment,"* early diagnosis of malignant neoplasms has been discouraged. It has been suggested that *"the term 'cancer' should be reserved for describing lesions with a reasonable likelihood of lethal progression if left untreated"* (whatever *"reasonable"* means).

Addressing overdiagnosis and overtreatment in cancer: a prescription for change

Laura J Esserman, Ian M Thompson, Brian Reid, Peter Nelson, David F Ransohoff, H Gilbert Welch, Shelley Hwang, Donald A Berry, Kenneth W Kinzler, William C Black, Mina Bissell, Howard Parnes, Sudhir Srivastava

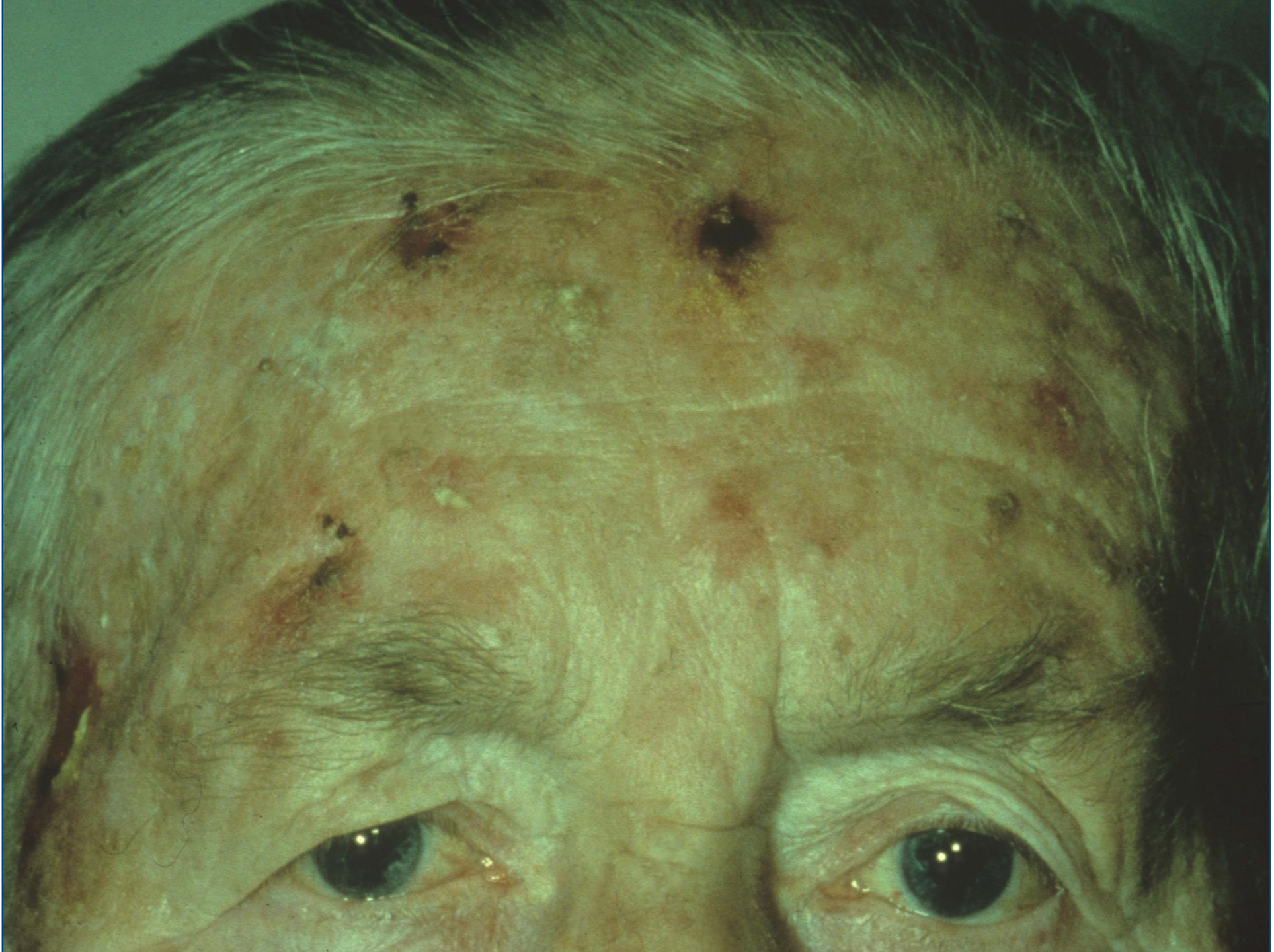
A vast range of disorders—from indolent to fast-growing lesions—are labelled as cancer. Therefore, we believe that several changes should be made to the approach to cancer screening and care, such as use of new terminology for indolent and precancerous disorders. We propose the term indolent lesion of epithelial origin, or IDLE, for those lesions (currently labelled as cancers) and their precursors that are unlikely to cause harm if they are left untreated. Furthermore, precursors of cancer or high-risk disorders should not have the term cancer in them. The rationale for this change in approach is that indolent lesions with low malignant potential are common, and screening brings indolent lesions and their precursors to clinical attention, which leads to overdiagnosis and, if unrecognised, possible overtreatment. To minimise that potential, new strategies should be adopted to better define and manage IDLEs. Screening guidelines should be revised to lower the chance of detection of minimal-risk IDLEs and inconsequential cancers with the same energy traditionally used to increase the sensitivity of screening tests. Changing the terminology for some of the lesions currently referred to as cancer will allow physicians to shift medicolegal notions and perceived risk to reflect the evolving understanding of biology, be more judicious about when a biopsy should be done, and organise studies and registries that offer observation or less invasive approaches for indolent disease. Emphasis on avoidance of harm while assuring benefit will improve screening and treatment of patients and will be equally effective in the prevention of death from cancer.

Introduction

On March 8–9, 2012, the National Cancer Institute convened a meeting to assess the problem of cancer overdiagnosis, which occurs when tumours that would

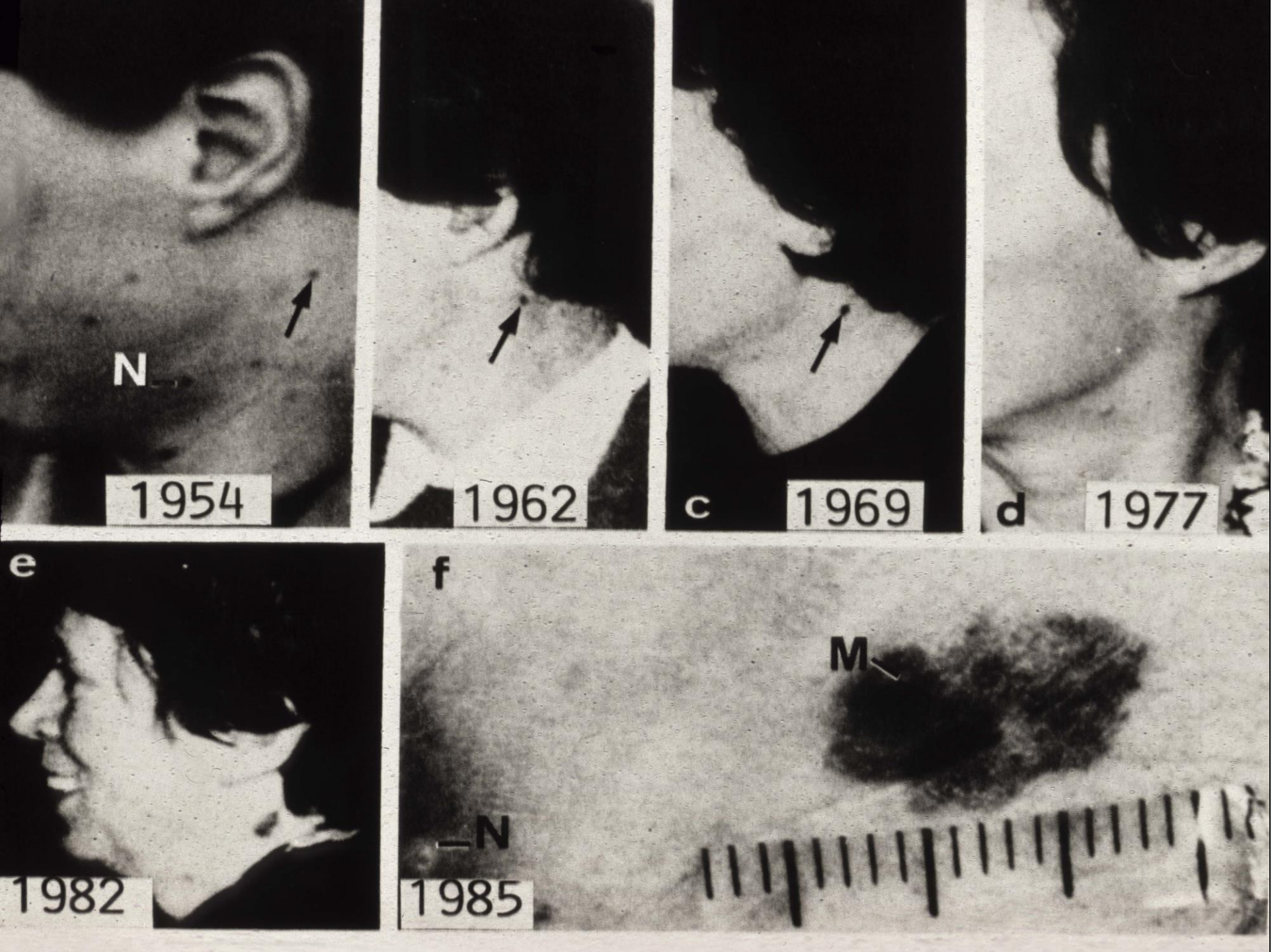
For some cancers, incidence of disease dropped after screening was initiated (eg, cervical and colon cancer), but it increased for others (eg, breast and prostate cancer).[1] In breast and prostate cancer, for example,

The term *"indolent lesion of epithelial origin, or ILDE"* has been proposed *"for those lesions (currently labelled as cancers) and their precursors that are unlikely to cause harm if they are left untreated,"* and it has even been proposed that *"screening guidelines should be revised to lower the chance of detection of minimal-risk IDLEs and inconsequential cancers with the same energy traditionally used to increase the sensitivity of screening tests."*



For dermatologists, this means that they have to press their eyes close energetically in order not to notice tiny lesions of cancer in the skin of their patients.

It is true that most of those lesions grow slowly and may not cause serious harm.



This includes melanoma which may take decades before a nodule occurs. But does this imply that early stages should be neglected? This is what epidemiologists suggest.

Skin biopsy rates and incidence of melanoma: population based ecological study

H Gilbert Welch, Steven Woloshin, Lisa M Schwartz

BMJ 2005; 331: 481

Abstract

Objectives To describe changes in skin biopsy rates and to determine their relation with changes in the incidence of melanoma.
Design Population based ecological study.
Setting Nine geographical areas of the United States.
Participants Participants of the Surveillance Epidemiology and End Results (SEER) programme aged 65 and older.
Main outcome measures For the period 1986 to 2001, annual skin biopsy rates for each surveillance area from Medicare claims and incidence rates for melanoma for the same population.
Results Between 1986 and 2001 the average biopsy rate across the nine participating areas increased 2.5-fold among people aged 65 and older (2847 to 7222 per 100 000 population). Over the same period the average incidence of melanoma increased 2.4-fold (45 to 108 per 100 000 population). Assuming that the occurrence of true disease was constant, the extra number of melanoma cases that were diagnosed after carrying out 1000 additional biopsies was 12.6 (95% confidence interval 11.2 to 14.0). After controlling for a potential increase in the true occurrence of disease, 1000 additional biopsies were still associated with 6.9 (3.1 to 10.8) extra melanoma cases diagnosed. Stage specific analyses suggested that 1000 biopsies were associated with 4.4 (2.1 to 6.8) extra cases of in situ melanoma diagnosed and 2.3 (0.0 to 4.6) extra cases of local melanoma, but not with the incidence of advanced melanoma. Mortality from melanoma changed little during the period.
Conclusion The incidence of melanoma is associated with biopsy rates. That the extra cases diagnosed were confined to early stage cancer while mortality remained stable suggests overdiagnosis—the increased incidence being largely the result of increased diagnostic scrutiny and not an increase in the incidence of disease.

disease.[1 3 7] Finally, whenever physicians look more closely for melanoma, they find more cases.[7-10]

Population based data have not been reported on skin biopsies, the critical end point of surveillance. We examined data from Medicare, a nationwide health insurance for older Americans, to determine whether changes in the biopsy rate relate to the incidence of melanoma.

Methods

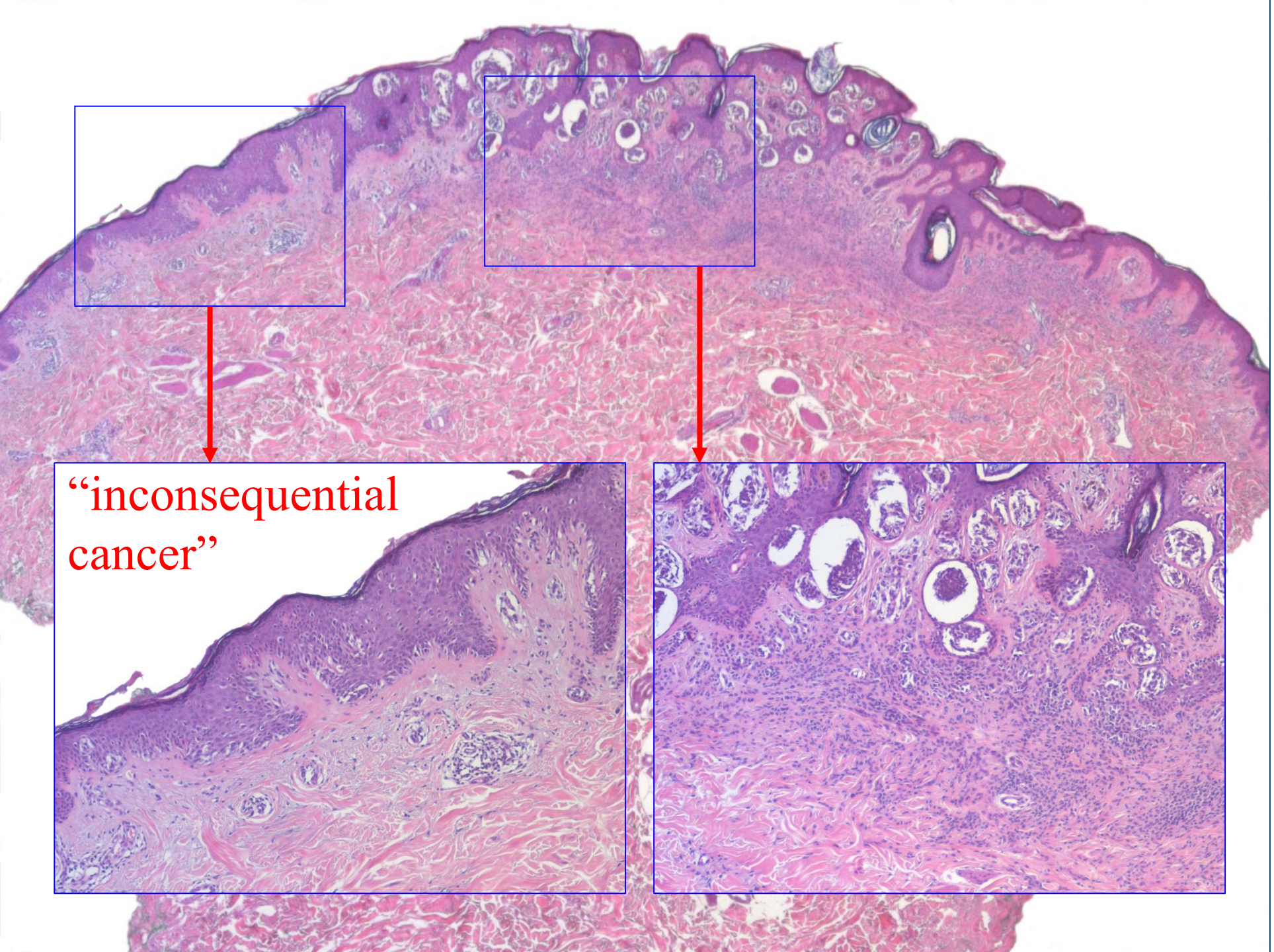
We used Medicare claims to obtain annual population based rates of skin biopsy for patients aged 65 and older in each of the nine geographical areas included in the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) programme from 1986 to 2001. We calculated the biopsy rates for each of 14 years (claims were unavailable for 1991 and 1992). To obtain the annual incidence of melanoma for the same population, we used the programme's statistical software (SEER*Stat, version 5.3.0).[11] We obtained stage specific incidence rates using the surveillance programme's four histological disease stages (in situ, local, regional, and distant) and summed them to produce an incidence rate for all stages combined. Using SEER*Stat's incidence based mortality method we also calculated melanoma incidence and disease specific mortality for all nine geographical areas combined.

Analysis

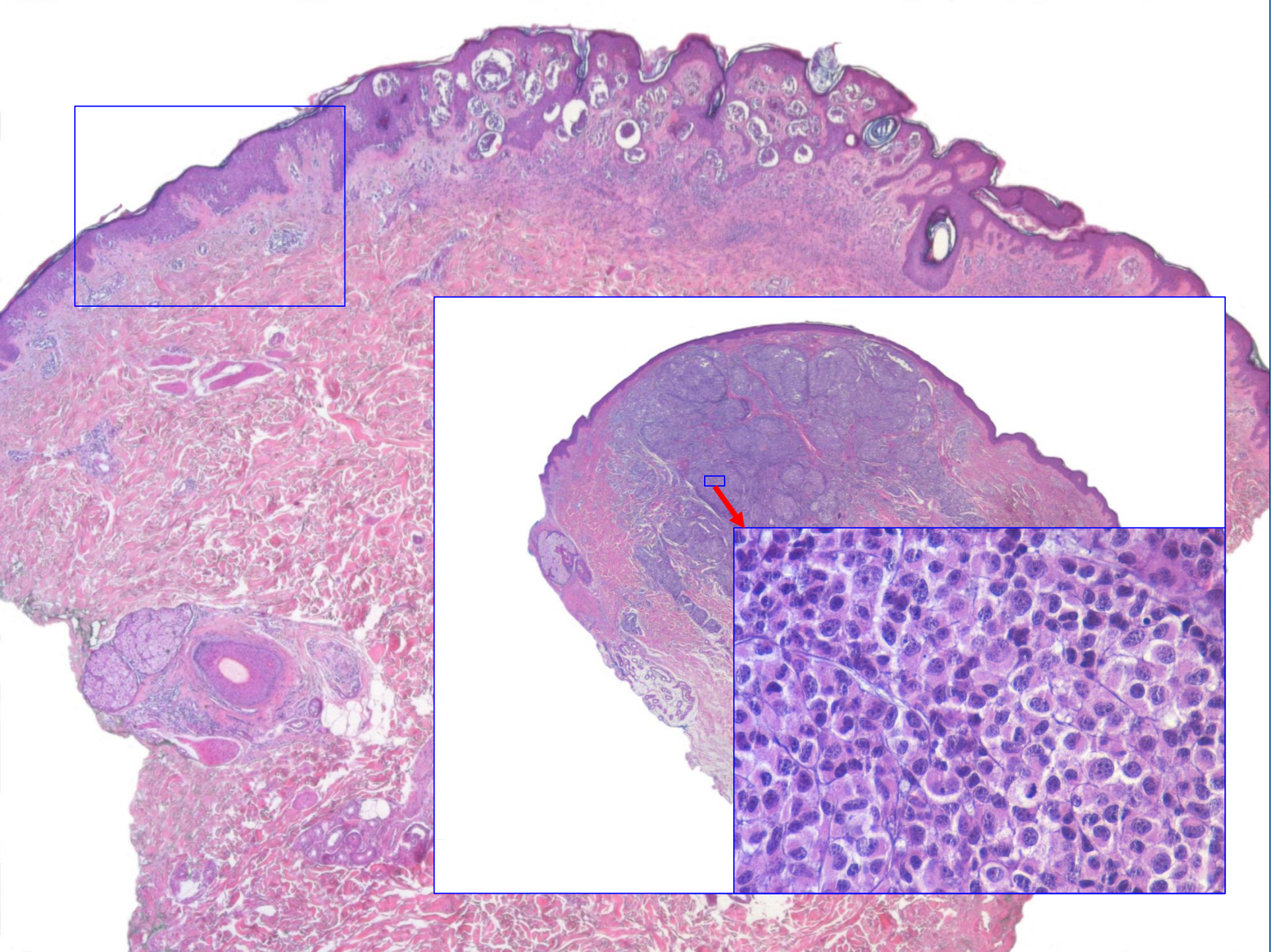
We used multiple linear regression to explore the relation between biopsy rate (independent variable) and melanoma rate (dependent variable). The unit of analysis was the surveillance programme's area in an individual year (nine areas, 14 years, 126 observations). To control for regional differences that may affect incidence (for example, latitude, racial composition, practice style) we included an indicator variable for area in all analyses. Our baseline analysis predicts the effect of 1000 additional biopsies on the number of melanoma diagnoses. The implicit

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.

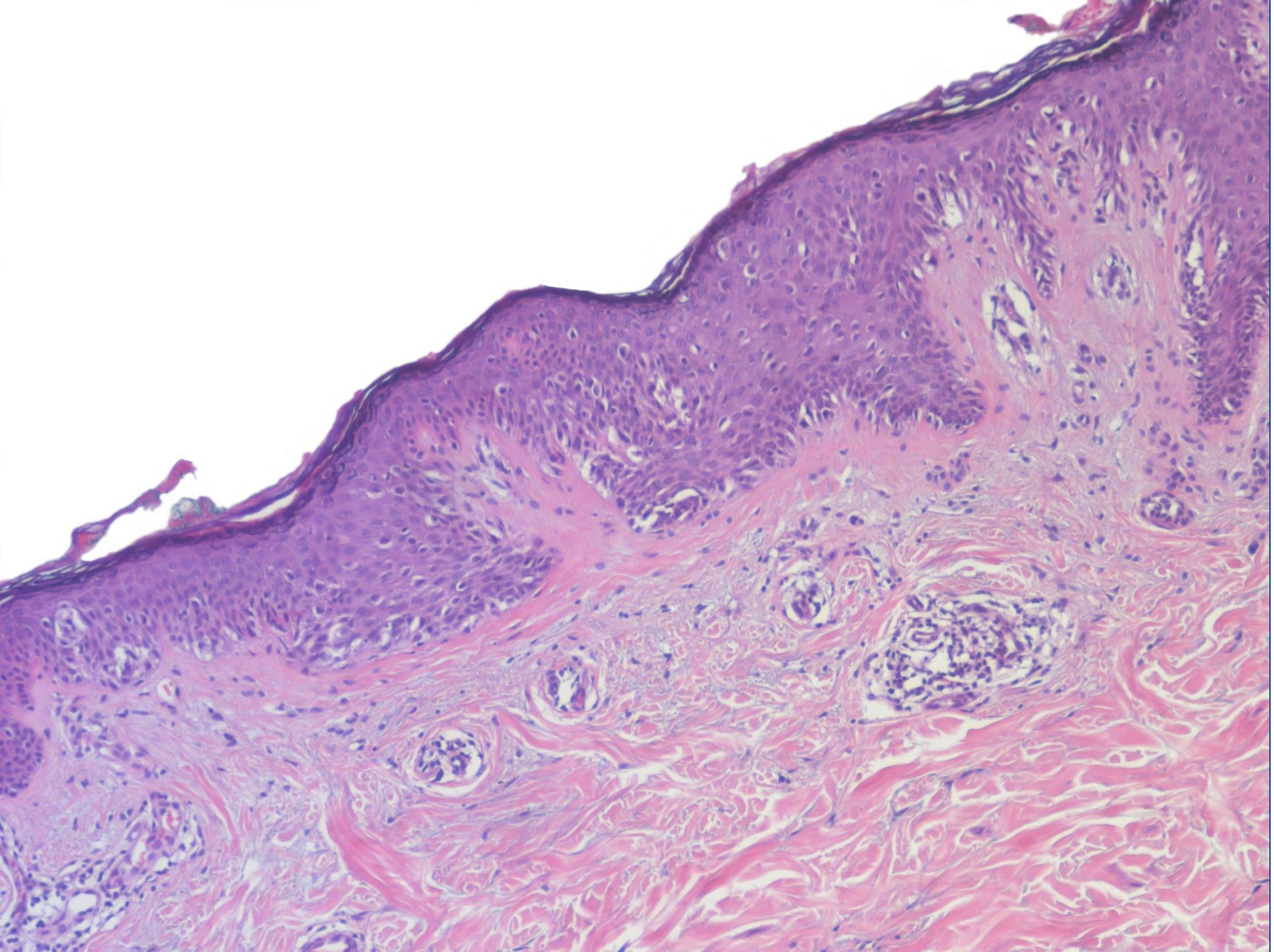
Those conclusions were based on statistics.



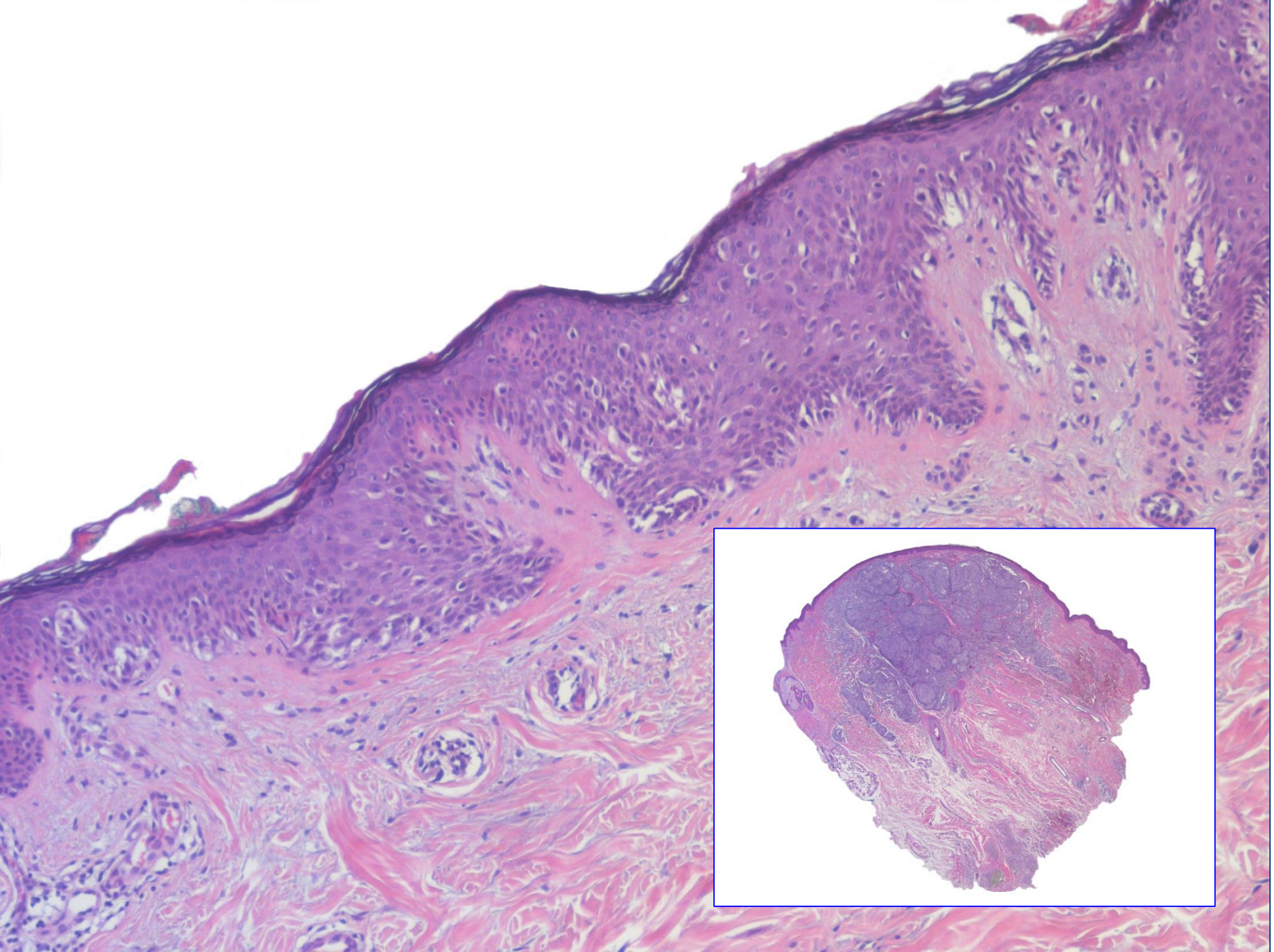
Here we have a practical example: a melanoma in situ at the edge of a congenital melanocytic nevus – in the terminology of epidemiologists *“inconsequential cancer”* for which the diagnosis of melanoma is an “overdiagnosis.” This, however, is only the case if the lesion is excised completely. Unfortunately, the melanoma in situ was present in only one of several sections, and the relevant section was overlooked.



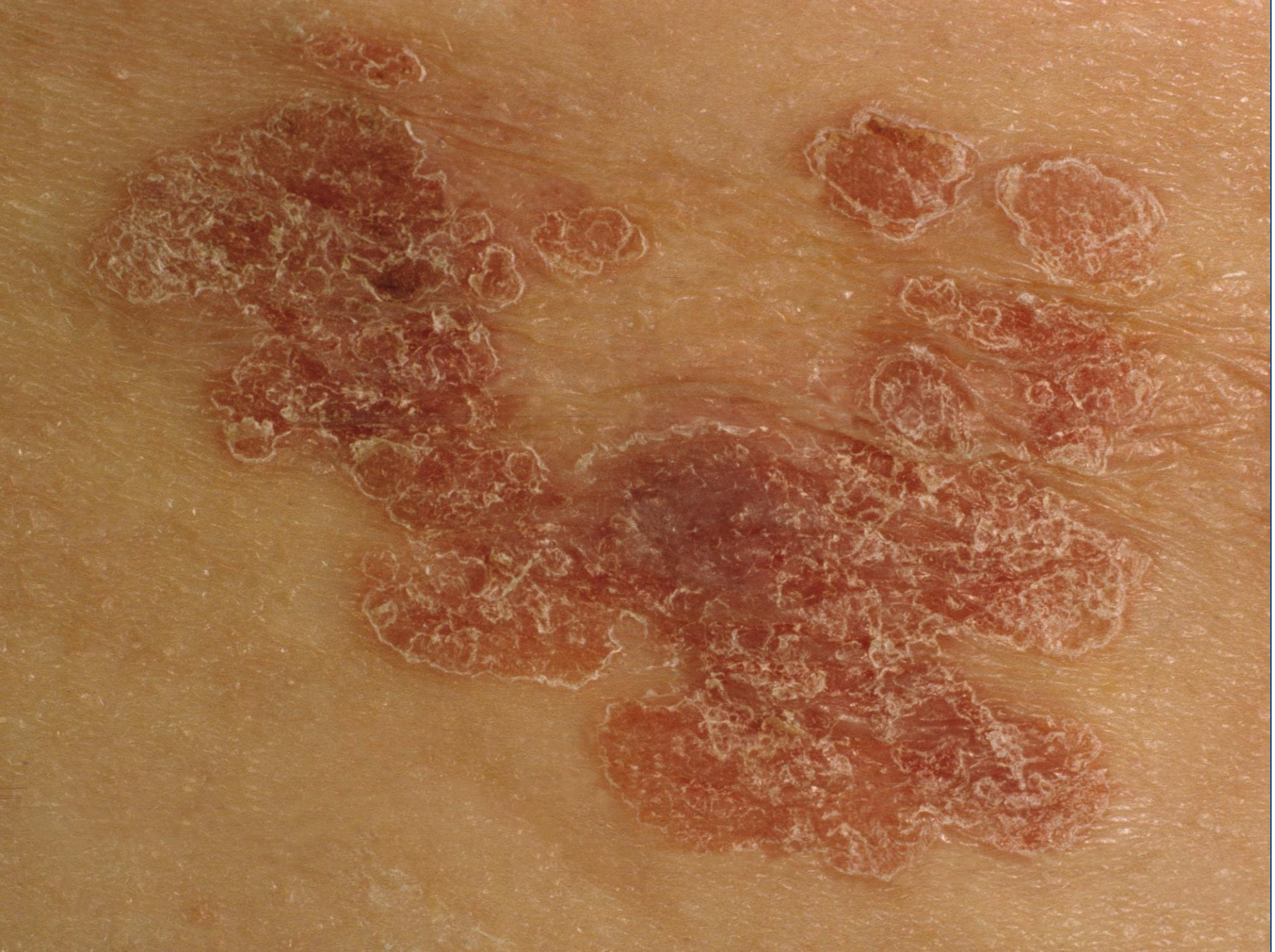
Two years later, the diagnosis of melanoma was no “overdiagnosis” any more because the lesion was no longer “inconsequential.” This example illustrates the purpose of cancer screening, namely, to prevent “inconsequential” cancer from becoming consequential. The diagnosis of melanoma should have been made at the in-situ stage,



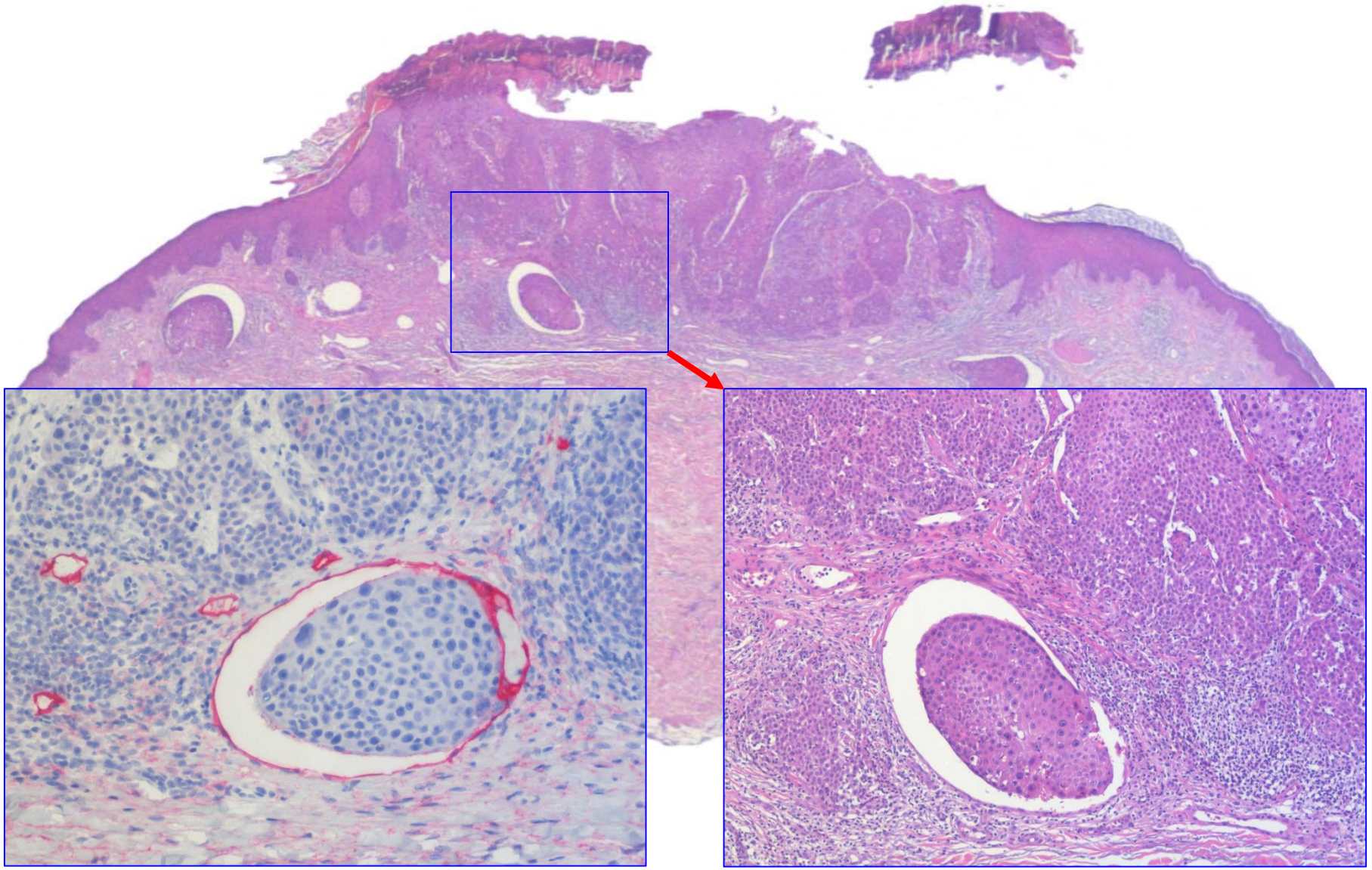
and it could have been made at that stage because criteria for melanoma were fulfilled: predominance of single melanocytes over nests, poorly confined nests, melanocytes in all reaches of the epidermis.



It is rare for a melanoma in situ to recur as a thick nodule within two years. But it may happen, and it demonstrates the importance of a correct diagnosis and of avoiding evasive terms that conceal it.



The same is true for other neoplasms such as Bowen’s disease that grows extremely slowly and practically never kills.



However, there are exceptions in which lymphogenic spread occurs already in tiny lesions.

Of course, statements concerning prognosis are justified and desirable, but they are not reliable, one reason being that the neoplasm is not the only player on stage.

Aggressive Behavior of N
Solid Organ Tra

Impact of concomitant immunosuppression on the presentation and prognosis of patients with melanoma

Amy Frankenthaler, Ryan J. Sullivan, Wei Wang, Sharon Renzi, Virginia Seery, Mee-Young Lee and Michael B. Atkins

American Journal of Transplantation 2011; 11: 1488–1497
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03598.x

but more likely to have died of melanoma than controls (42 vs. 23%) ($P=0.01$, log-rank test). These findings suggest that immunosuppressive therapy is associated with a more aggressive disease course in patients with melanoma. The additional observation that the stage-specific recurrence rates were similar, however, suggests that routine dermatologic screening of

Increased Incidence and Mortality Associated With Skin Cancers After Cardiac Transplant

M. Alam[a,*], R. N. Brown[b], D. H. Silber[c], G. M. Mullen[d], D. S. Feldman[e], R. M. Oren[f], C. W. Yancy[g] and the Cardiac Transplant Research Database Group

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[b] Department of Surgery, Division of Cardiothoracic

cell carcinor
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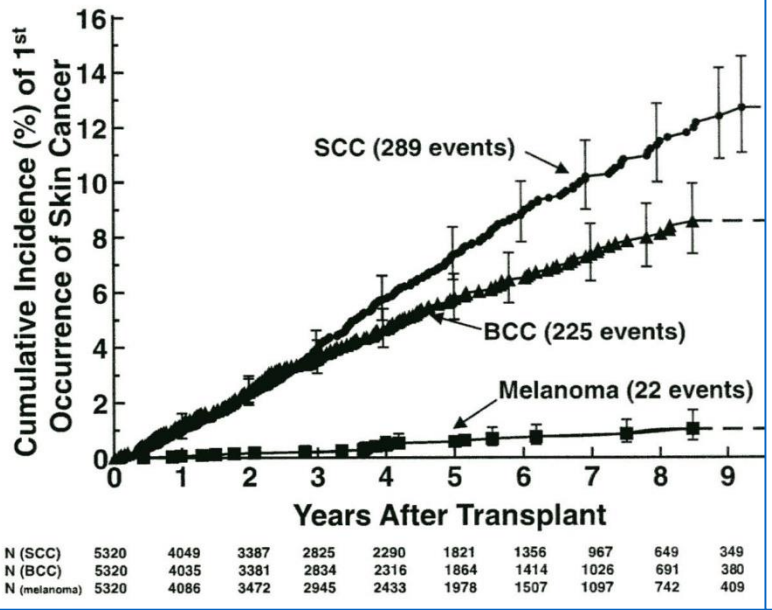
Introducti

Skin Cancers After Cardiac Trans



Aggressive Cutaneous Malignancies following Cardiothoracic Transplantation

The Australian Experience

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Colin S. Ong, M.B., B.S.[3]
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BACKGROUND. The development of malignancies in recipients of a cardiothoracic transplant (CTT)—that is, heart, lung, or heart and lung recipients—is of concern. Cutaneous and lymphoproliferative malignancies comprise the two major groups of malignancies encountered. A small subgroup of patients will develop potentially life-threatening aggressive cutaneous malignancies (ACM); these are poorly defined and documented in the literature. The authors report the results for 619 CTT recipients from a single institution.

METHODS. Between 1984 and 1995, 619 recipients received a CTT. With a minimum follow-up of 2 years, 66 patients (10.7%) were diagnosed with a major malignancy, and 27 of these 66 patients developed ACM. ACM were defined as having one or more of the following characteristics: local invasion and/or regional metastases at diagnosis, poor differentiation, and locoregional and/or systemic relapse following therapy. All malignant melanomas were considered ACM. Data on malignancy occurrence were documented in the clinical notes of the heart and lung transplant unit. A retrospective analysis was undertaken from these notes.

RESULTS. Tumor histology was predominantly poorly differentiated squamous cell carcinoma (55%) (SCC) and malignant melanoma (30%) (MM). No patient developed Kaposi sarcoma (KS). The median time from transplant to diagnosis of ACM was 52 months (range, 8–127 months). Thirteen of 27 patients have died; 10 of them died of metastatic disease. The mean time to death was 20 months (range, 8–54 months). Of 14 patients alive, 5 have disease. All but one of the 19 patients diagnosed with nonmelanoma ACM received radiotherapy, either as part of initial treatment or on relapse. Eight patients have subsequently suffered an infield relapse.

CONCLUSIONS. The development of ACM in CTT recipients resulted in substantial morbidity and mortality. Poor results were obtained with standard surgery and radiotherapy. Treatment modalities for and the underlying pathobiology of ACM in organ transplant recipients require detailed research if improved outcomes are to be achieved. ***Cancer*** **1999;85:1758–64.** © *1999 American Cancer Society.*

It is situated in an organism that may modify its evolution. In immunosuppressed patients, malignant neoplasms behave far more aggressively than in immunocompetent ones,

Hautarzt (1989) 40:23–27

Regression von über 150 Hautmetastasen eines malignen Melanoms bei homöopathi

Franz Ehring
Dermatologische Abteilung der Fachklinik Hornheide an der Westfälischen Wilh
(Leitender Arzt: Prof. Dr. M. Hundeiker)

Zusammenfassung. Bei einer Patient
gnem Melanom an der Wade traten i
bung innerhalb von 7 Jahren über 15
stasen auf. Innerhalb der folgenden 8
ten sie sich mit einer Ausnahme wi
Ein Jahr später starb die Patientin an
Hirnmetastasen. Diskutiert wird de
liche Verlauf und welche Bedeutung
der entscheidenden Zeit allein durch

Acta Oncologica, 2006; 45: 226–228

LETTER TO THE EDITOR

Unexpected 10 years complete remission after cortisone mono-therapy in metastatic renal cell carcinoma

ASBJØRN O. CHRISTOPHERSEN[1], A. KATHRINE LIE[2] & SOPHIE D. FOSSÅ[1,3]

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Int J Clin Oncol (2007) 12:448–454
DOI 10.1007/s10147-007-0711-9

ORIGINAL ARTICLE

Masakazu Kurita · Koichi Hirano · Satoshi Ebihara
Akihiko Takushima · Kiyonori Harii · Takashi Fujino
Yasunori Fujioka

Spontaneous regression of cervical lymph node metastasis in a patient with mesopharyngeal squamous cell carcinoma of the tongue: possible association between apoptosis and tumor regression

Received: June 7, 2007 / Accepted: July 24, 2007

Abstract
Background. We report a case of mesopharyngeal squamous cell carcinoma with spontaneous regression of lymph node metastasis. Spontaneous regression of lymph node

findings were considered to contribute to evidence of spontaneous regression in squamous cell carcinoma of the head and neck resulting from enhanced apoptosis.

Key words Squamous cell carcinoma · Metastasis · Lymph

Int J Clin Oncol (2007) 12:448–454
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Spontaneous regression of cervical lymph node metastasis in a patient with mesopharyngeal squamous cell carcinom
association between apoptosis and tumo

Complete Spontaneous Regression of Metastatic Merkel Cell Carcinoma: A Case Report and Review of the Literature

J. C. Wooff, MD, J. R. Trites, MD, FRCSC,† N. M. G. Walsh, MD, MRCPI, FRCP (C), FRCPath (UK),* and M. J. Bullock, MD, FRCP (C)**

Abstract: Merkel cell carcinoma (MCC) is a rare aggressive primary cutaneous neuroendocrine neoplasm with a high rate of recurrence and metastasis. We report a case of a 94-year-old woman who experienced complete spontaneous regression of metastatic MCC. Nine months after complete excision of the primary MCC on her left eyebrow, metastatic MCC was confirmed with a fine-needle aspiration of a 4-cm mass on the left side of her neck. Three months later the mass had reduced in size to 2 cm and a neck dissection was performed. Her submandibular gland, thoracic duct and 25 lymph nodes were negative for MCC. Two of the lymph nodes, the larger measuring 1.3 cm, contained extensive amounts of fibrosis, with accumulation of macrophages and other chronic inflammatory cells. The literature documents 6 similar cases of complete spontaneous regression of metastatic MCC. The mechanism for regression is not well understood and is thought to involve T-cell–mediated immune response and apoptosis.

Key Words: merkel cell carcinoma, regression, metastatic, spontaneous, complete

(*Am J Dermatopathol* 2010;32:614–617)

mucosal tissues, but they lack innervation and may be functionally different from innervated Merkel cells. Their precise role is currently unknown.[1]

Merkel cell carcinoma (MCC) is a rare aggressive primary cutaneous neuroendocrine neoplasm. It was first described by Toker[2] in 1972 as trabecular carcinoma. It was initially thought to be of eccrine origin but the finding, later, of neurosecretory granules linked it to Merkel cells. It typically presents as a rapidly growing, asymptomatic nodule with overlying skin discoloration ranging from violet to pink. The vast majority of MCCs occur on sun-exposed areas, with the head and neck being most commonly affected, followed by the extremities. Older whites and immunosuppressed individuals seem to be at the highest risk for developing MCC.

Complete spontaneous regression (CSR) of MCC was first described in 1986 by O'Rouke and Bell.[3] Since then, additional cases have been reported, bringing the total to 14. Of these cases, 6 demonstrated CSR of metastatic MCC. This study presents a seventh case of CSR of metastatic MCC. In only 1 prior case of CSR of metastatic MCC was pathologic documentation of regression available. We present the second case with histopathologic study of the site of regression of metastatic MCC.

and in the latter, complete regression may occur even in the presence of widespread metastases. Such events are rare but they demonstrate that behavior is unpredictable.

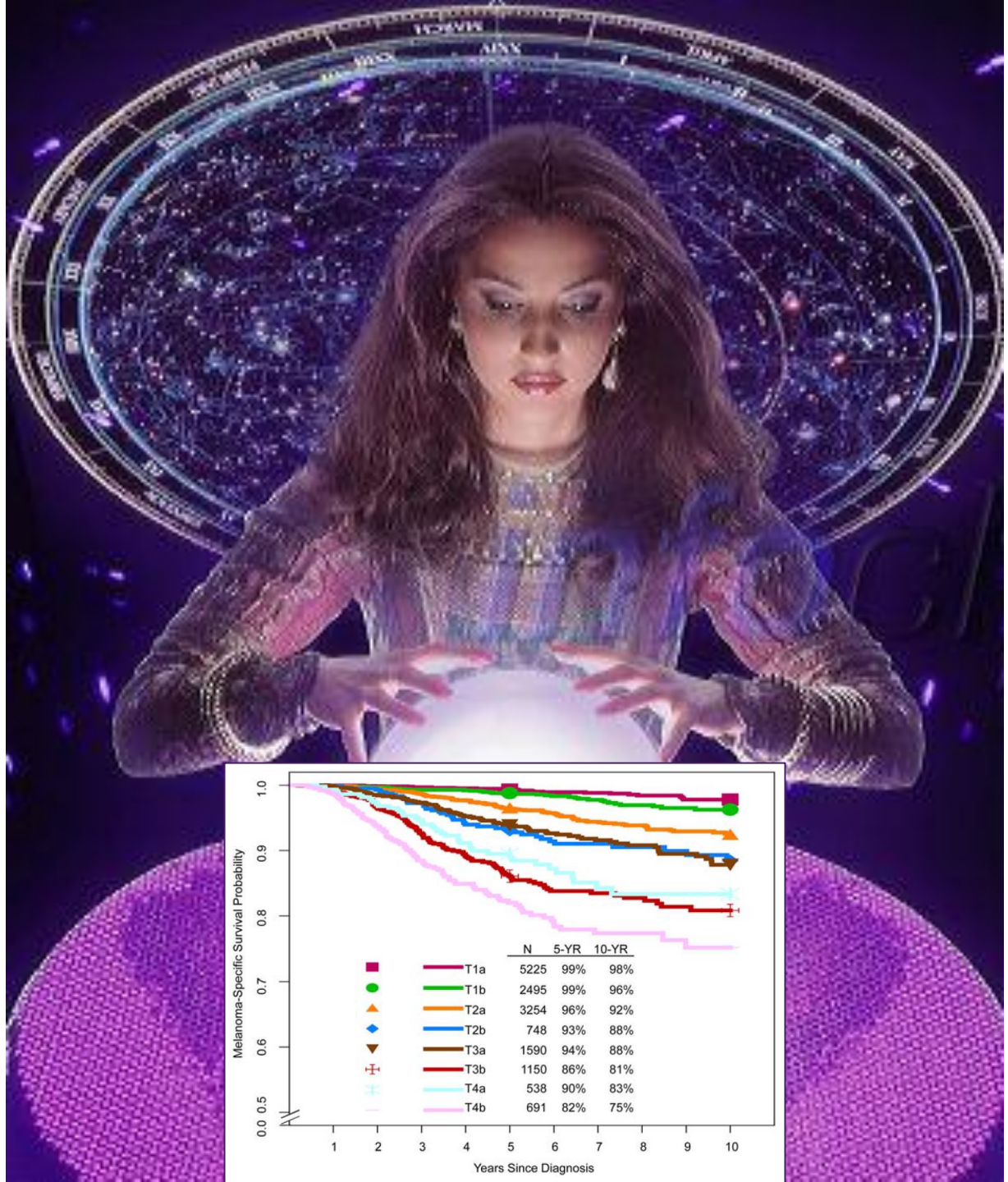
This is exactly what makes prognosis so attractive for pathologists. Diagnoses are expected to be accurate,

and any error may be extremely costly, especially in the United States. By contrast, prognosis is known to be unpredictable and, therefore, anything goes.

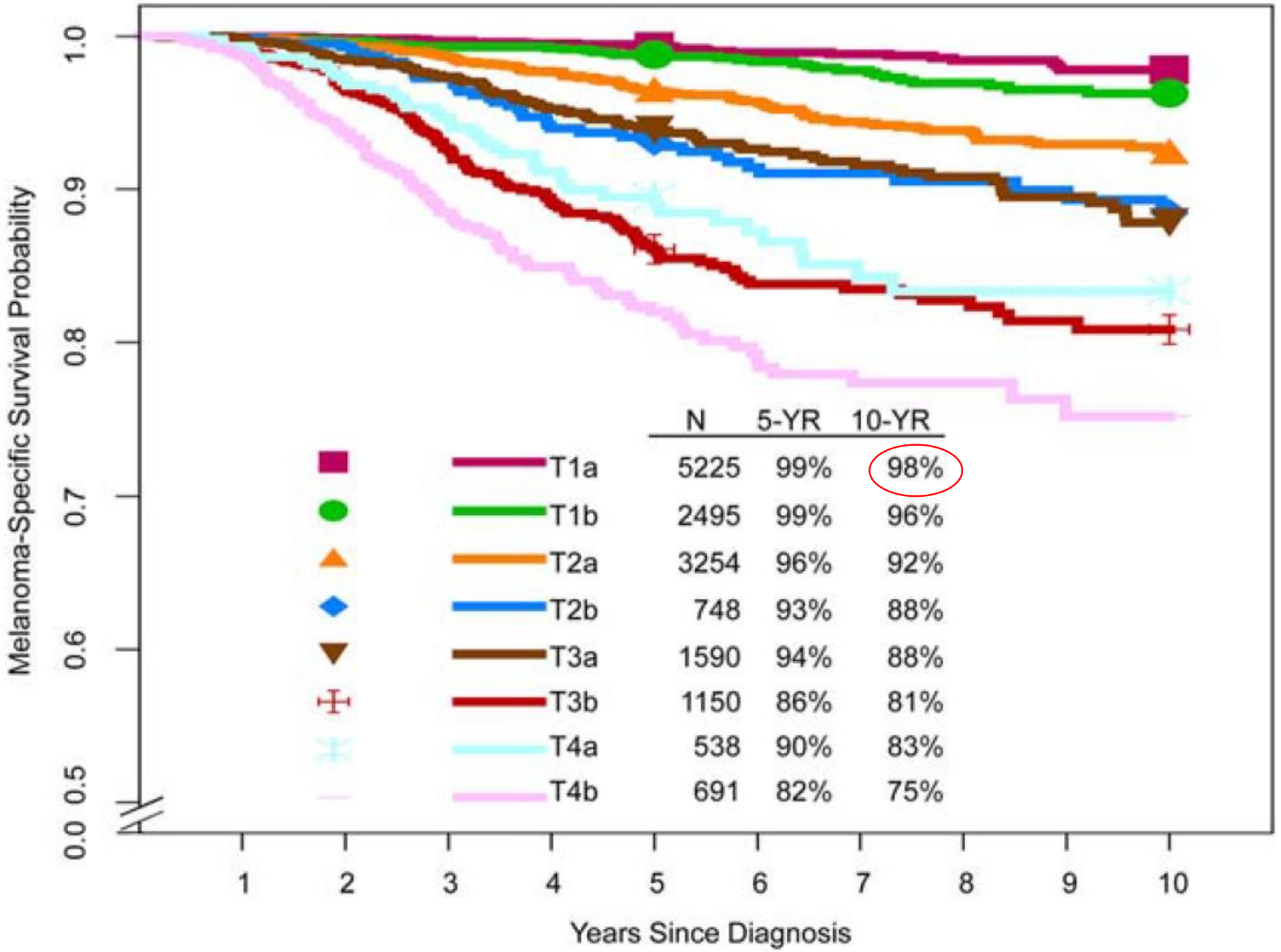
TUMOR THICKNESS SUBGROUP	PROGNOSTIC MODEL	DEFINITION AND CODING OF THE COVARIATE (X_i) WITHIN THE TUMOR THICKNESS SUBGROUP
<0.76 mm	$\hat{S}_1(t) = [\hat{S}_{10}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -1.11316(X_1 - 0.55769) + 0.73644(X_2 - 0.40247)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (level of invasion) = 0, if level II; = 1, if other levels.
0.76–1.49 mm	$\hat{S}_2(t) = [\hat{S}_{20}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -1.02481(X_1 - 0.90731) - 0.78450(X_2 - 0.55459) + 1.21636(X_3 - 0.89395)$	X_1 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_2 (lesion location) = 0, if axial; = 1, if extremity. X_3 (level of invasion) = 0, if level II; = 1, if other levels.
1.50–2.49 mm	$\hat{S}_3(t) = [\hat{S}_{30}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.61149(X_1 - 0.52813) - 0.58611(X_2 - 0.66705) - 0.79938(X_3 - 0.49024)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_3 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.
2.50–3.99 mm	$\hat{S}_4(t) = [\hat{S}_{40}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.35556(X_1 - 0.50000) - 0.33959(X_2 - 0.56157) - 0.38754(X_3 - 0.41791) - 0.46234(X_4 - 0.54851)$	X_1 (lesion location) = 0, if axial; = 1, if extremity. X_2 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_3 (sex) = 0, if male; = 1, if female. X_4 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.
4.00–7.99 mm	$\hat{S}_5(t) = [\hat{S}_{50}(t)]^{\exp(x\hat{\beta})}$ where $x\hat{\beta} = -0.56653(X_1 - 0.41690) + 0.54407(X_2 - 0.81690) - 0.76193(X_3 - 0.45352)$	X_1 (ulceration) = 0, if ulcerated; = 1, if not ulcerated. X_2 (level of invasion) = 0, if levels II, III; = 1, if levels IV, V. X_3 (surgical treatment) = 0, if WLE only; = 1, if WLE + RND.

Of course, there are many prognostic parameters that have even been integrated into sophisticated formulas in order to calculate prognosis, but that approach

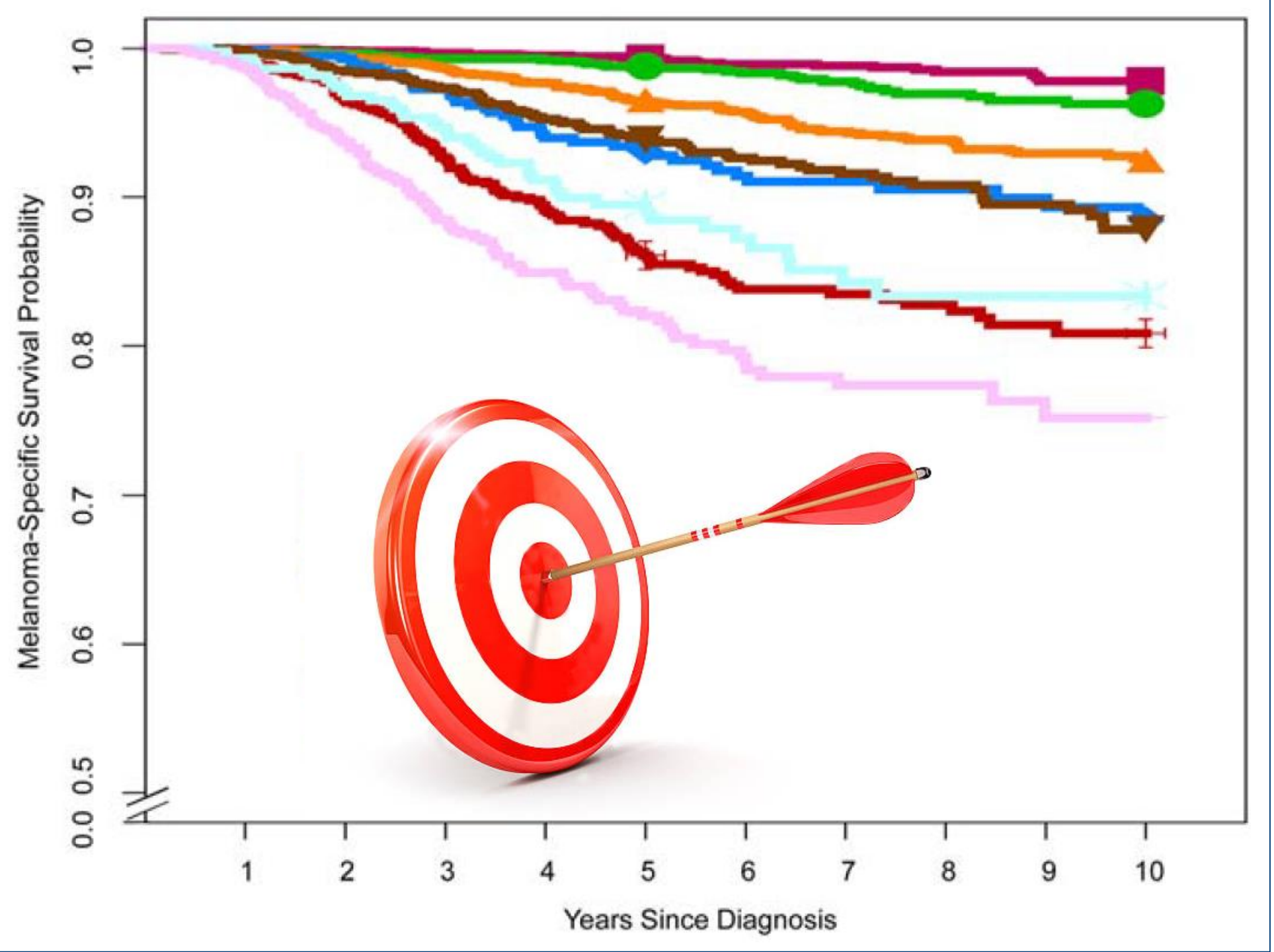
reminds of one of astrologists who also resort calculations in order to attach some scientific apparel to their predictions.



Like the prophecies of astrologists, prognostic statements of oncologists always remain vague, and they are always right.

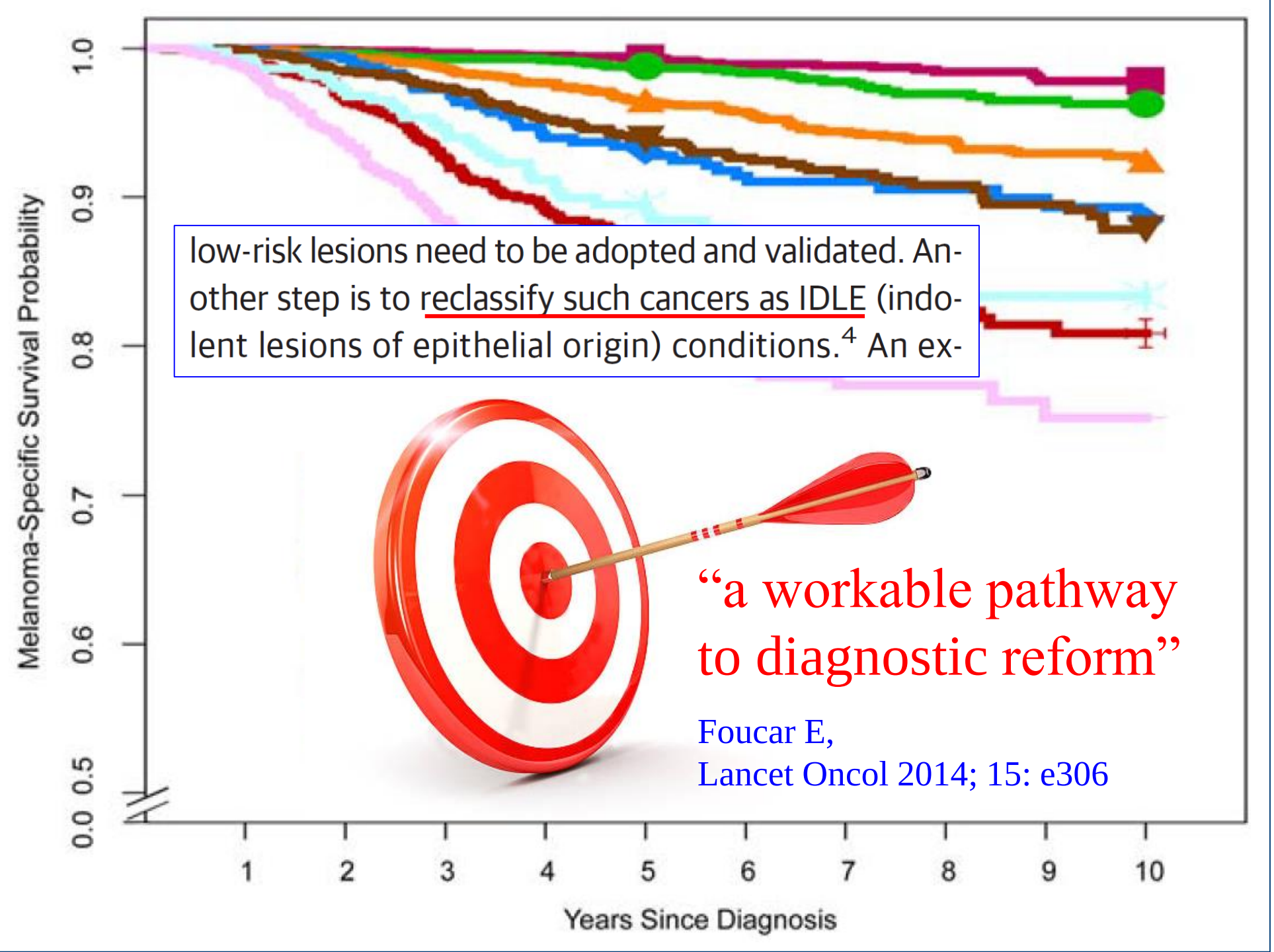


For example, according to the new AJCC melanoma classification, melanomas in stage T1a have a 10-year survival rate of 98%. If the patient survives, this is the expected outcome; if he dies, he belongs to the unhappy 2%,



but the prediction was on target. One cannot err with prognosis.

This is why suggestions to waive diagnosis in favor of prognosis are so welcome.



low-risk lesions need to be adopted and validated. Another step is to reclassify such cancers as IDLE (indolent lesions of epithelial origin) conditions.[4] An ex-

"a workable pathway to diagnostic reform"

Foucar E,
Lancet Oncol 2014; 15: e306

Esserman proposed to reclassify early cancer as "indolent lesion of epithelial origin," that sacrifice of a specific diagnosis was praised by some pathologists as *"a workable pathway to diagnostic reform."*

Schematic Representation of SIL

Normal	Low-grade squamous intraepithelial lesion (LSIL)		High-grade squamous intraepithelial lesion (HSIL)	
	Condyloma	CIN/AIN grade 1	CIN/AIN grade 2	CIN/AIN grade 3
	Very mild to mild dysplasia		Moderate dysplasia	Severe dysplasia / *In Situ* carcinoma

In gynecopathology, the term “squamous intraepithelial lesion” of various grades has replaced specific diagnoses like condyloma and carcinoma and is used for both of them.

Schematic Representation of SIL

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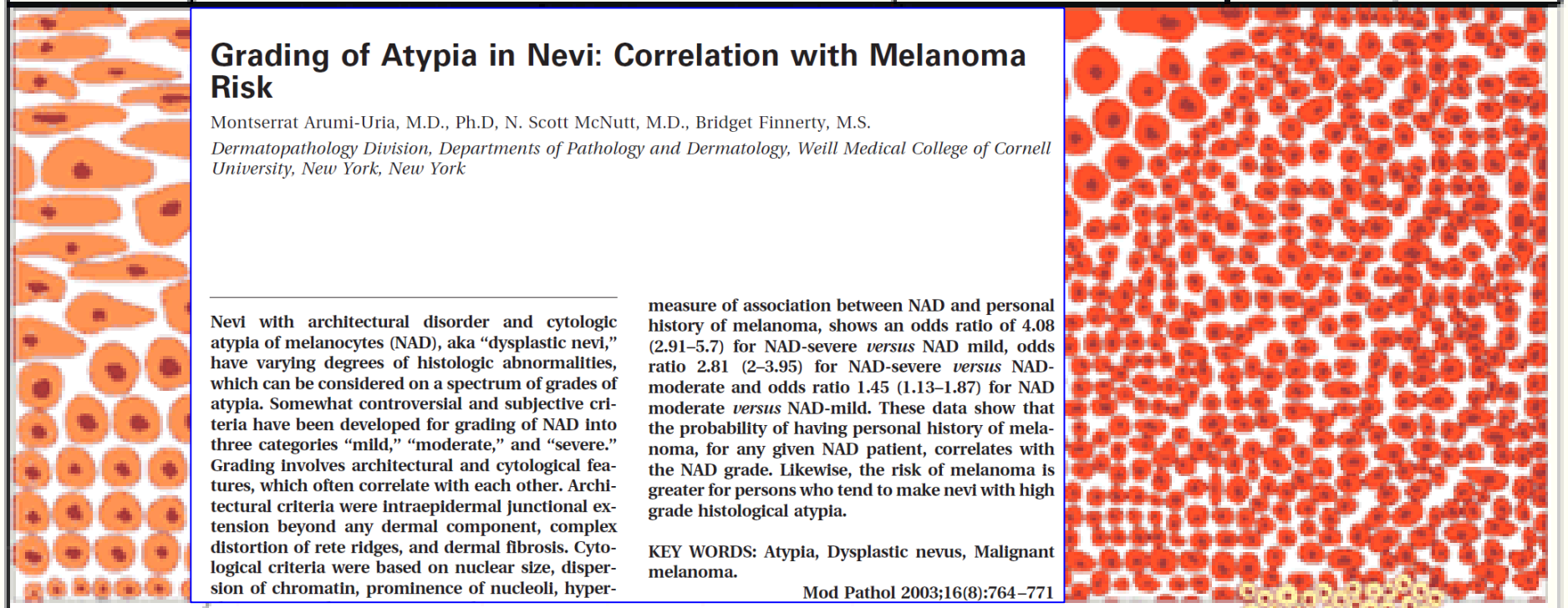


Grading of Atypia in Nevi: Correlation with Melanoma Risk

Montserrat Arumi-Uria, M.D., Ph.D, N. Scott McNutt, M.D., Bridget Finnerty, M.S.

Dermatopathology Division, Departments of Pathology and Dermatology, Weill Medical College of Cornell University, New York, New York

Nevi with architectural disorder and cytologic atypia of melanocytes (NAD), aka "dysplastic nevi," have varying degrees of histologic abnormalities, which can be considered on a spectrum of grades of atypia. Somewhat controversial and subjective criteria have been developed for grading of NAD into three categories "mild," "moderate," and "severe." Grading involves architectural and cytological features, which often correlate with each other. Architectural criteria were intraepidermal junctional extension beyond any dermal component, complex distortion of rete ridges, and dermal fibrosis. Cytological criteria were based on nuclear size, dispersion of chromatin, prominence of nucleoli, hyper-measure of association between NAD and personal history of melanoma, shows an odds ratio of 4.08 (2.91–5.7) for NAD-severe *versus* NAD mild, odds ratio 2.81 (2–3.95) for NAD-severe *versus* NAD-moderate and odds ratio 1.45 (1.13–1.87) for NAD moderate *versus* NAD-mild. These data show that the probability of having personal history of melanoma, for any given NAD patient, correlates with the NAD grade. Likewise, the risk of melanoma is greater for persons who tend to make nevi with high grade histological atypia.

KEY WORDS: Atypia, Dysplastic nevus, Malignant melanoma.

Mod Pathol 2003;16(8):764–771

Koilocytes

Microinvasive carcinoma

Likewise, "grading of atypia" has been proposed for nevi in order to overcome diagnostic difficulties.

Modern Pathology (2006) 19, S21–S33

www.modernpathology.org

The Spitzoid lesion: rethinking Spitz tumors, atypical variants, 'Spitzoid melanoma' and risk assessment

Raymond L Barnhill

Departments of Dermatology and Pathology, University of Miami Miller School of Medicine, Miami, FL, USA

Although much remains to be learned about Spitzoid lesions, there is increasing evidence that these tumors may be a type of melanocytic neoplasm distinct from conventional melanocytic nevi and malignant melanoma. In the current communication, the author has attempted to describe accurately the state-of-the-art surrounding these lesions, their nomenclature, and assessment of risk. Acknowledging the peculiar nature of Spitzoid lesions, the author prefers the term Spitz tumor rather than 'Spitz nevus' (except perhaps for the most typical lesions) and argues against using the term 'Spitzoid melanoma' until more information is available to justify such a term. The author also believes that patients are best served by the comprehensive evaluation of Spitzoid lesions and their classification into three categories: (1) Spitz tumor without significant abnormality, (2) Spitz tumor with one or more atypical features (atypical Spitz tumor), including those judged to have indeterminate biological potential, and (3) malignant melanoma, rather than the two categories of 'Spitz nevus' and melanoma. Only rigorous characterization of sufficient numbers of Spitzoid lesions and long-term follow-up of patients will provide truly objective information for the formulation of optimal guidelines for the management of patients with these lesions.
Modern Pathology (2006) **19**, S21–S33. doi:10.1038/modpathol.3800519

Keywords: Spitz nevus, Spitz tumor, melanoma

One example are "Spitzoid lesions" for which a distinction between nevus and melanoma has been abandoned by some authors who, in the absence of a diagnosis, engage in *"risk assessment"*

Modern Pathology (2006) 19, S21–S33

www.modernpathology.org

The Spitzoid lesion: rethinking Spitz tumors, atypical variants, 'Spitzoid melanoma' and risk assessment

Raymond L Barnhill

Departments of Dermatology and Pathology, Univ ... *USA*

Although much remains to be learned about Spitz ... **rs may be a type of melanocytic neoplasm distinct fro** ... **na. In the current communication, the author has attem** ... **ng these lesions, their nomenclature, and assessme** ... **id lesions, the author prefers the term Spitz tumor ra** ... **al lesions) and argues against using the term 'Spitzo** ... **ify such a term. The author also believes that patients** ... **id lesions and their classification into three categorie** ... **itz tumor with one or more atypical features (atypical** ... **te biological potential, and (3) malignant melanoma, ra** ... **na. Only rigorous characterization of sufficient number** ... **vill provide truly objective information for the formula** ... **nts with these lesions.**
Modern Pathology (2006) **19,** S21–S33. doi:10.1038/n

Keywords: Spitz nevus, Spitz tumor, melanoma

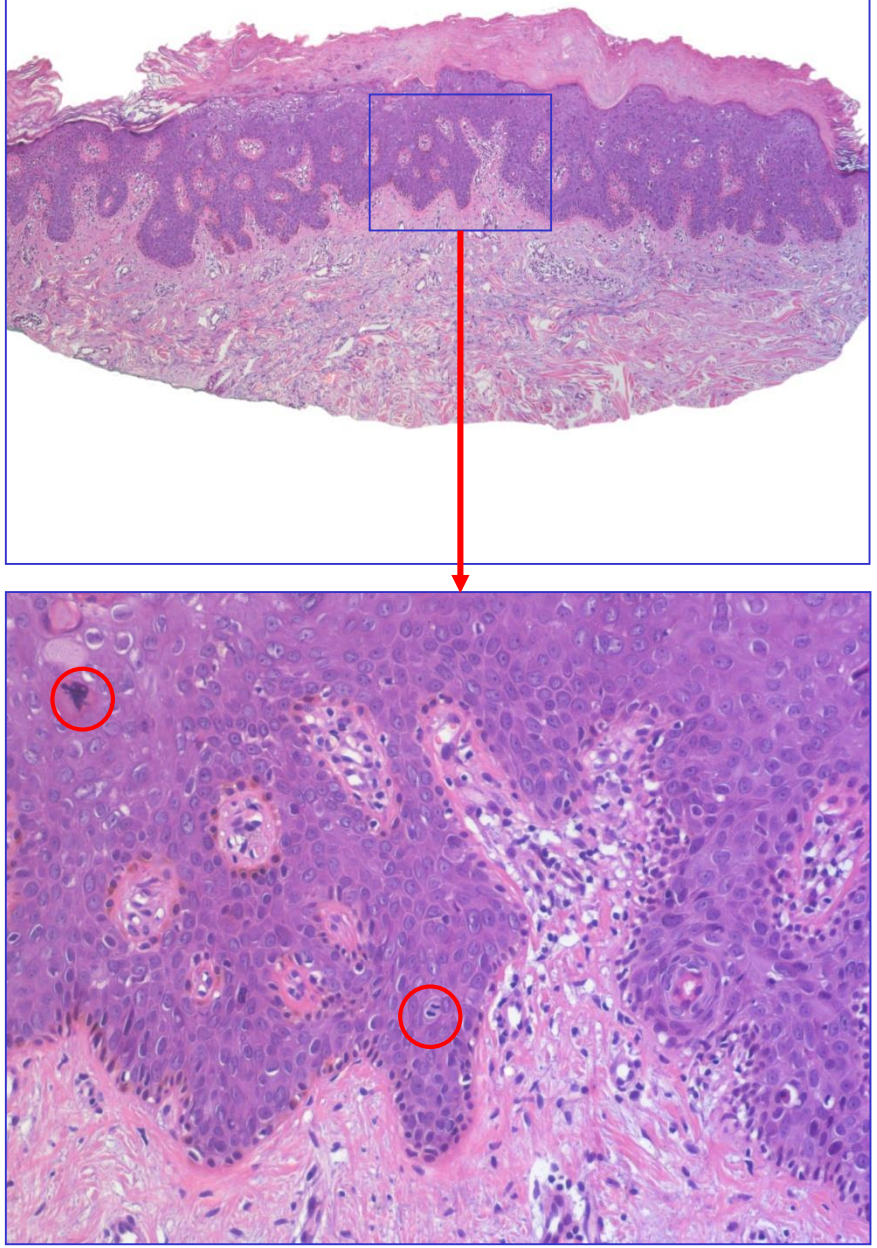
Table 6 Assessment of Spitz tumors in children and adolescents for risk for metastasis[30]

Parameter	*Score*[a]
Age (years)	
0–10	0
11–17	1
Diameter (mm)	
0–10	0
>10	1
Involvement of subcutaneous fat	
Absent	0
Present	2
Ulceration	
Absent	0
Present	2
Mitotic activity (mm²)	
0–5	0
6–8	2
>9	5

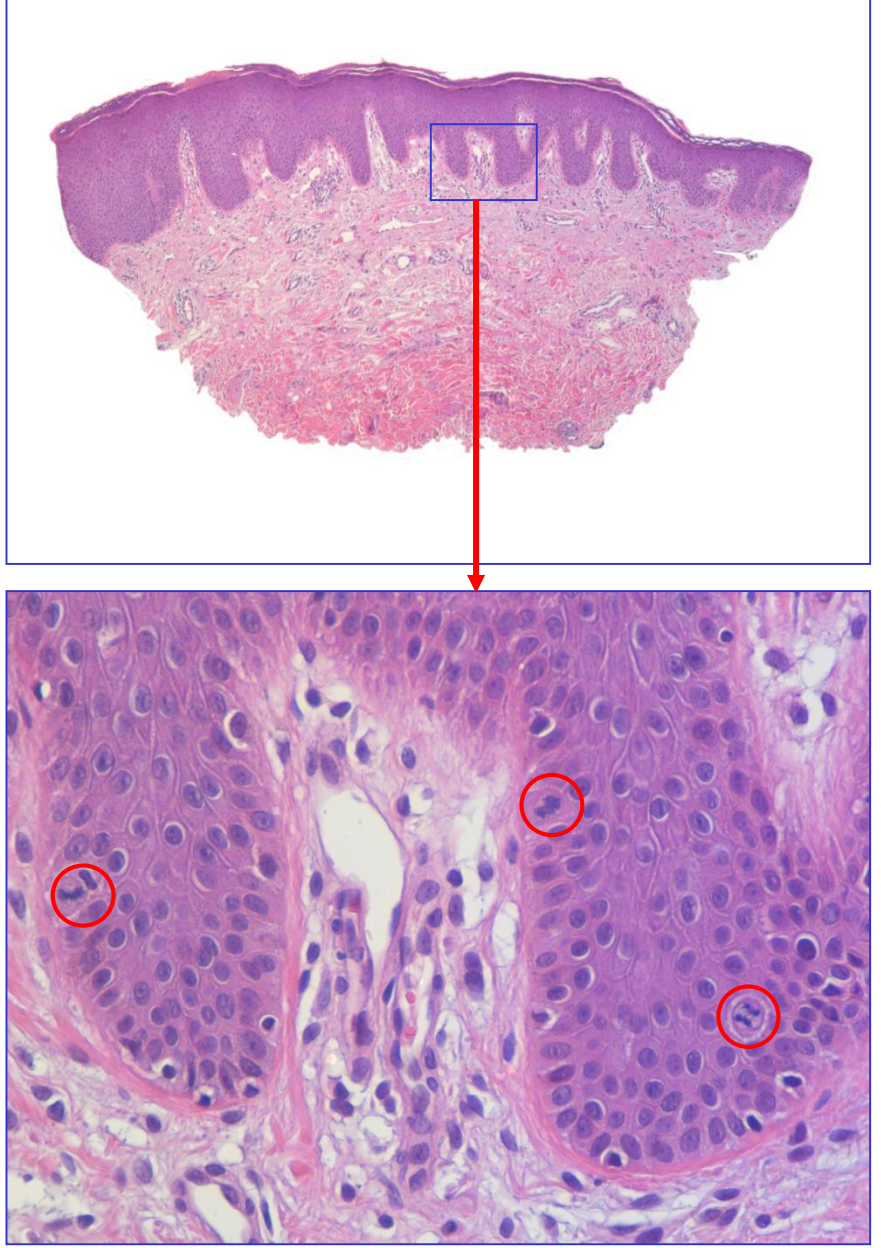
[a]Total score indicates increasing risk for metastasis.

by adding up a variety of prognostic factors, such as age, diameter, and mitotic activity.

Bowen’s disease



Psoriasis



This is the same as if we would not distinguish between Bowen’s disease and psoriasis but try to predict outcome by the degree of epithelial hyperplasia and the number of mitotic figures,

or if one would not distinguish dogs and sheep but try to predict behavior based on the color of their fur

and the size of their teeth.

Obviously, before any statement about potential behavior can be made, a diagnosis is essential. Recognition of biologic entities may not be easy, but, in general, it is possible on the basis of a constellation of criteria, and the more criteria we can assess, not only fur and teeth,

but also nose, eyes, ears,

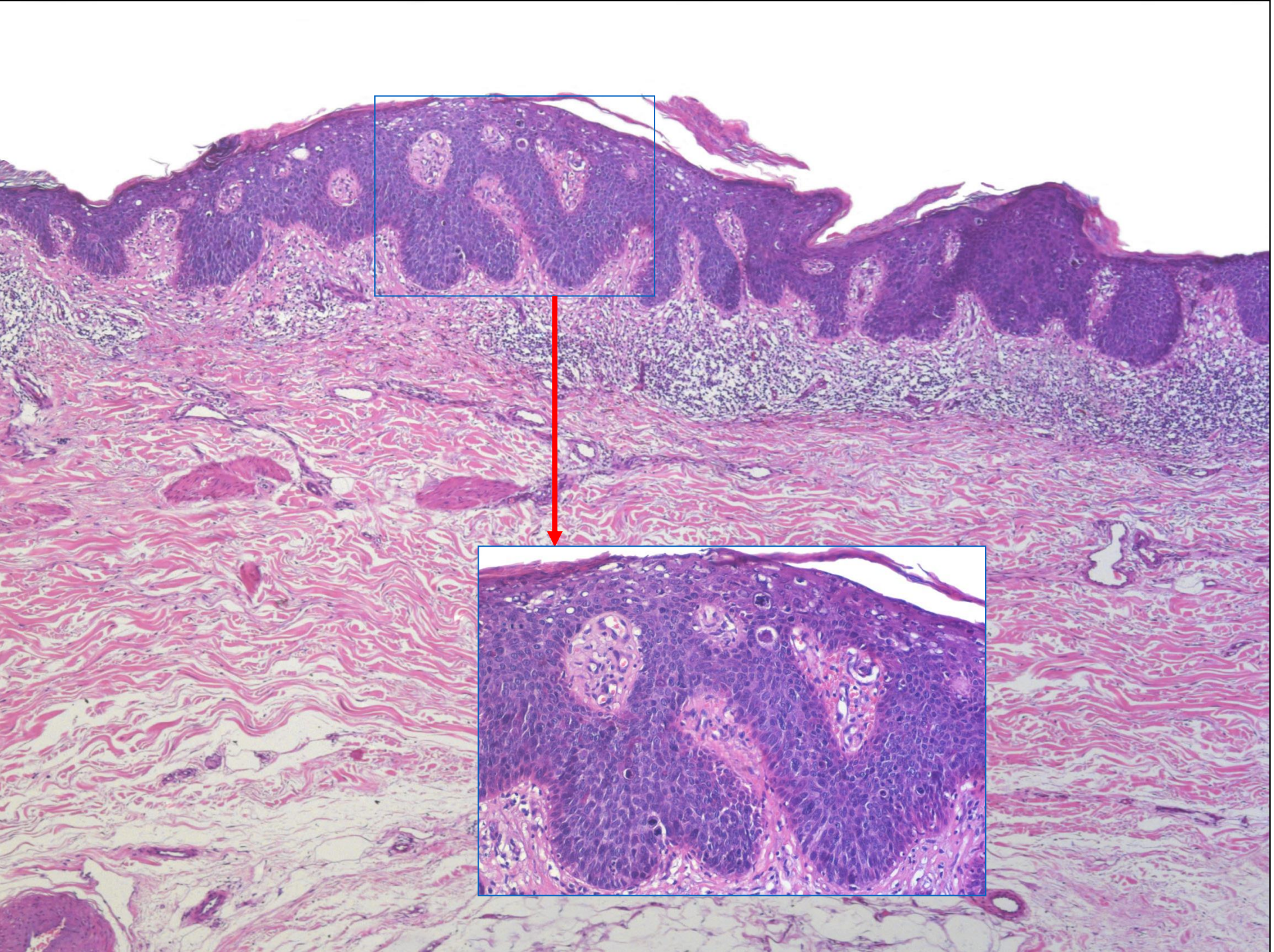
and maybe legs, the easier it gets. Once a diagnosis has been made, certain assumptions concerning behavior are justified. For example, sheep tend to grass. This does not imply that behavior can be calculated;

surprises are always possible. But if we base our acumen on aspects of behavior,

meaningful statements are impossible.

If medicine wants to retain a place among the natural sciences, entities must be acknowledged. The expected behavior of examples of a given entity differs in dependence from myriad factors,

chief among them the stage of development. This tiger puppy will behave different from its adult counterpart. It may be an “indolent example of the family of cats,” but it is also, and more specifically, a tiger.



Likewise, this example of Bowen's disease may be an "indolent lesion of epithelial origin," but it is also, and more specifically, an incipient squamous-cell carcinoma, and it is not an overdiagnosis to refer to it that way.

The New York Times

The Opinion Pages | OP-ED CONTRIBUTOR

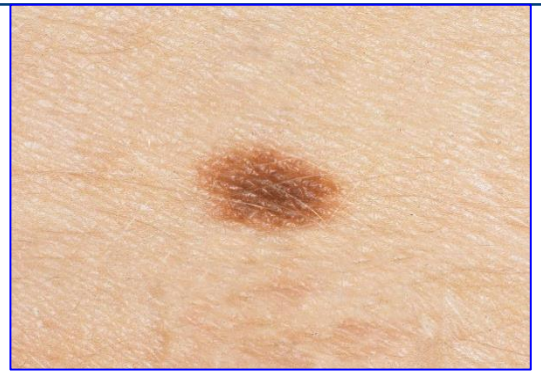
Cancer Survivor or Victim of Overdiagnosis?

By H. GILBERT WELCH NOV. 21, 2012

Nonetheless, the question whether cancer survivors are, in actuality, “victims of overdiagnosis” is justified. Overdiagnoses are a serious problem – not the overdiagnoses of epidemiologists but real overdiagnoses,

i.e., misdiagnoses of benign lesions as malignant. Those misdiagnoses have become more common

The New York Times

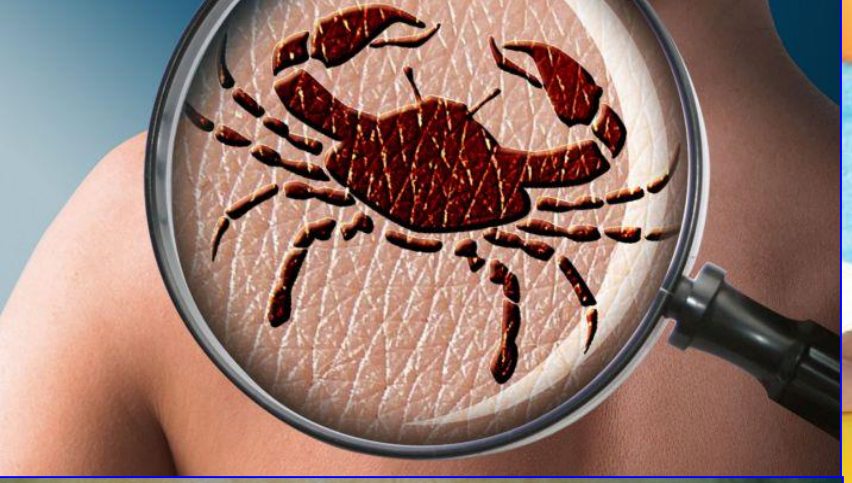


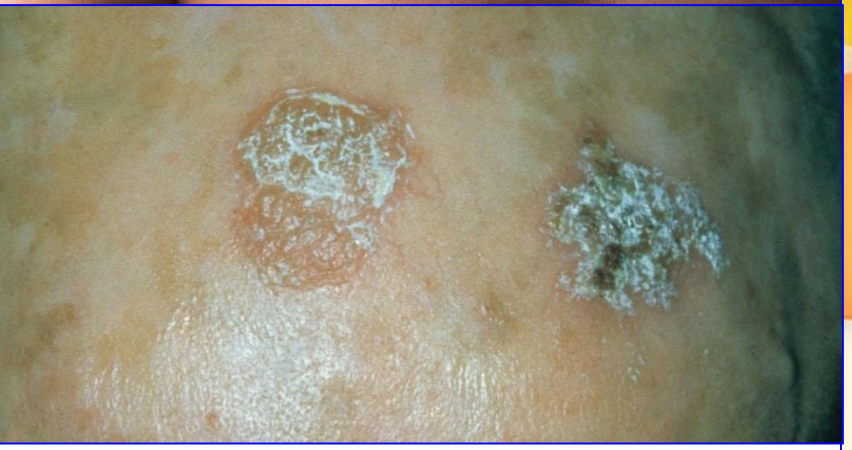
The Opinion Pages | OP-ED CONTRIBUTOR

Cancer Survivor or Victim of Overdiagnosis?

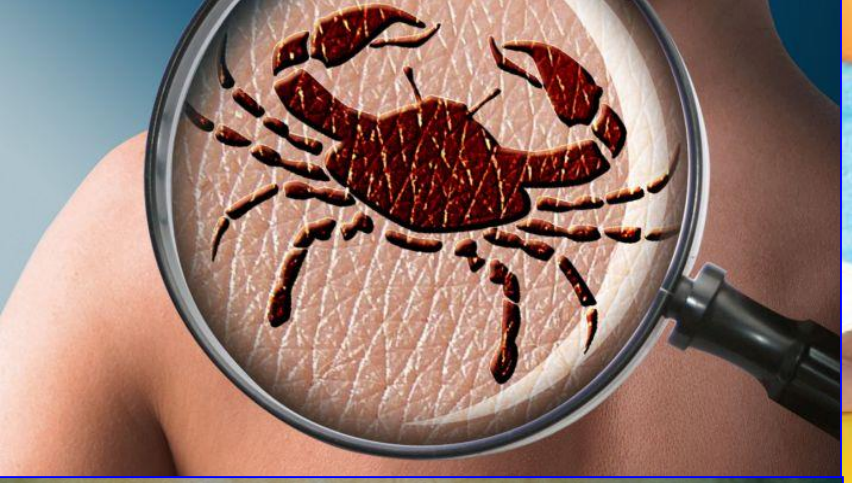
By H. GILBERT WELCH NOV. 21, 2012

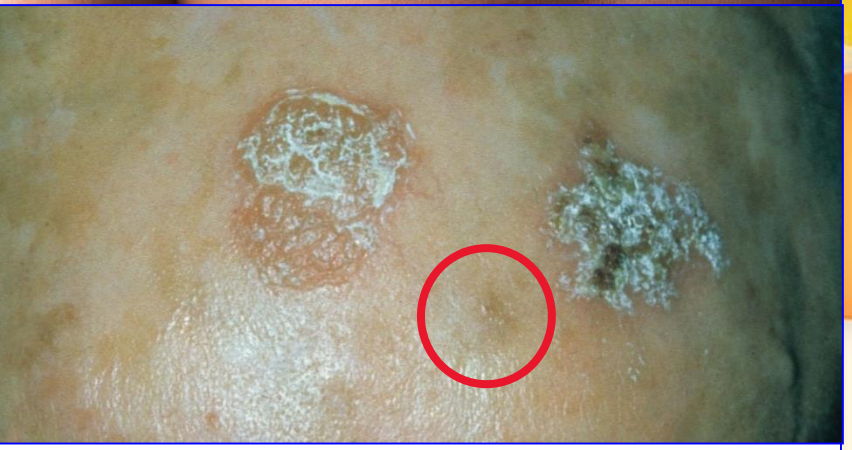
Melanoma



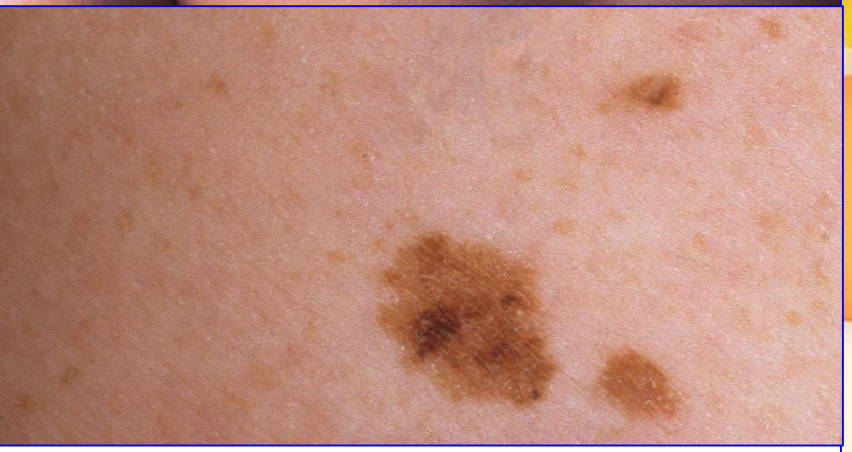


as a result of skin cancer screening. Patients present themselves with lesions at progressively earlier stages, and physicians are under great pressure not to overlook anything. The challenge is no longer diagnosis of squamous-cell carcinoma in situ

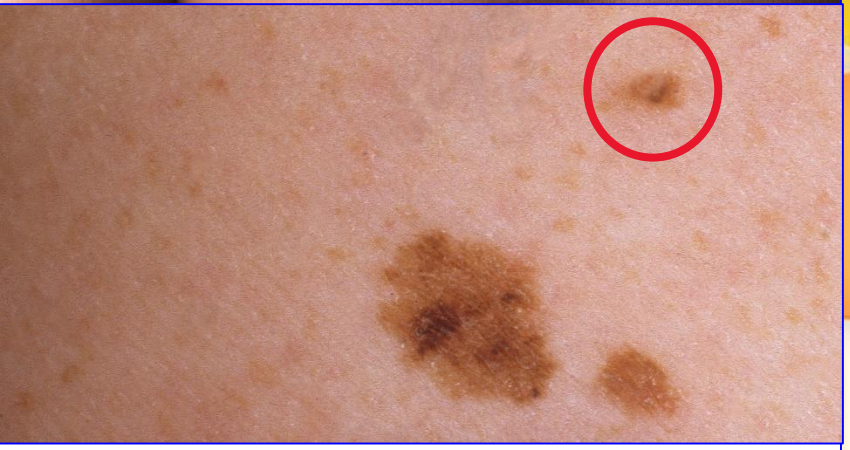




but of lesions that may represent incipient squamous-cell carcinoma in situ,



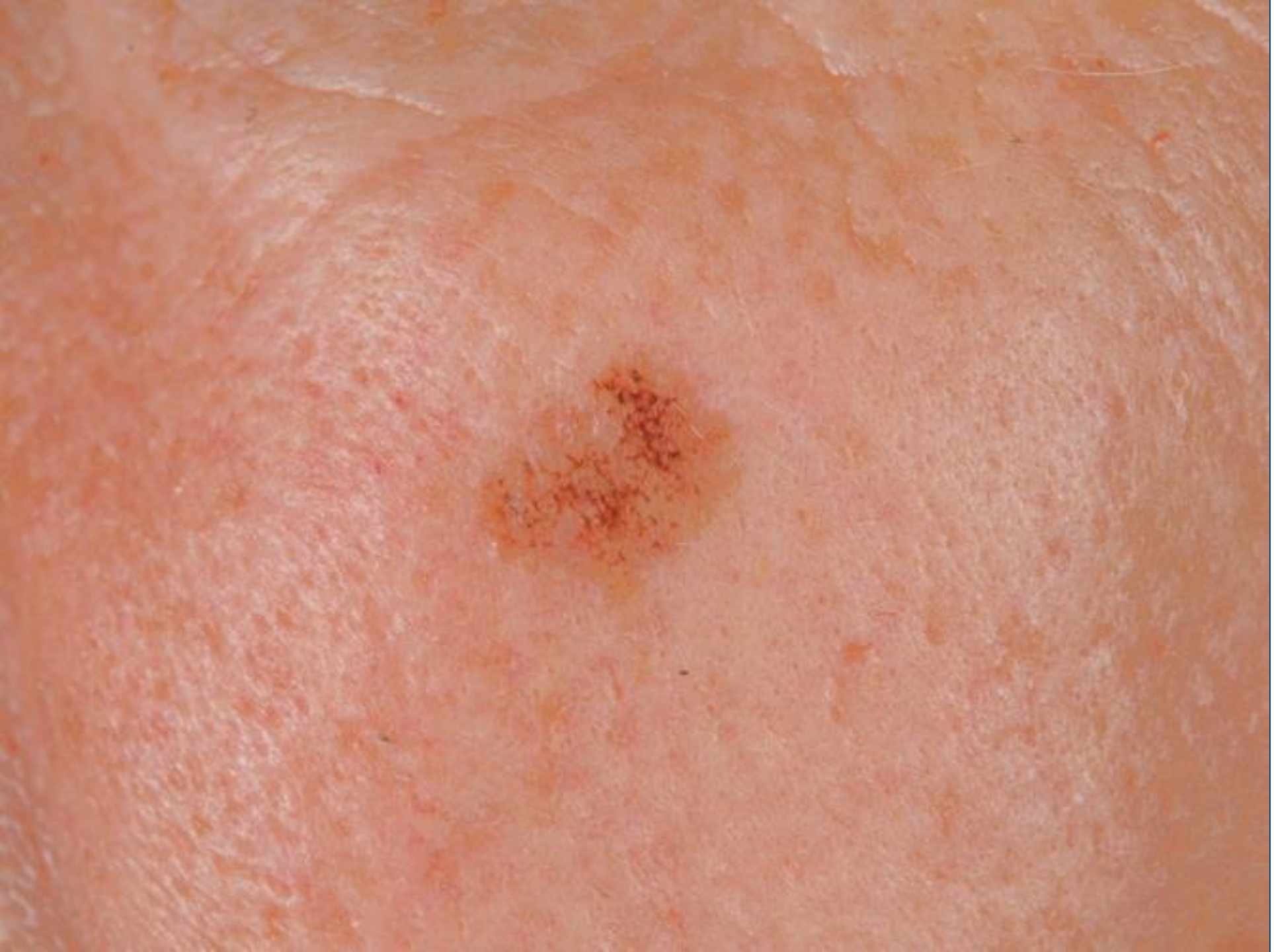
no longer of melanoma in situ



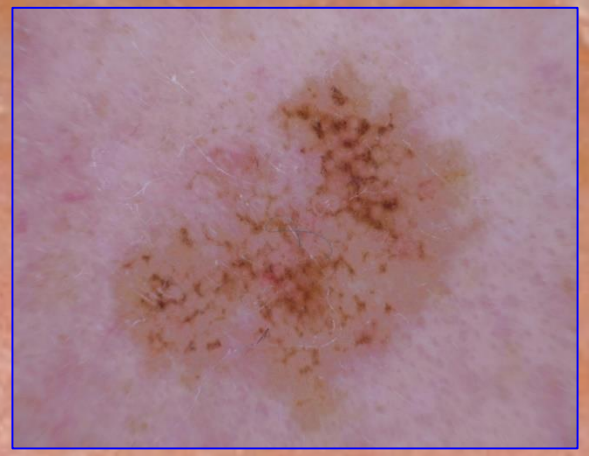
but of lesions that may represent incipient melanoma in situ. In cases of doubt, those lesions are biopsied,

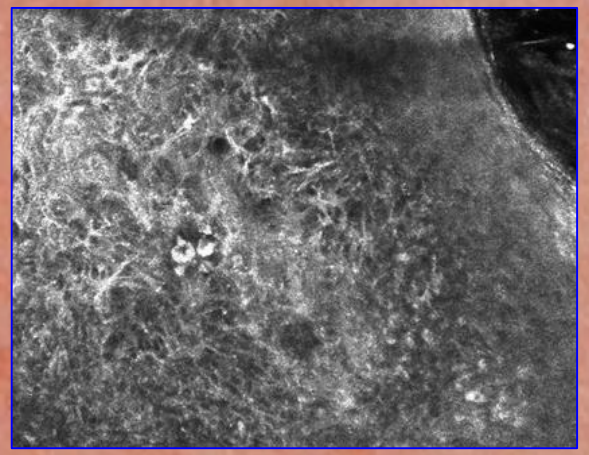
- Unnecessary biopsies of countless benign lesions
- Enhanced risk of histopathologic misdiagnosis
- Reduced quality of biopsies as a result of enhanced frequency

the result being unnecessary biopsies of countless benign lesions. The situation is aggravated further by an enhanced risk of histopathologic misdiagnosis in early lesions and by reduced quality of biopsies as a result of enhanced frequency of them. Let's take a closer look at those problems.

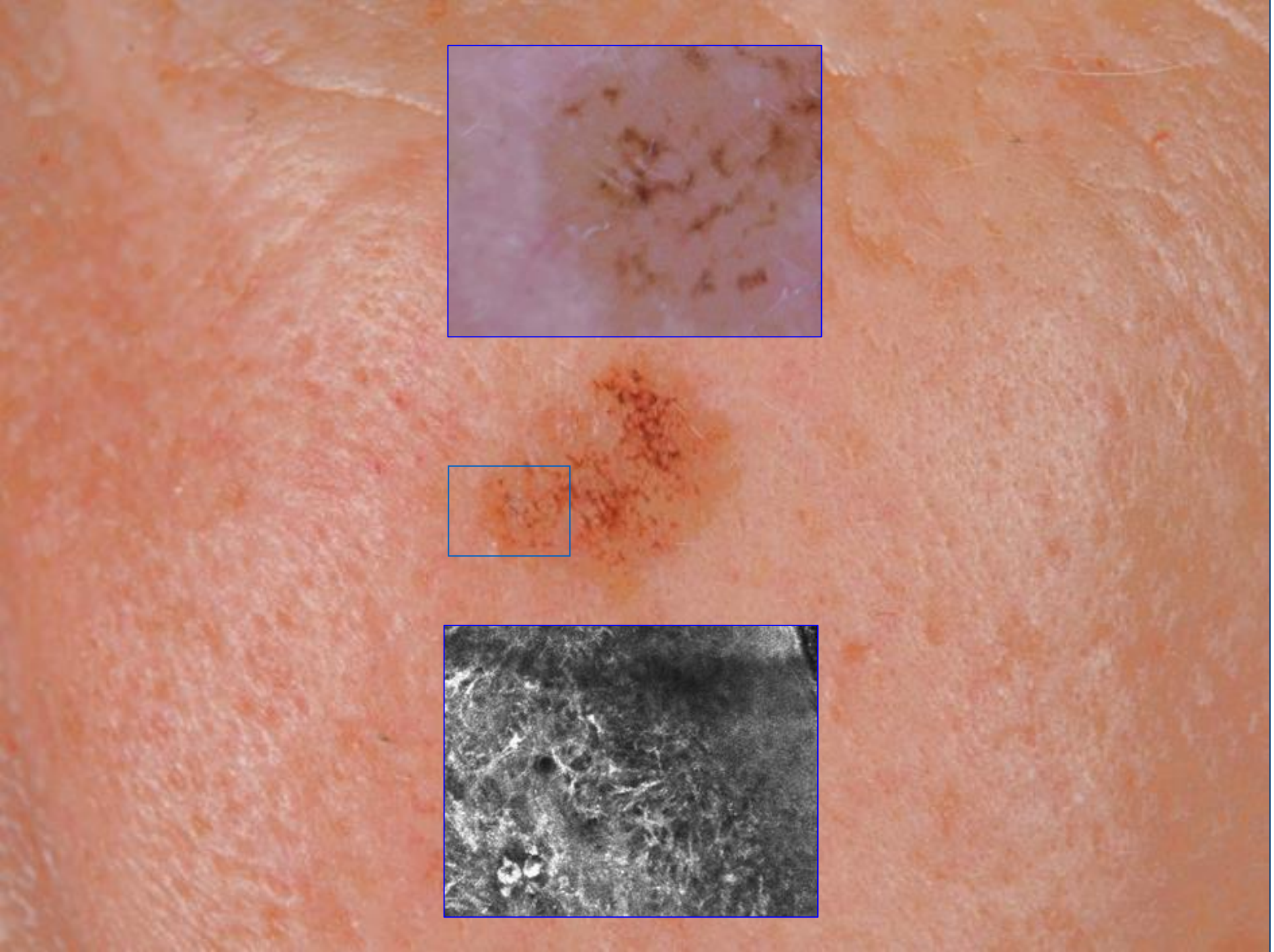


Malignant neoplasms differ from benign ones morphologically by greater size and greater irregularity in internal structure and outline. In neoplasms of the skin, those qualities are readily detectable,

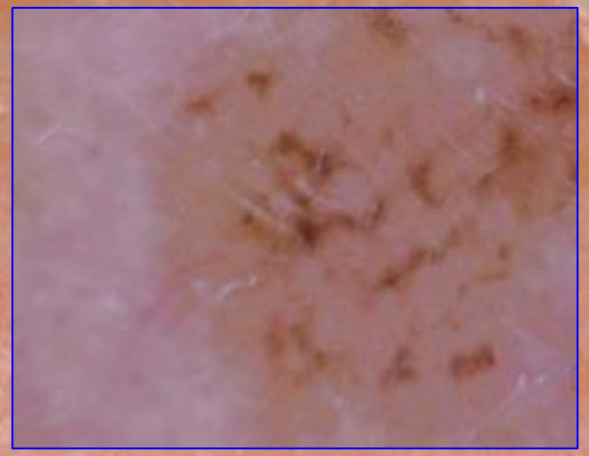


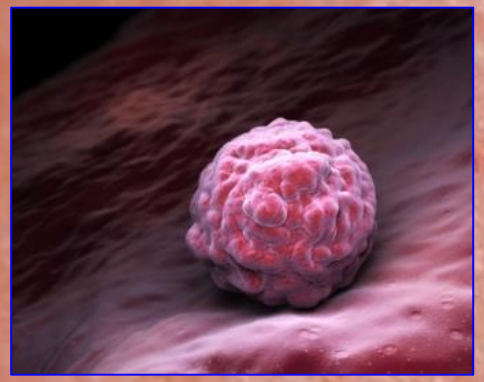


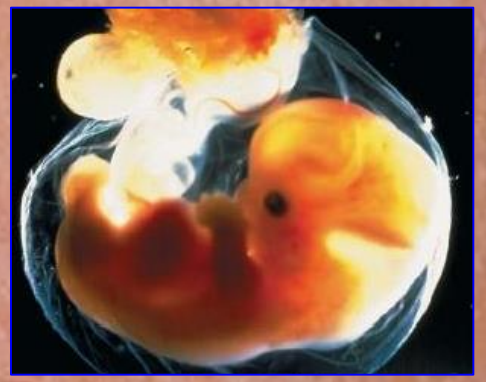
and recognition can be enhanced by adjunctive techniques such as dermatoscopy and confocal microscopy.

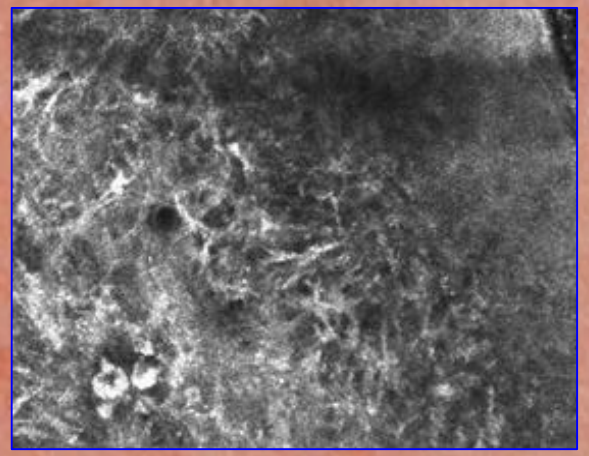


However, diagnostic features need some time to develop, and if the lesion is too small, diagnosis may be impossible,









just as one cannot tell mouse from man in the earliest stages of embryogenesis. If diagnoses are pursued at a stage that early, errors are inevitable, and because benign lesions are more common than malignant ones, many unnecessary biopsies will be performed.

Clinical dermatology • **Original article**

CED
Clinical and Experimental Dermatology

The number of benign moles excised for each malignant melanoma: the number needed to treat

S. Sidhu, O. Bodger, N. Williams* and D. L. Roberts†

*The Welsh Institute of Dermatology, University Hospital of Wales, Cardiff, UK; School of Medicine, Swansea University, UK; and Departments of *Histopathology and †Dermatology, Singleton Hospital, Swansea, UK*

doi:10.1111/j.1365-2230.2011.04148.x

Summary

Background. The ratio of benign moles excised for each malignant melanoma (MM) diagnosed, i.e. the number needed to treat (NNT), may be a useful indicator of diagnostic accuracy and the efficient use of healthcare resources, and may have personal implications for the patient.

Aim. To assess the NNT for a group of consultant dermatologists serving a population of 600 000, and to compare this with similar studies from other countries.

Methods. This was a retrospective analysis of data on pigmented lesions excised over a 5-year period (2005–2009). The lesions were divided into three groups: benign naevi (BN), dysplastic naevi (DN) and MM. The NNT ratio was calculated as (BN + DN + MM)/MM.

Results. In total, 4691 lesions were examined. The overall mean NNT was 6.3, with a range of 4.9–11.3 for each of nine consultant dermatologists. The mean NNT was 7.6 for female and 4.8 for male patients. There were more patients with BN (n = 3534; 75%) than with DN (n = 407; 9%) or MM (n = 750; 16%). The gender representation was similar in the DN and MM groups, but had a disproportionately female bias in the

The ratio of benign moles excised for each melanoma has been referred to as the *"number needed to treat"*

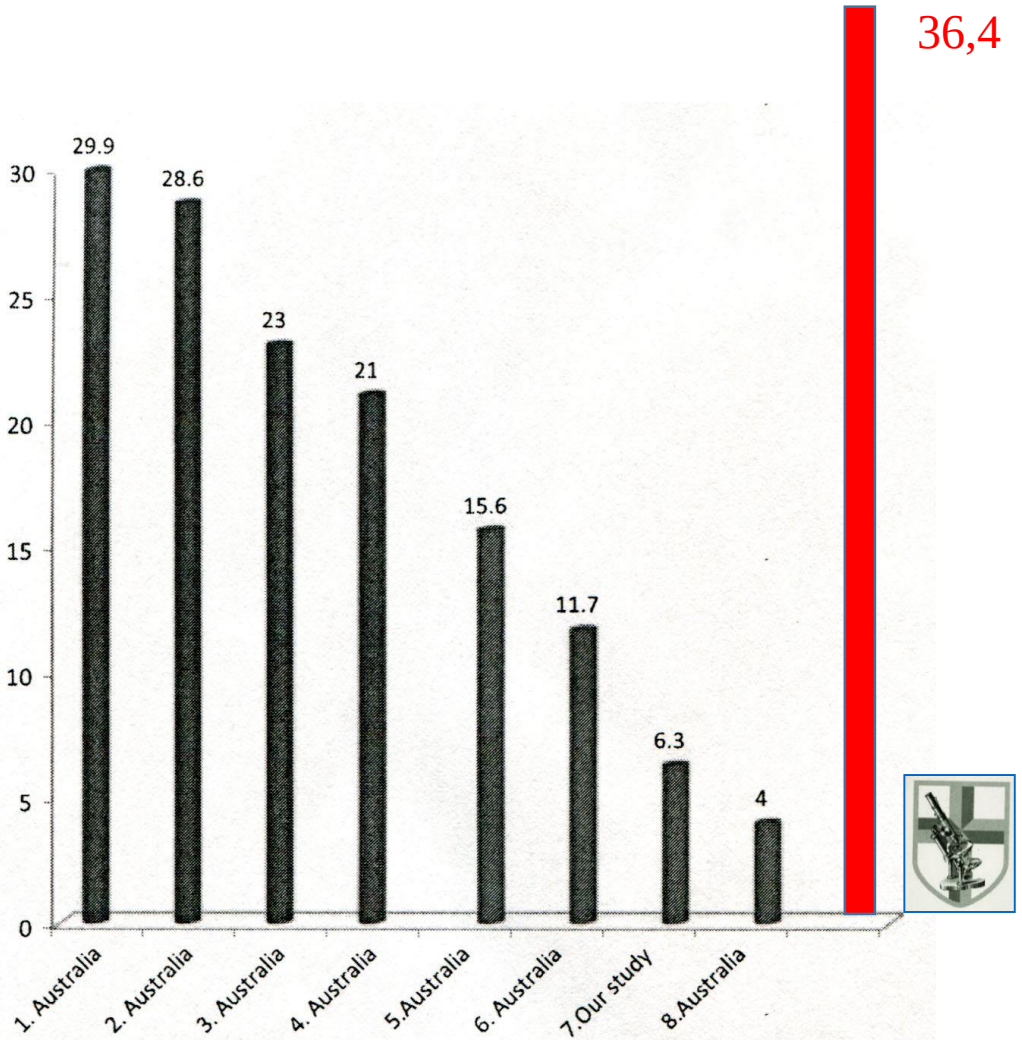
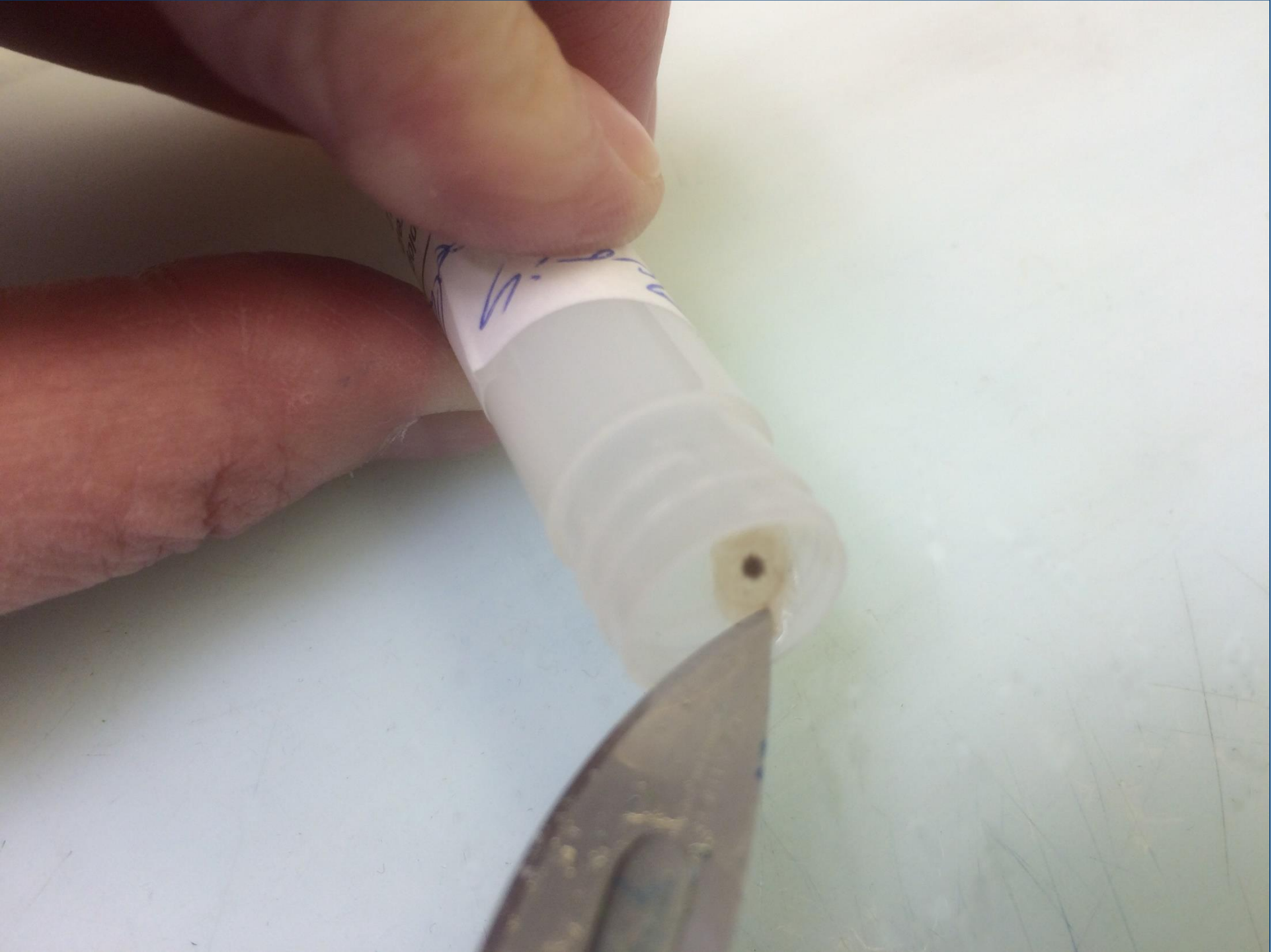
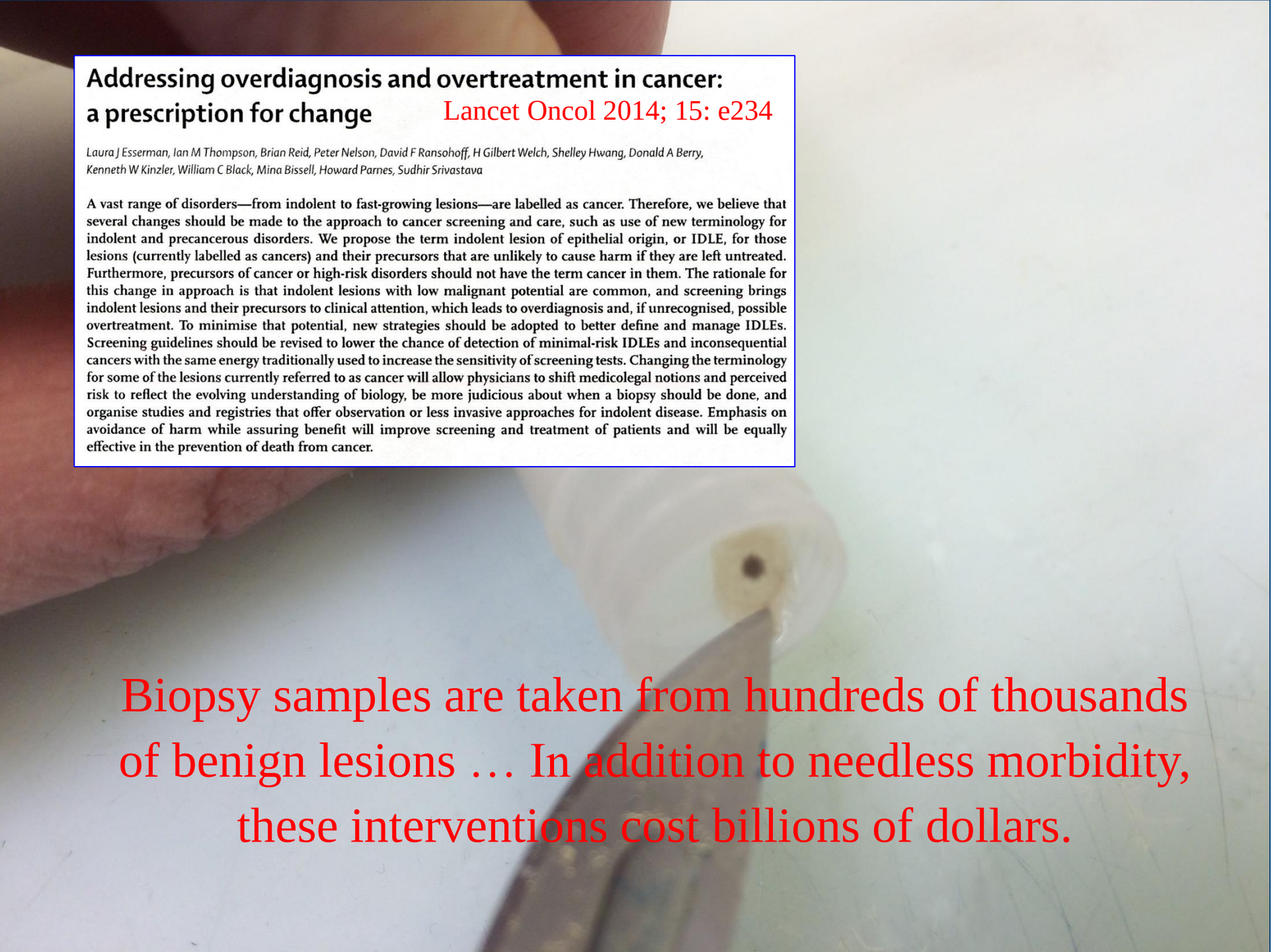


Figure 2 Comparison of number needed to treat published in various studies. Bars (left to right): Marks *et al.*[6]; Wilkinson *et al.*[5]; Hansen *et al.*[1]; English *et al.*[2]; Baade *et al.*[3]; Marks *et al.*[6]; present study; Chia *et al.*[4].

and varies considerably between different studies. I recently looked at our own figures, i.e., the ratio between nevi and melanomas at a big laboratory of dermatopathology in Germany where regular skin cancer screening has been implemented ten years ago, and our numbers are far higher.



The majority of those nevi were very small, too small to exhibit clinical criteria for melanoma such as an irregular border or irregular distribution of pigment. In the absence of such criteria, most pigmented lesions are going to be nevi, rather than early melanomas,



Addressing overdiagnosis and overtreatment in cancer: a prescription for change

Lancet Oncol 2014; 15: e234

Laura J Esserman, Ian M Thompson, Brian Reid, Peter Nelson, David F Ransohoff, H Gilbert Welch, Shelley Hwang, Donald A Berry, Kenneth W Kinzler, William C Black, Mina Bissell, Howard Parnes, Sudhir Srivastava

A vast range of disorders—from indolent to fast-growing lesions—are labelled as cancer. Therefore, we believe that several changes should be made to the approach to cancer screening and care, such as use of new terminology for indolent and precancerous disorders. We propose the term indolent lesion of epithelial origin, or IDLE, for those lesions (currently labelled as cancers) and their precursors that are unlikely to cause harm if they are left untreated. Furthermore, precursors of cancer or high-risk disorders should not have the term cancer in them. The rationale for this change in approach is that indolent lesions with low malignant potential are common, and screening brings indolent lesions and their precursors to clinical attention, which leads to overdiagnosis and, if unrecognised, possible overtreatment. To minimise that potential, new strategies should be adopted to better define and manage IDLEs. Screening guidelines should be revised to lower the chance of detection of minimal-risk IDLEs and inconsequential cancers with the same energy traditionally used to increase the sensitivity of screening tests. Changing the terminology for some of the lesions currently referred to as cancer will allow physicians to shift medicolegal notions and perceived risk to reflect the evolving understanding of biology, be more judicious about when a biopsy should be done, and organise studies and registries that offer observation or less invasive approaches for indolent disease. Emphasis on avoidance of harm while assuring benefit will improve screening and treatment of patients and will be equally effective in the prevention of death from cancer.

Biopsy samples are taken from hundreds of thousands of benign lesions … In addition to needless morbidity, these interventions cost billions of dollars.

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."*

- Unnecessary biopsies of countless benign lesions
- Enhanced risk of histopathologic misdiagnosis
- Reduced quality of biopsies as a result of enhanced frequency

The problem of trying to detect melanomas at the earliest possible stage, however, is not only overdiagnosis clinical, but also histopathological.

In cases of doubt, clinicians perform a biopsy and transfer the responsibility for diagnosis to the histopathologist who usually has the last word.

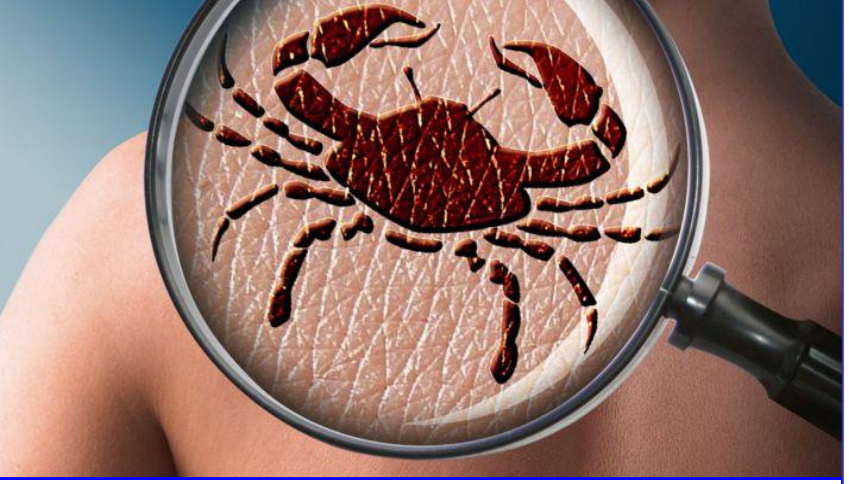


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TABLE I. *Criteria for the Histologic Diagnosis of Malignant Melanoma*

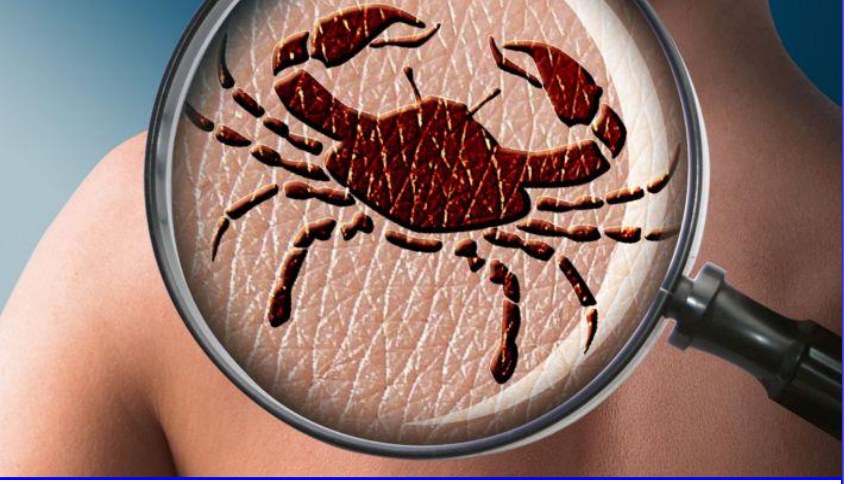
Architectural Pattern:

- Wide lateral extent of the lesion, i.e., greater than 6 mm
- Asymmetry of the lesion
- Horizontal extension of atypical melanocytes within the epidermis, beyond the bulk of the intraepidermal and intradermal components of the neoplasm
- Increased number of atypical melanocytes, singly and/or in nests, within the epidermis
- Atypical melanocytes at all levels of the epidermis, even the cornified layer
- Variation in sizes and shapes of nests of atypical melanocytes within the epidermis; shapes irregular
- Confluence of nests of melanocytes within the epidermis and the dermis
- Presence of atypical melanocytes in epithelial structures of adnexa
- Failure of maturation of atypical melanocytes with progressive descent into the dermis (i.e., the nuclei do not become smaller)

Cytologic features:

- Atypical melanocytes
- Melanocytes in mitosis (some of them may be atypical)
- Necrotic melanocytes

In principle, this makes sense because histopathologists have far more criteria to evaluate, ranging from architectural pattern to cytologic features.



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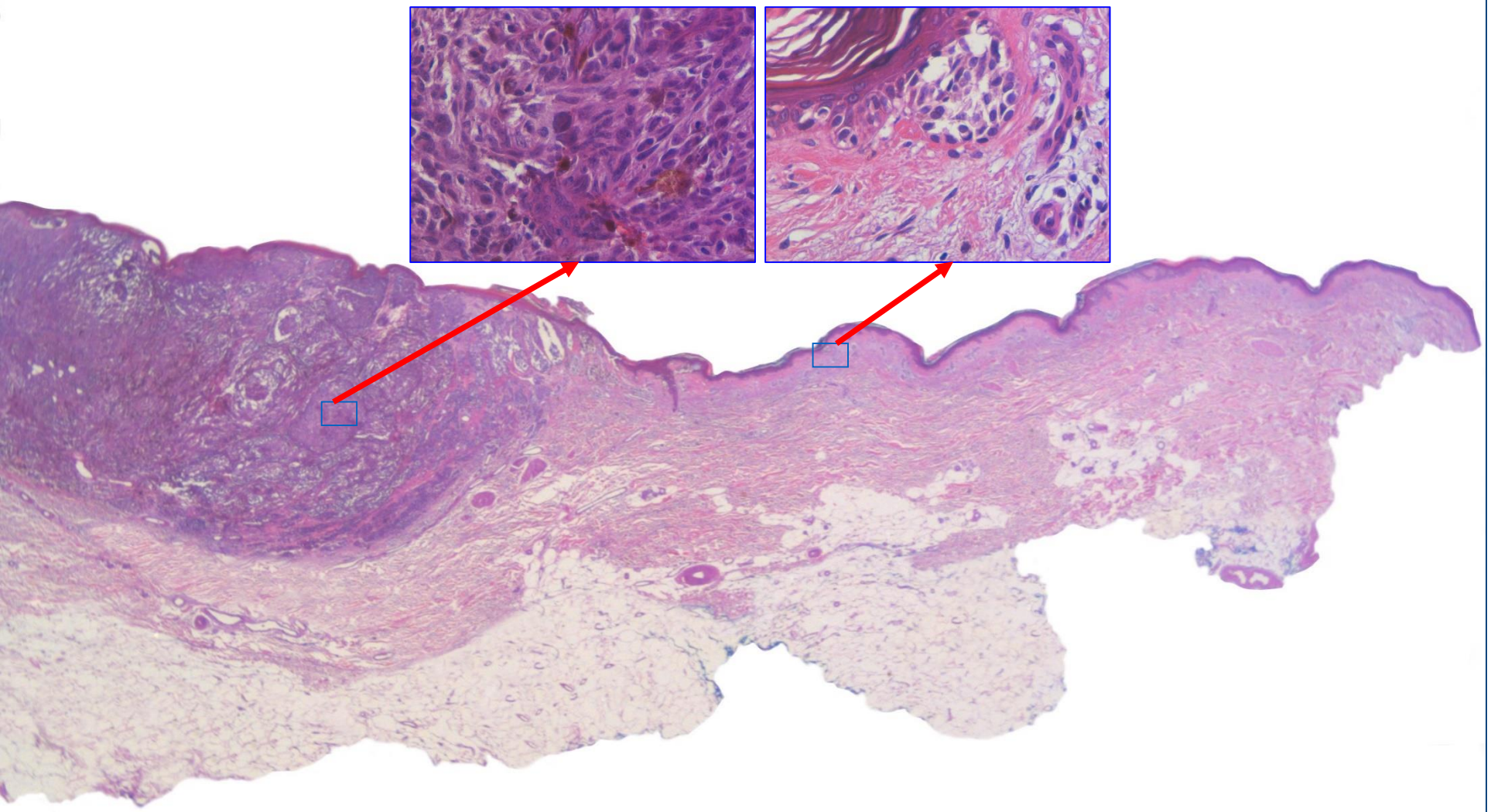
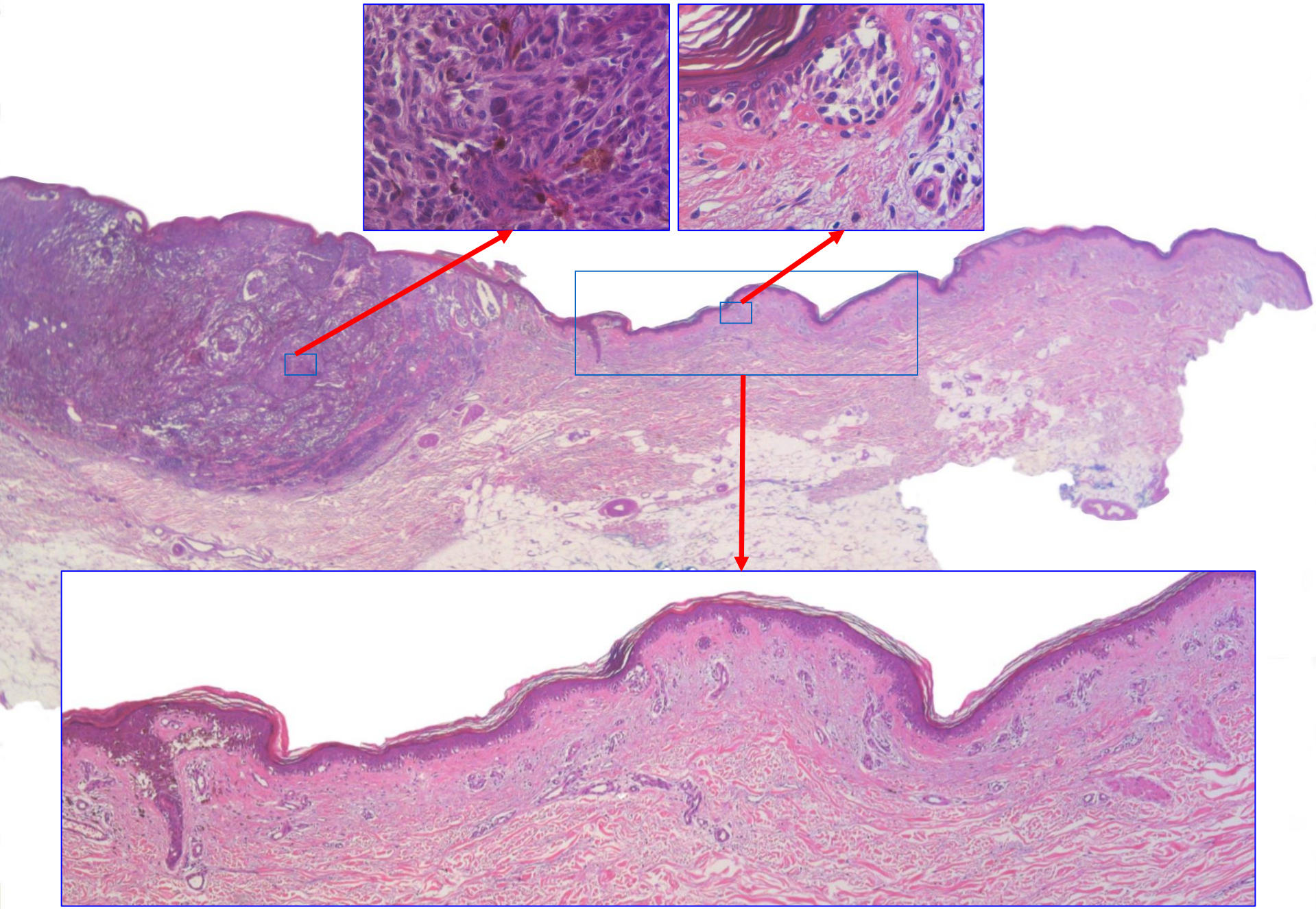
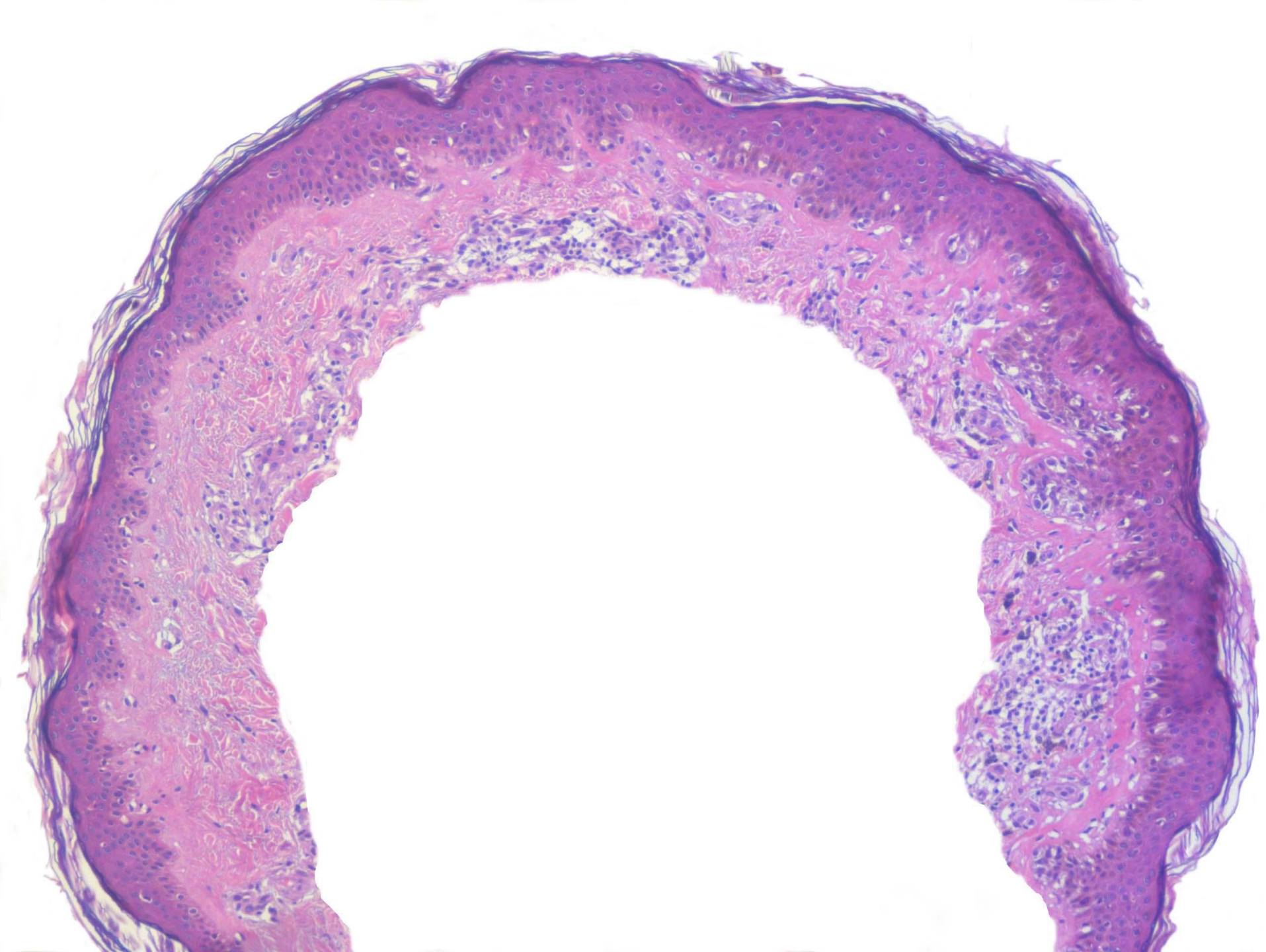
In early stages, however, many of those criteria cannot be used because changes have not been given the time to develop. For example, cytological signs of malignancy



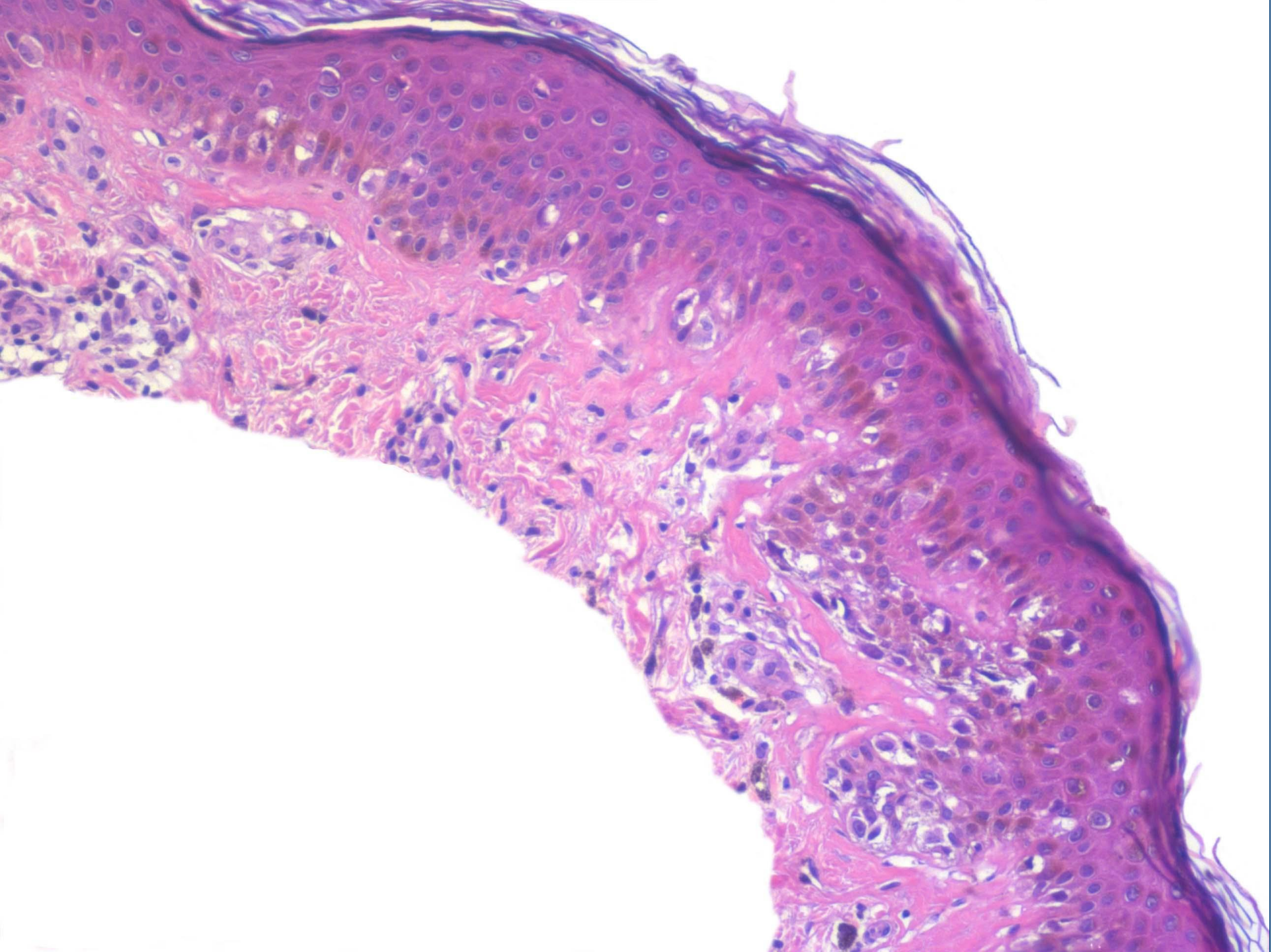
tend to be confined to advanced stages. In nodules of melanoma, nuclei are often large and hyperchomatic, but those in the in situ-component are usually small and monomorphous and cannot be distinguished from those of a Clark's nevus. Nevertheless, they are part of the melanoma,



as evidenced by the irregular architectural pattern. Melanocytes are distributed unevenly: there are confluent nests on the left, then solitary melanocytes only, followed by a larger isolated nest, then smaller nests next to one another, then few solitary melanocytes, then melanocytes crowded closely. The fluctuating architectural pattern is a direct consequence of biologic behavior, namely, irregular growth, and it can be assessed early-on because most criteria pertain to changes in the epidermis where melanocytes are situated physiologically and where the neoplastic process starts.



The irregularity of growth, however, is difficult to evaluate if the diameter of the lesion is too small. In a lesion measuring only three or four millimetres in diameter, there are not enough foci exhibiting different patterns for a reliable judgment to be made. Maturation cannot be assessed because there is no dermal component. Single melanocytes predominate over nests, but there are no discrete nests – they were not given the time to form.



If a lesion such as this one shows some unusual features, such as a few melanocytes above the junction, diagnosis becomes a guessing game: This may be a nevus, but a melanoma cannot be excluded, and because nobody wants to overlook a melanoma, overdiagnoses are so common. Because what happens in the event of error?

Nevus → Melanoma

If a benign lesion is classified as malignant, one gets a medical laurel wreath because patients believe they have been saved;

Nevus → Melanoma

Melanoma → Nevus

if a malignant lesion is classified as benign, a recurrence may occur, and one may be taken to court. This is a strong incentive to err on the malignant side.

J Cutan Pathol 2011: 38: 264–267
doi: 10.1111/j.1600-0560.2010.01660.x
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Journal of
Cutaneous Pathology

Perspectives in Dermatopathology

The melanoma 'epidemic', a dermatopathologist's perspective

Over the past several decades, the rise in melanoma incidence has been termed "epidemic." However, detailed analysis of mortality data suggests that the true incidence of melanoma has not increased dramatic
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J Cutan Pathol 2011; 38: 264–267. © 2011 John Wiley & Sons A/S.

Earl J. Glusac

Department of Pathology and Dermatology,
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tology,

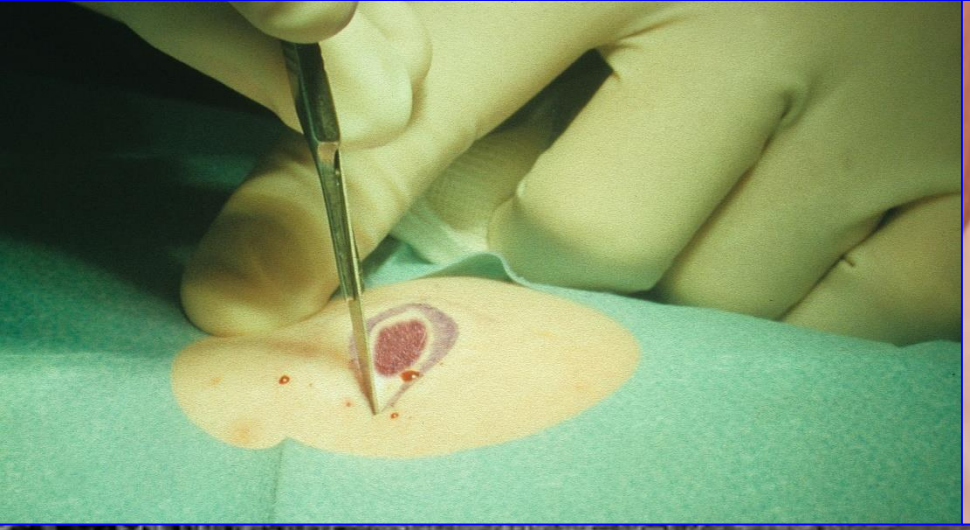
Accepted for publication December 10, 2010

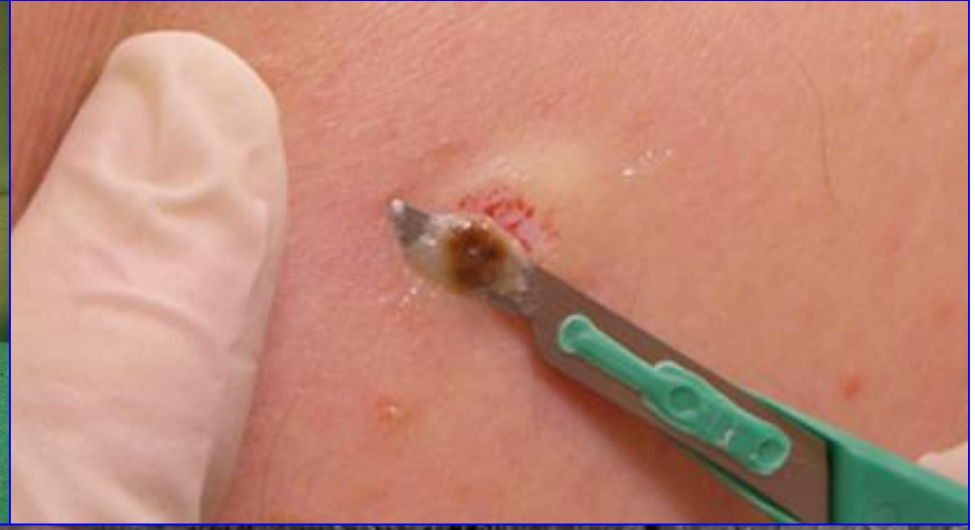
I believe that the overdiagnosis of melanoma is arguably the most difficult problem that we face in dermatopathology today.

The so-called *"melanoma 'epidemic'"* is probably caused, in part, by *"overdiagnosis of melanoma"* to which Earl Glusac referred as *"arguably the most difficult problem that we face in dermatopathology today."*

- Unnecessary biopsies of countless benign lesions
- Enhanced risk of histopathologic misdiagnosis
- Reduced quality of biopsies as a result of enhanced frequency

The problem is aggravated by a reduced quality of biopsies as a result of enhanced frequency of them.





Just a few decades ago, melanocytic neoplasms were nearly always excised completely, and usually with a narrow margin of normal skin. With biopsies being performed in industrial proportions, that procedure has been given up as too costly and too time-consuming. Today, most biopsies are performed by shave technique.

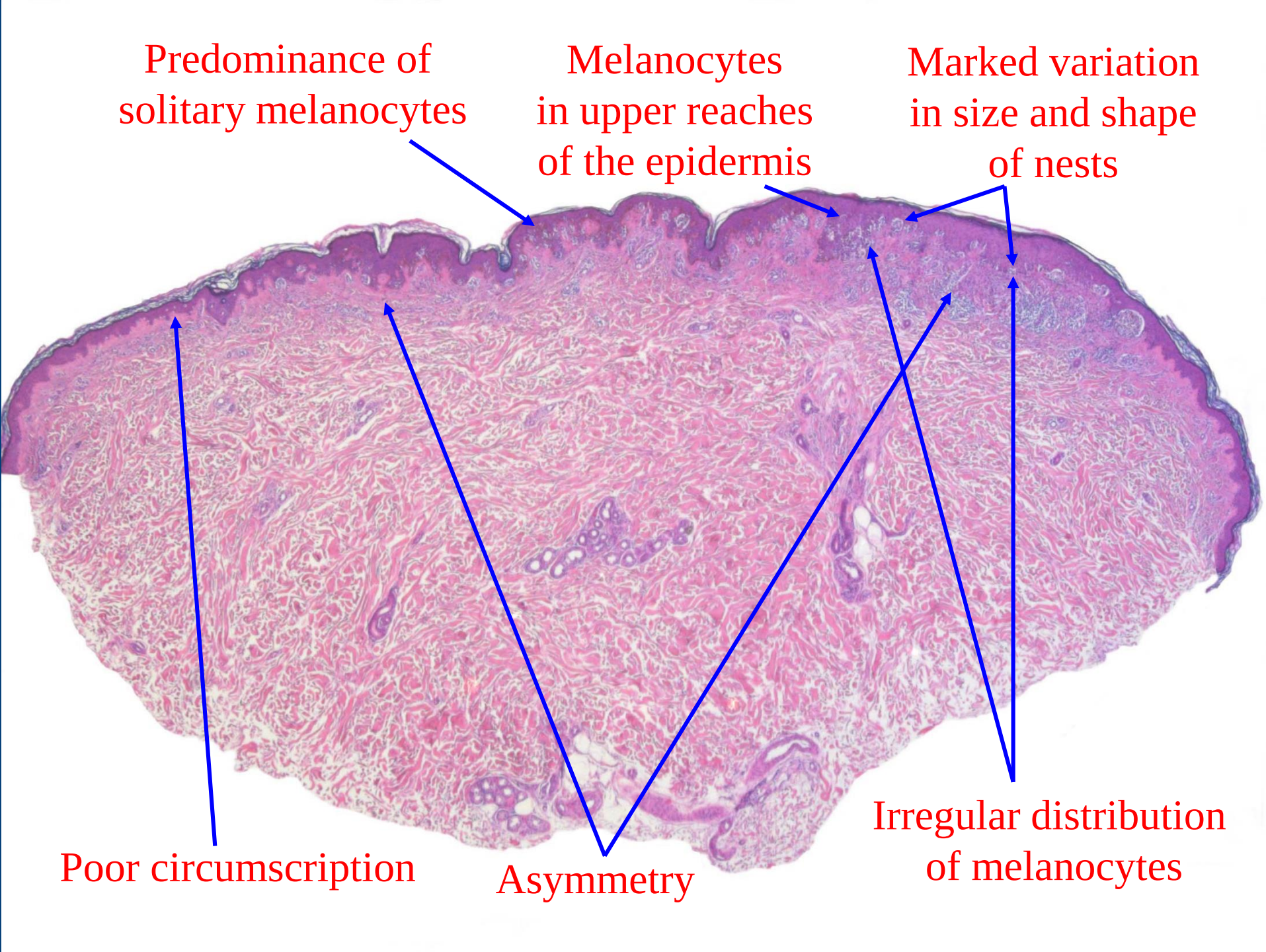
The shift in biopsy practices was initiated by studies demonstrating the safety of incisional biopsies.

Does biopsy type influence survival in clinical Stage I cutaneous melanoma?

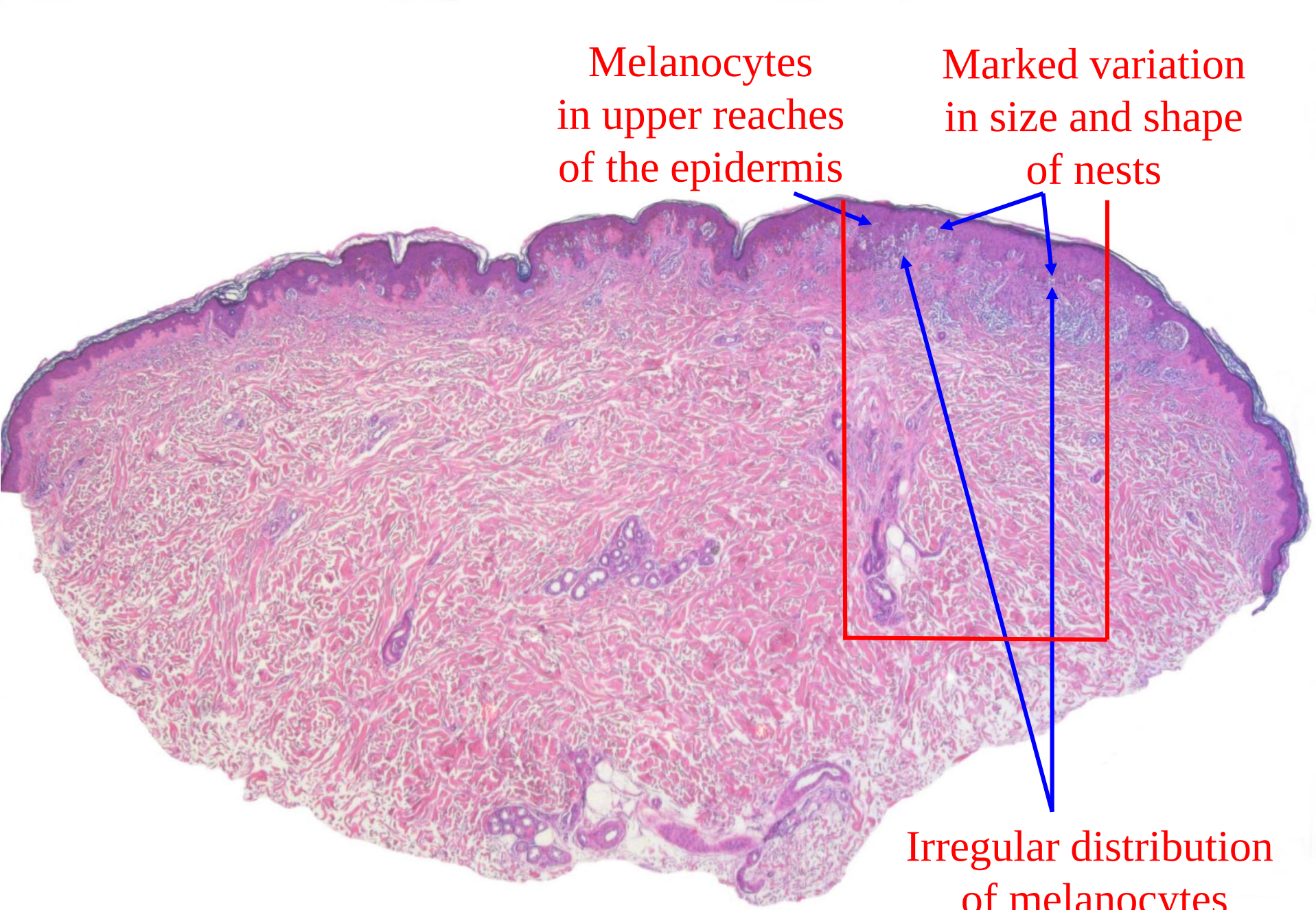
Josiane S. Lederman, M.D., and Arthur J. Sober, M.D. *Boston, MA*

A total of 472 patients with clinical Stage I cutaneous melanoma were analyzed to determine influence of type of diagnostic biopsy on survival. Of these patients, 119 had had an incisional biopsy (either punch or incision) and 353 had an excisional biopsy. Patients were grouped by thickness category and outcome compared between the biopsy types. Within each thickness category, there is no statistically significant difference in survival between the two groups. The observation that none of the seventy-six patients with primary tumors <1.70 mm have died following incisional biopsy strongly argues against any deleterious effect of incisional biopsy in this group. Alternatively, if the two highest-risk groups (≥1.70 mm) are analyzed as a single group, an adverse effect is seen in the incisional biopsy group ($p < 0.05$). However, when the data from these groups are subjected to multivariate analysis, biopsy type is not a significant factor in the model. This study shows that either biopsy method may be used in first evaluating patients with suspected melanoma. (J Am Acad Dermatol **13**:983-987, 1985.)

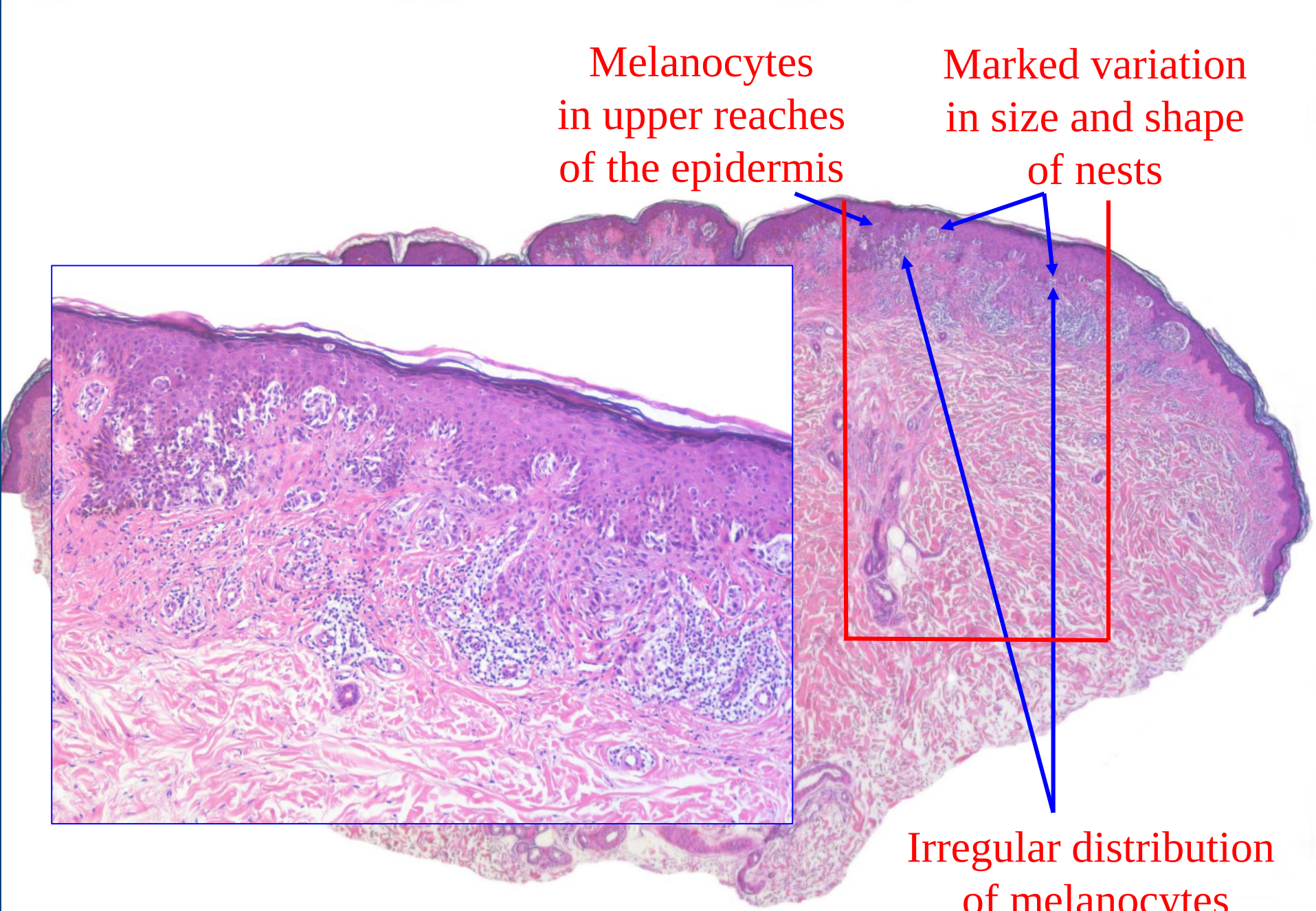
In 1985, Lederman and Sober found that incisional biopsies by either punch or scalpel resulted in *"no statistically significant difference in survival,"* and they concluded that *"either biopsy method may be used in first evaluating patients with suspected melanoma."* However, they considered only survival and turned a blind eye to diagnostic difficulties.



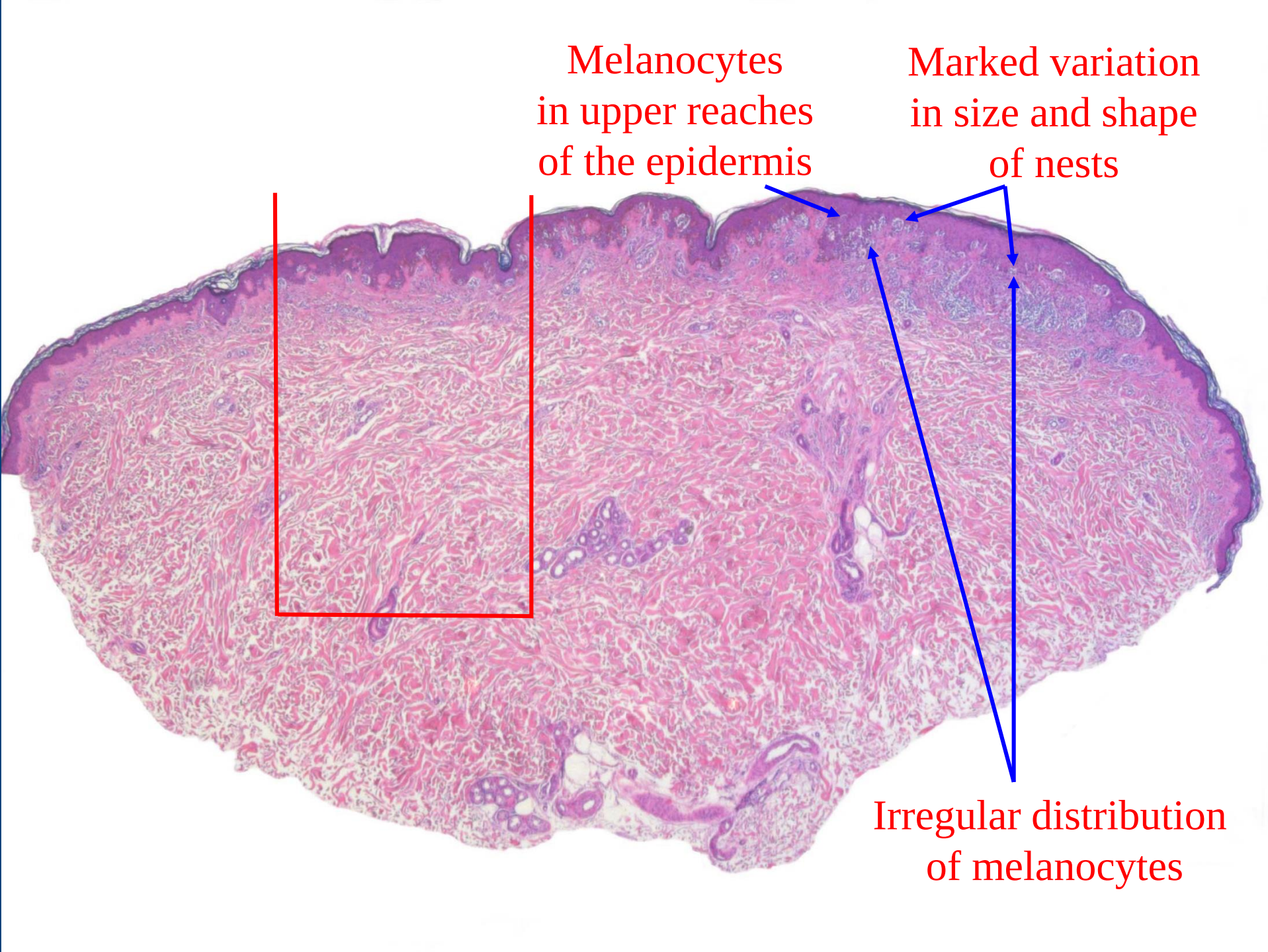
In excisional biopsies, many criteria can be evaluated, such as predominance of solitary melanocytes in foci, melanocytes in the upper reaches of the epidermis, marked variation in the size and shape of nests, and, of course, poor circumscription, asymmetry, and irregular distribution of melanocytes.



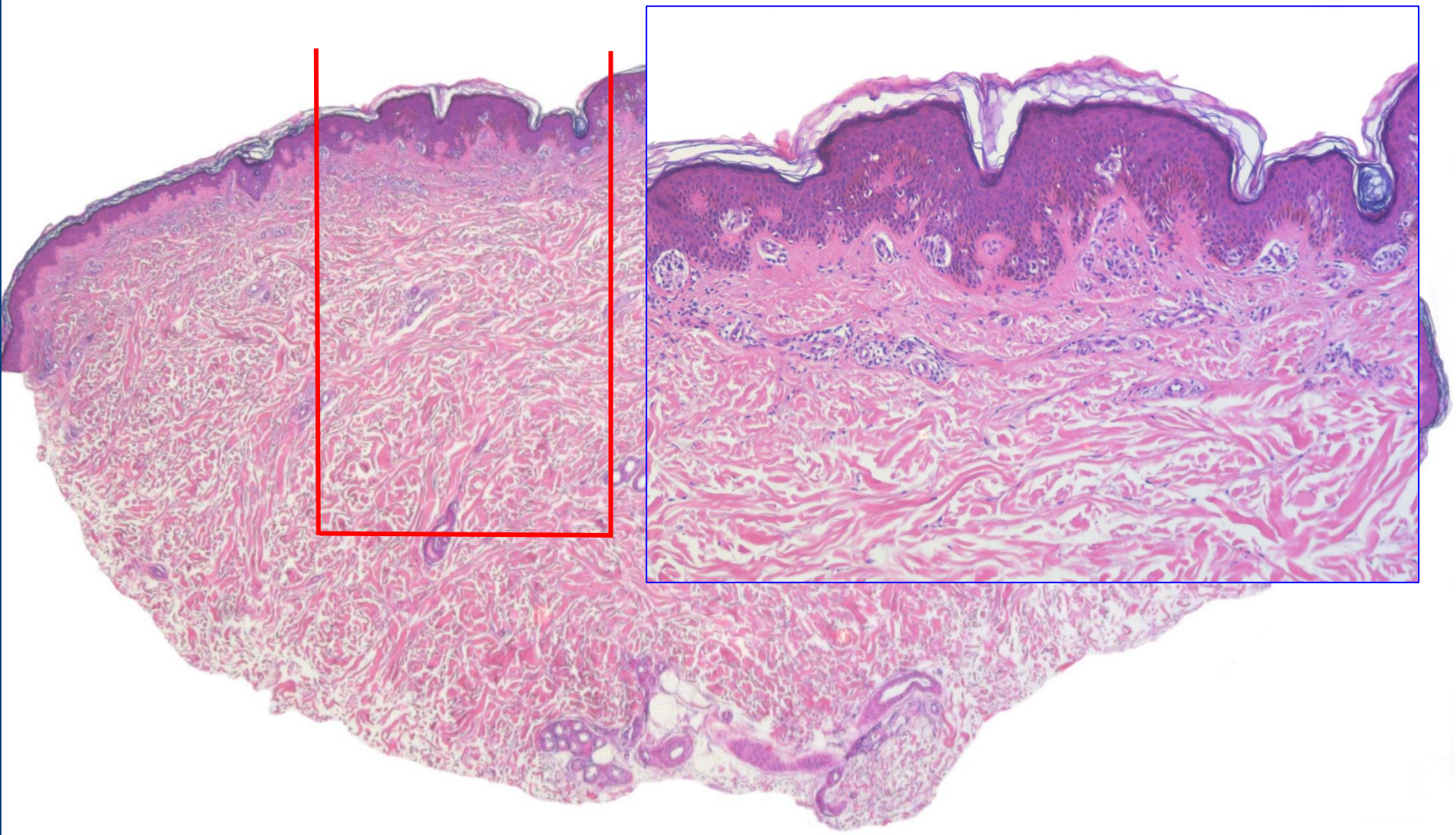
In a punch biopsy, many of those criteria cannot be assessed.



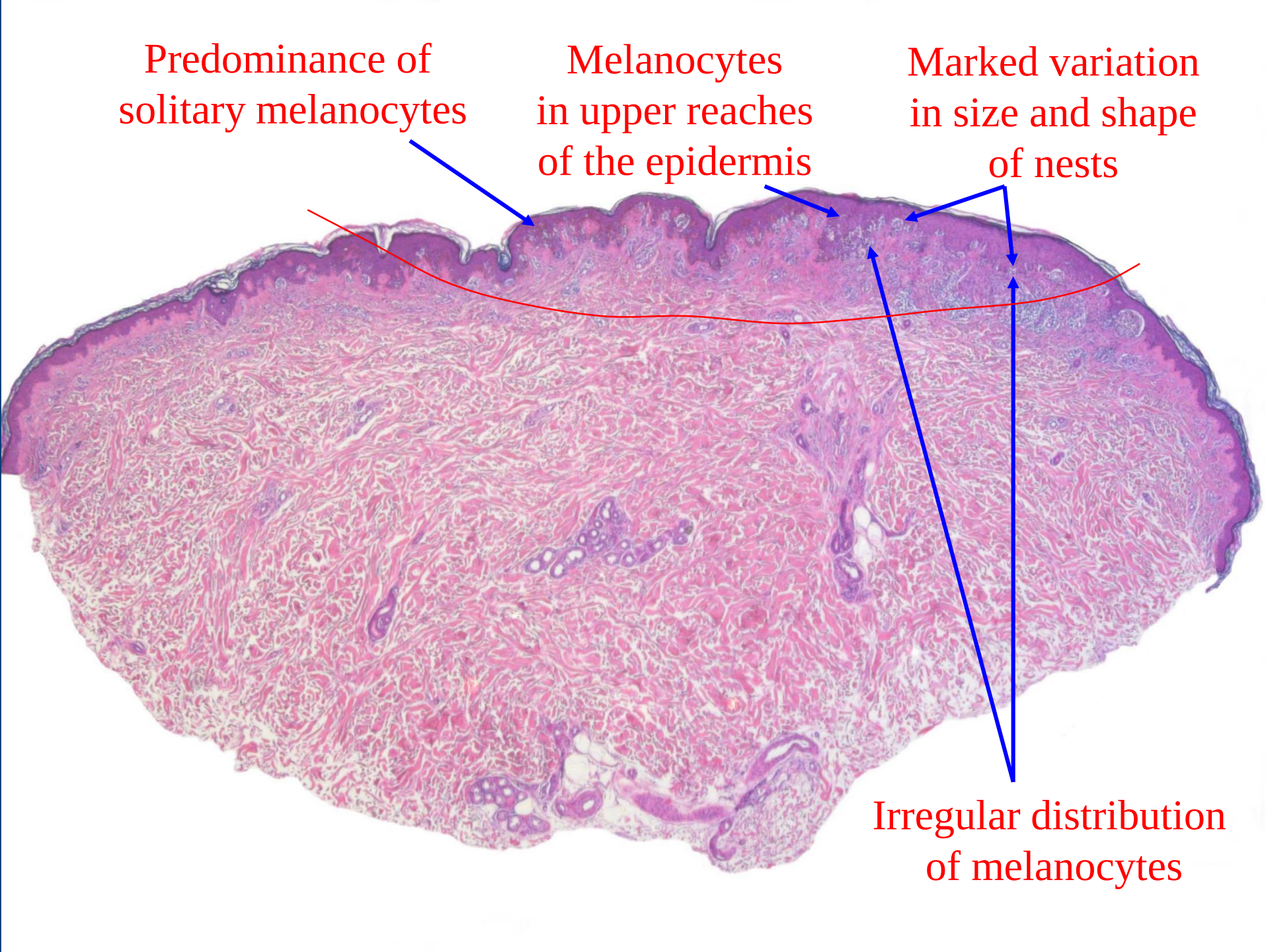
Those that are still available may allow a definite diagnosis to be made, but if, by chance,



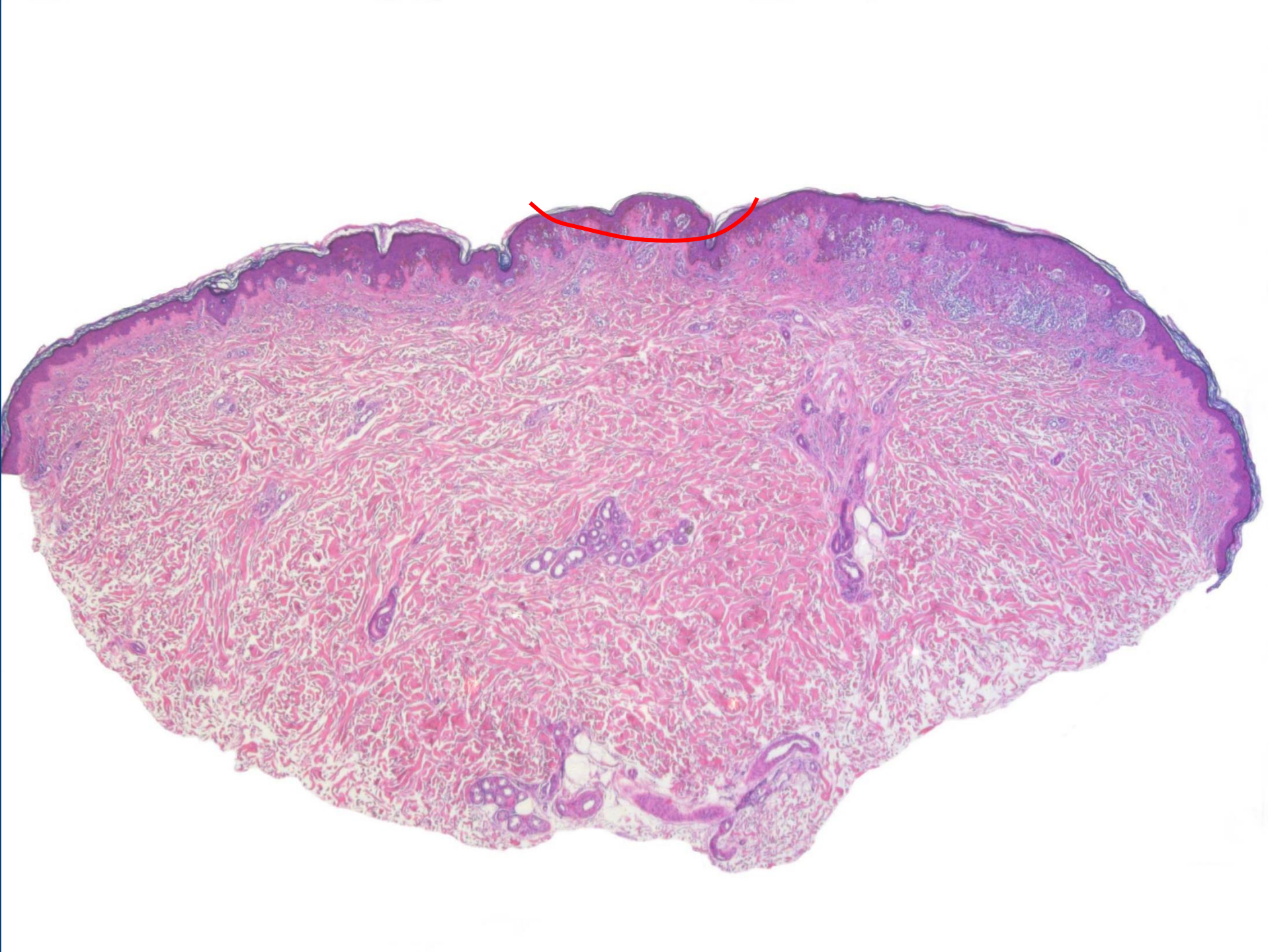
an area is sampled in which there are no diagnostic findings, the risk of misinterpretation is substantial.



In an area such as this one, composed nearly exclusively of tiny nests of small melanocytes at the dermo-epidermal junction, misdiagnosis as a nevus in almost inevitable.

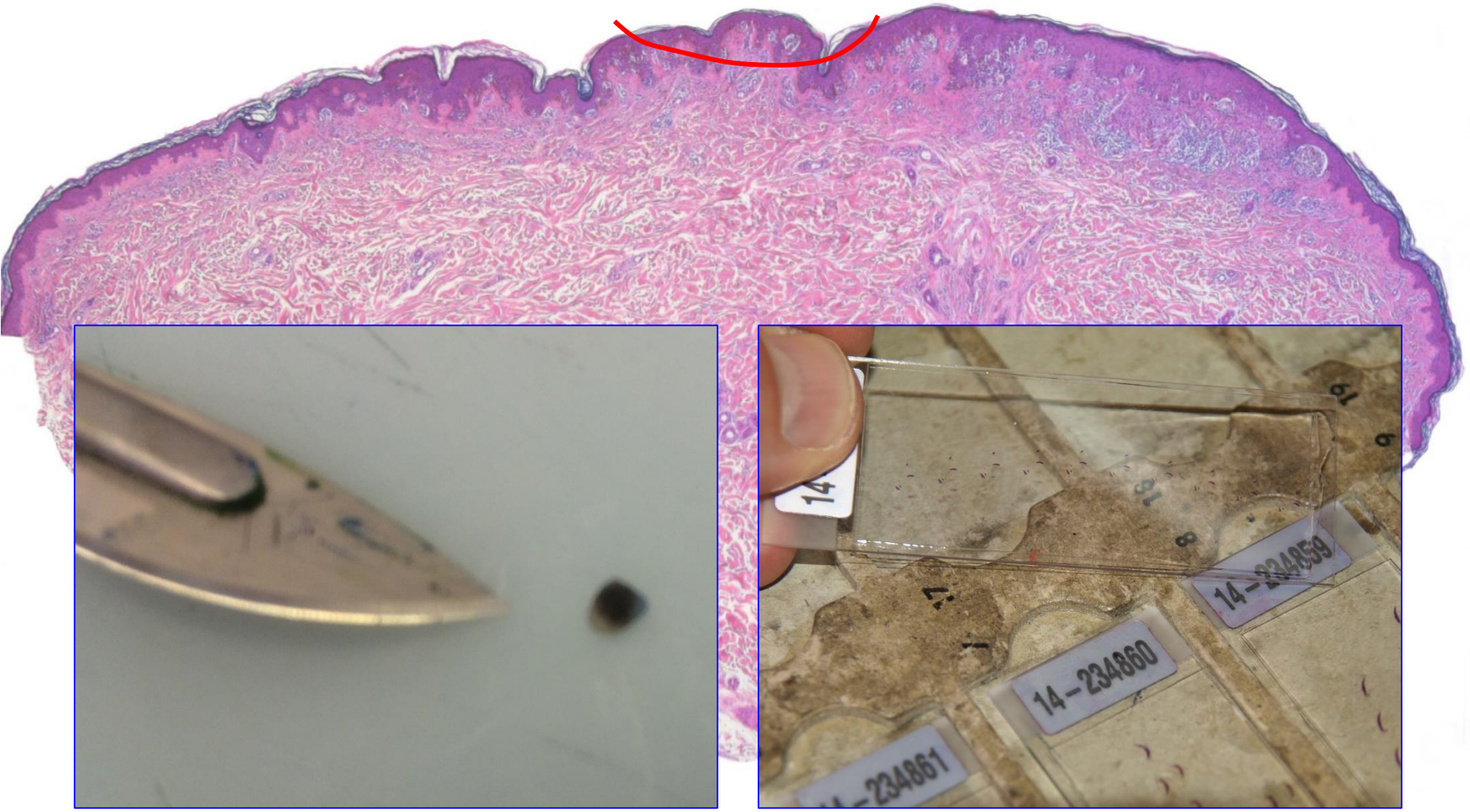


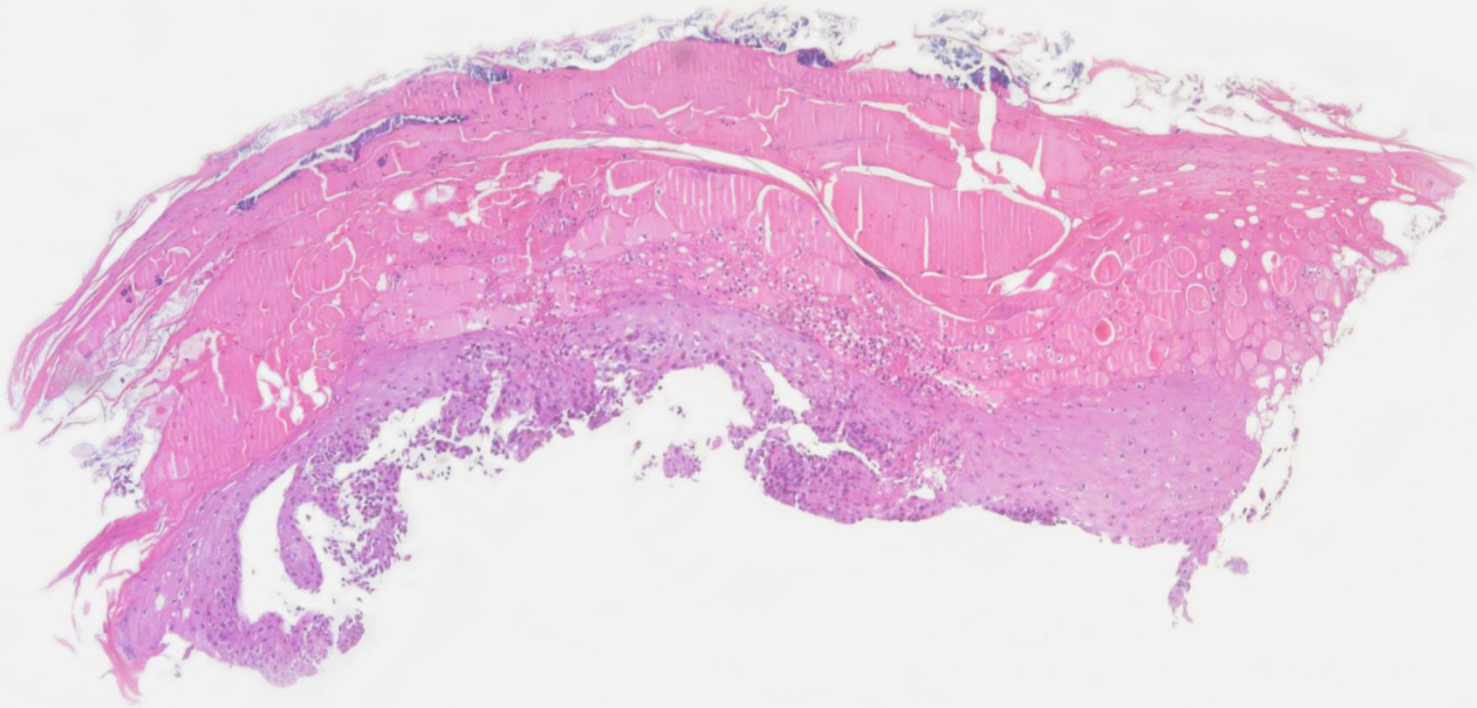
By contrast, a broad shave bears a much greater chance to reveal diagnostic features but only if it is broad enough.



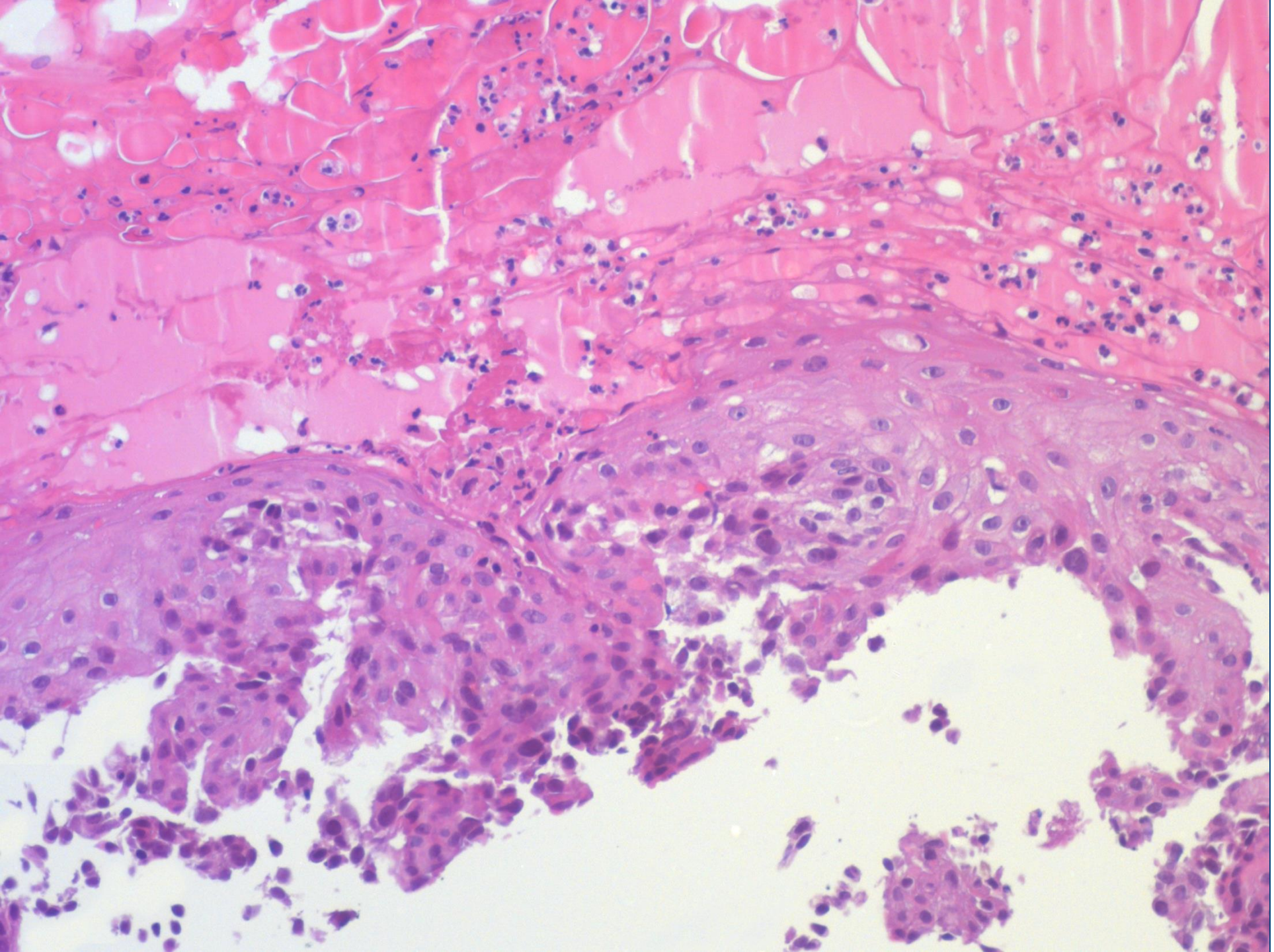
A shave too small precludes accurate interpretation because no criteria remain. In large pigmented lesions, such narrow shaves are rare,

but they are the rule in tiny lesions in which the degree of clinical suspicion is low.

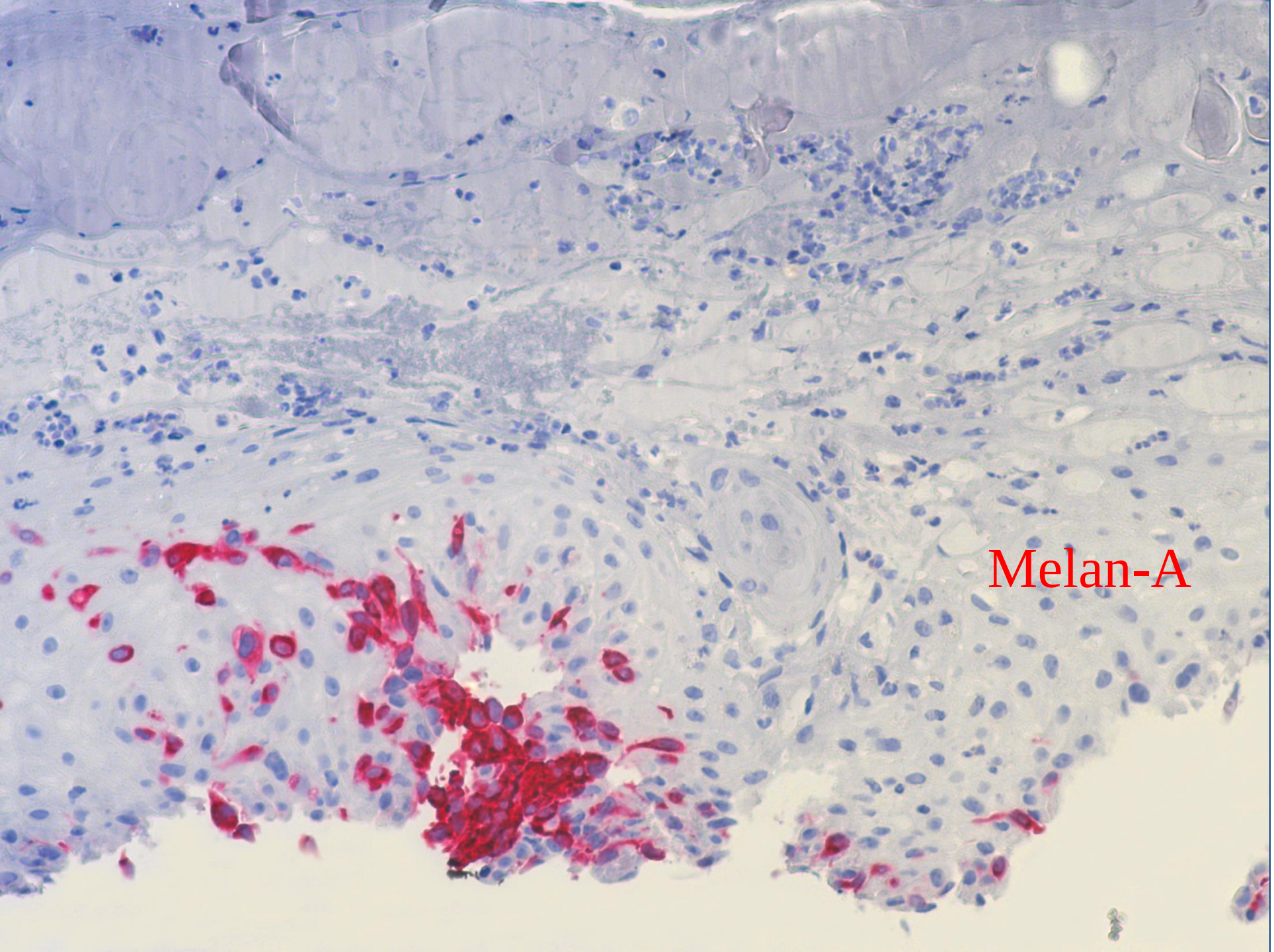




Not infrequently, only parts of the epidermis are sampled, and it requires great alertness

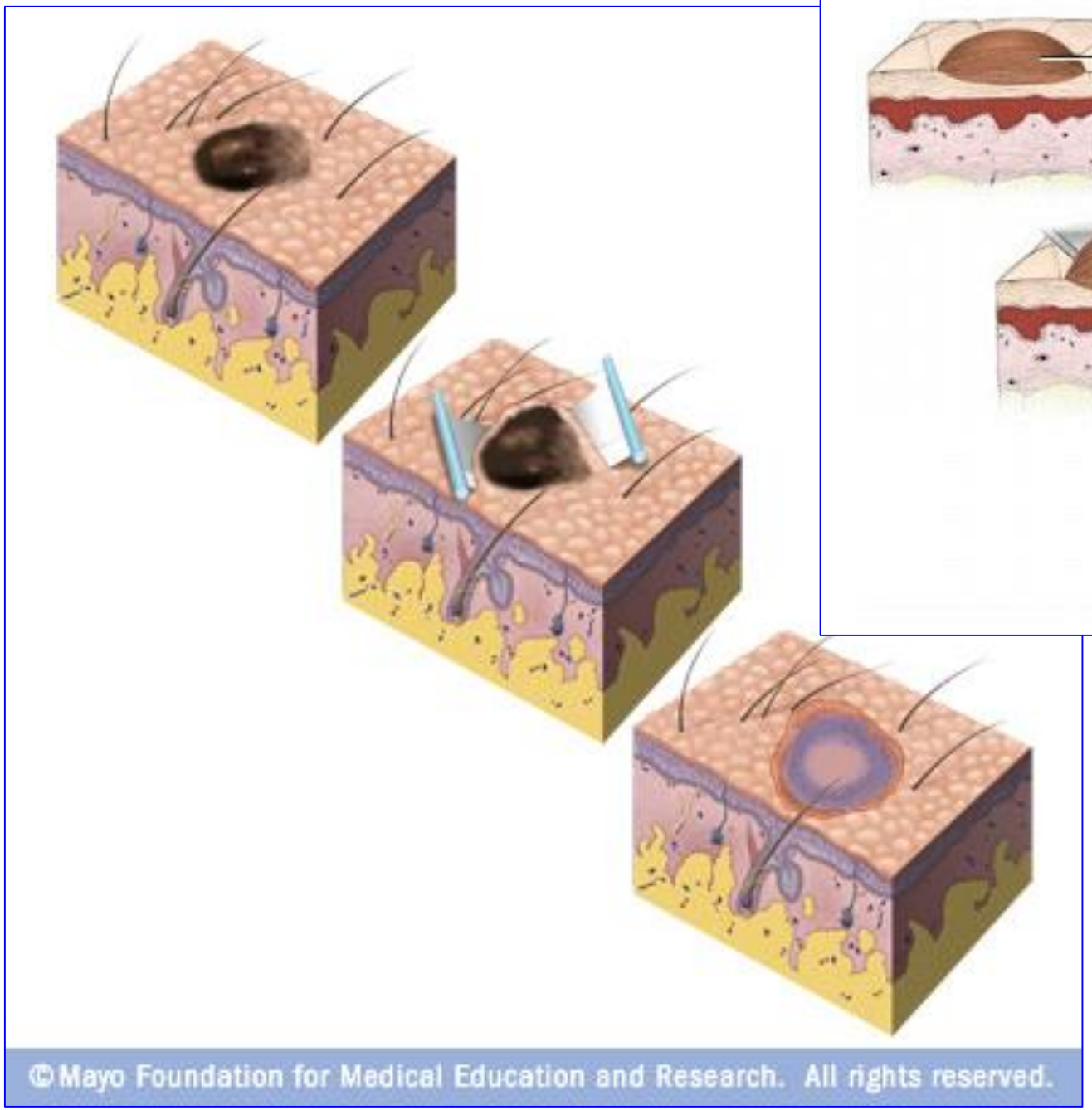


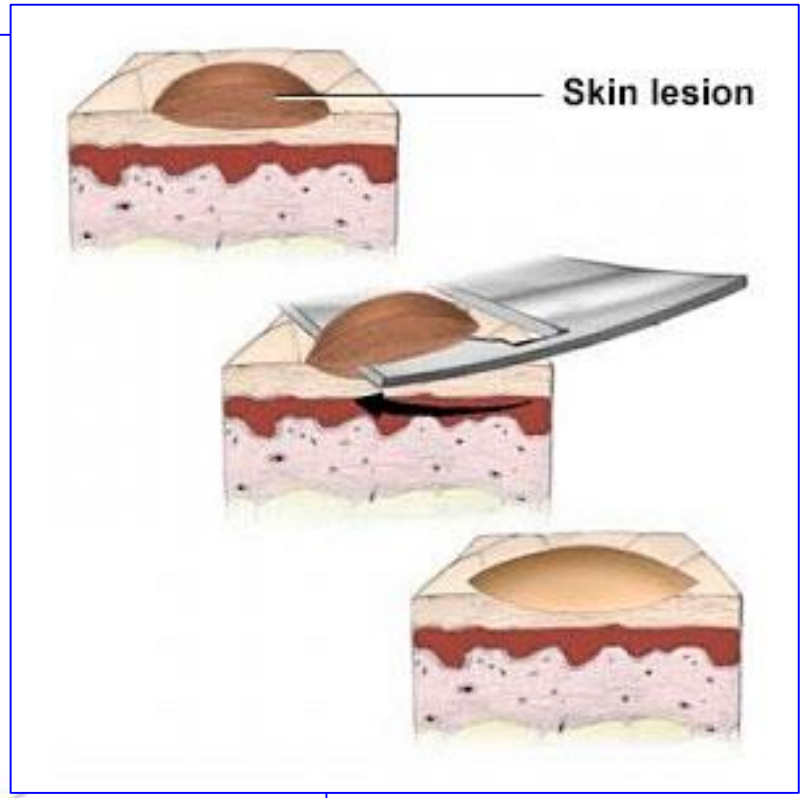
and experience to suspect a melanocytic lesion in specimens such as this one and to order immunohistochemical stains



that reveal what is probably a melanoma.

The poor quality of shave biopsies





is not surprising if one considers how the method is being taught: not into the dermis, not even into the viable epidermis, but only through the cornified layer, as in these illustrations by the *"Mayo Foundation for Medical Education and Research. All rights reserved."*

The Vanishing Biopsy: The Trend Toward Smaller Specimens

Emmy M. Fernandez, MD; Thomas Helm, MD; Michael Ioffreda, MD; Klaus F. Helm, MD

Dermatopathologists have noted an increased number of smaller biopsy specimens. Our objective was to determine whether dermatologists are changing their choice of biopsy technique and the size of biopsy specimens. We conducted a retrospective study of 500 biopsies performed by dermatologists for the purpose of diagnosis in 1988, 1993, 1998, and 2003. Our study results indicate that dermatologists are performing fewer punch biopsies and more shave biopsies. What's more, there has been a decrease in the size of shave biopsy specimens. We believe that the decreased number of punch biopsies being performed combined with the decreased size of shave biopsy specimens may affect patient care.

Cutis. 2005;76:335-339.

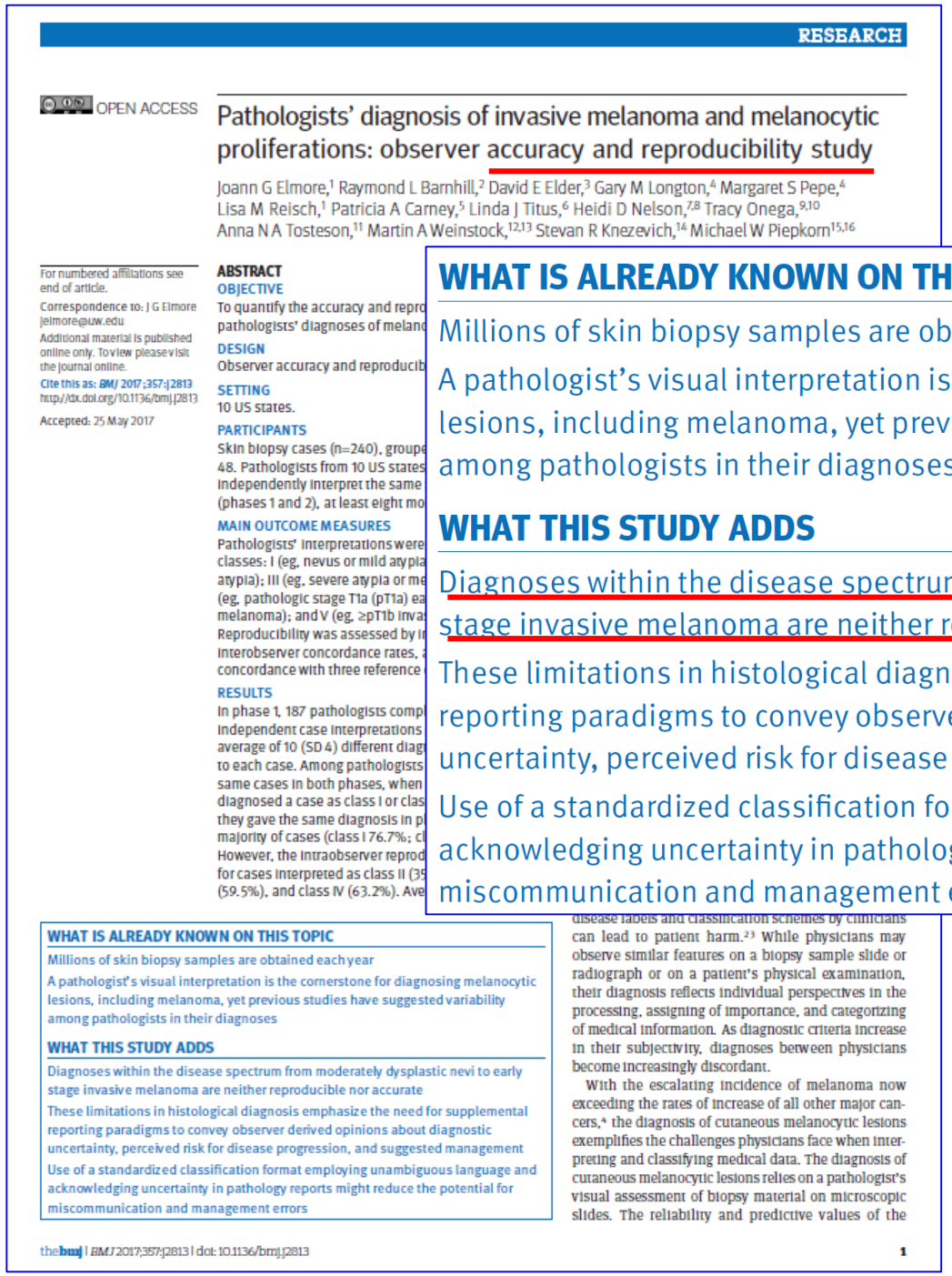
A skin biopsy may be performed for either therapeutic reasons or to aid in the diagnosis of cutaneous diseases. Edward Keyes[1] adapted the punch biopsy technique in 1887. During the choice of biopsy technique and the size of the resultant biopsy specimen.

Materials and Methods

A retrospective review of pathology reports was conducted at the Pennsylvania State Milton S. Hershey Medical Center, with approval by the institutional review board. Using the CoPathPlus® Anatomic Pathology database and archived pathology data, we analyzed 500 pathology reports of randomly selected skin biopsies performed by academic and private practice dermatologists in 1988, 1993, 1998, and 2003. Both punch and shave biopsy specimens were included in the study; excisional specimens were excluded, as were punch and shave biopsies that were performed for therapeutic rather than diagnostic intent (eg, biopsies performed to remove indubitable seborrheic keratoses, typical nevi, or acrochordons).

A total of 500 pathology reports—125 consecutive biopsies from each of the 4 study years—were

Considering the importance of the issue, it is surprising that problems caused by the "vanishing biopsy" are hardly ever addressed in the medical literature.



RESEARCH

OPEN ACCESS

Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study

Joann G Elmore,[1] Raymond L Barnhill,[2] David E Elder,[3] Gary M Longton,[4] Margaret S Pepe,[4] Lisa M Reisch,[1] Patricia A Carney,[5] Linda J Titus,[6] Heidi D Nelson,[7,8] Tracy Onega,[9,10] Anna N A Tosteson,[11] Martin A Weinstock,[12,13] Stevan R Knezevich,[14] Michael W Piepkorn[15,16]

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Accepted: 25 May 2017

ABSTRACT

OBJECTIVE

To quantify the accuracy and repro
pathologists' diagnoses of melanc

DESIGN

Observer accuracy and reproducib

SETTING

10 US states.

PARTICIPANTS

Skin biopsy cases (n=240), groupe
48. Pathologists from 10 US states
independently interpret the same
(phases 1 and 2), at least eight mo

MAIN OUTCOME MEASURES

Pathologists' interpretations were
classes: I (eg, nevus or mild atypia
atypia); III (eg, severe atypia or me
(eg, pathologic stage T1a (pT1a) ea
melanoma); and V (eg, ≥pT1b invas
Reproducibility was assessed by in
interobserver concordance rates,
concordance with three reference

RESULTS

In phase 1, 187 pathologists compl
independent case interpretations
average of 10 (SD 4) different diagn
to each case. Among pathologists
same cases in both phases, when
diagnosed a case as class I or clas
they gave the same diagnosis in p
majority of cases (class I 76.7%; cl
However, the intraobserver reprod
for cases interpreted as class II (35
(59.5%), and class IV (63.2%). Ave

WHAT IS ALREADY KNOWN ON THIS TOPIC

Millions of skin biopsy samples are obtained each year

A pathologist's visual interpretation is the cornerstone for diagnosing melanocytic lesions, including melanoma, yet previous studies have suggested variability among pathologists in their diagnoses

WHAT THIS STUDY ADDS

Diagnoses within the disease spectrum from moderately dysplastic nevi to early stage invasive melanoma are neither reproducible nor accurate

These limitations in histological diagnosis emphasize the need for supplemental reporting paradigms to convey observer derived opinions about diagnostic uncertainty, perceived risk for disease progression, and suggested management

Use of a standardized classification format employing unambiguous language and acknowledging uncertainty in pathology reports might reduce the potential for miscommunication and management errors

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disease labels and classification schemes by clinicians can lead to patient harm.[23] While physicians may observe similar features on a biopsy sample slide or radiograph or on a patient's physical examination, their diagnosis reflects individual perspectives in the processing, assigning of importance, and categorizing of medical information. As diagnostic criteria increase in their subjectivity, diagnoses between physicians become increasingly discordant.

With the escalating incidence of melanoma now exceeding the rates of increase of all other major cancers,[4] the diagnosis of cutaneous melanocytic lesions exemplifies the challenges physicians face when interpreting and classifying medical data. The diagnosis of cutaneous melanocytic lesions relies on a pathologist's visual assessment of biopsy material on microscopic slides. The reliability and predictive values of the

For example, last year Elmore and co-workers, in an "accuracy and reproducibility study" of melanocytic lesions, found that *"diagnoses within the disease spectrum from moderately dysplastic nevi to early stage invasive melanoma are neither reproducible nor accurate."*

RESEARCH

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disease labels and classification schemes by clinicians can lead to patient harm.[23] While physicians may observe similar features on a biopsy sample slide or radiograph or on a patient's physical examination,

Biopsy case development

Cutaneous melanocytic lesions from shave, punch, and excisional specimens were included.[13 14 16] We selected

preting and classifying medical data. The diagnosis of cutaneous melanocytic lesions relies on a pathologist's visual assessment of biopsy material on microscopic slides. The reliability and predictive values of the

They noted that *"cutaneous melanocytic lesions from shave, punch, and excisional specimens were included,"* but they refrained from discussing those biopsy techniques although the latter clearly have an impact on the accuracy of diagnosis.

Shave Biopsy Is a Safe and Accurate Method for the Initial Evaluation of Melanoma

Jonathan S Zager, MD, FACS, Steven N Hochwald, MD, FACS, Suroosh S Marzban, BS, Rony Francois, BS, Kimberly M Law, BS, Ashley H Davis, BS, Jane L Messina, MD, Vladimir Vincek, MD, PhD, Christina Mitchell, MD, Ann Church, MD, Edward M Copeland, MD, FACS, Vernon K Sondak, MD, FACS, Stephen R Grobmyer, MD, FACS

BACKGROUND: Shave biopsy of cutaneous lesions is simple, efficient, and commonly used clinically. However, this technique has been criticized for its potential to hamper accurate diagnosis and microstaging of melanoma, thereby complicating treatment decision-making.

STUDY DESIGN: We retrospectively analyzed a consecutive series of patients referred to the University of Florida Shands Cancer Center or to the Moffitt Cancer Center for treatment of primary cutaneous melanoma, initially diagnosed on shave biopsy to have Breslow depth < 2 mm, to determine the accuracy of shave biopsy in T-staging and the potential impact on definitive surgical treatment and outcomes.

RESULTS: Six hundred patients undergoing shave biopsy were diagnosed with melanoma from extremity (42%), trunk (37%), and head or neck (21%). Mean (± SEM) Breslow thickness was 0.73 ± 0.02 mm; 6.2% of lesions were ulcerated. At the time of wide excision, residual melanoma was found in 133 (22%), resulting in T-stage upstaging for 18 patients (3%). Recommendations for additional wide excision or sentinel lymph node biopsy changed in 12 of 600 (2%) and 8 of 600 patients (1.3%), respectively. Locoregional recurrence occurred in 10 (1.7%) patients and distant recurrence in 4 (0.7%) patients.

CONCLUSIONS: These data challenge the surgical dogma that full-thickness excisional biopsy of suspicious cutaneous lesions is the only method that can lead to accurate diagnosis. Data obtained on shave biopsy of melanoma are reliable and accurate in the overwhelming majority of cases (97%). The use of shave biopsy does not complicate or compromise management of the overwhelming majority of patients with malignant melanoma. (J Am Coll Surg 2011;212:454–462. © 2011 by the American College of Surgeons)

In recent years, biopsy techniques have been discussed nearly exclusively by surgeons who averred that *"shave biopsy is a safe and accurate method for the initial evaluation of melanoma,"* but only as far as *"accuracy of shave biopsy in T staging is concerned."*

For surgeons, thickness of lesions is of prime importance because their guidelines require wider excisions of thicker lesions. Whether or not the diagnosis is correct is not their business.

The Impact of Partial Biopsy on Histopathologic Diagnosis of Cutaneous Melanoma

Experience of an Australian Tertiary Referral Service

Jonathan C. Ng, MBBS, MBiomedSc; Sarah Swain, MBBS, FRCPA; John P. Dowling, FRCPA; Rory Wolfe, BSc, PhD; Pamela Simpson, BSc; John W. Kelly, MD, BS, FACD

Objective: To compare partial and excisional biopsy techniques in the accuracy of histopathologic diagnosis and microstaging of cutaneous melanoma.

Design: Prospective case series.

Setting: Tertiary referral, ambulatory care, institutional practice.

Patients: Consecutive cases from 1995 to 2006.

Interventions: Partial and excisional biopsy. Other factors considered were anatomic site, physician type at initial management, hypomelanosis, melanoma subtype, biopsy sample size, multiple biopsies, and tumor thickness.

Main Outcome Measures: Histopathologic diagnosis (false-negative misdiagnosis—overall or with an adverse outcome—and false-positive misdiagnosis) and microstaging accuracy. Odds ratios (ORs) and 95% confidence intervals (CIs) obtained from multinomial logistic regression.

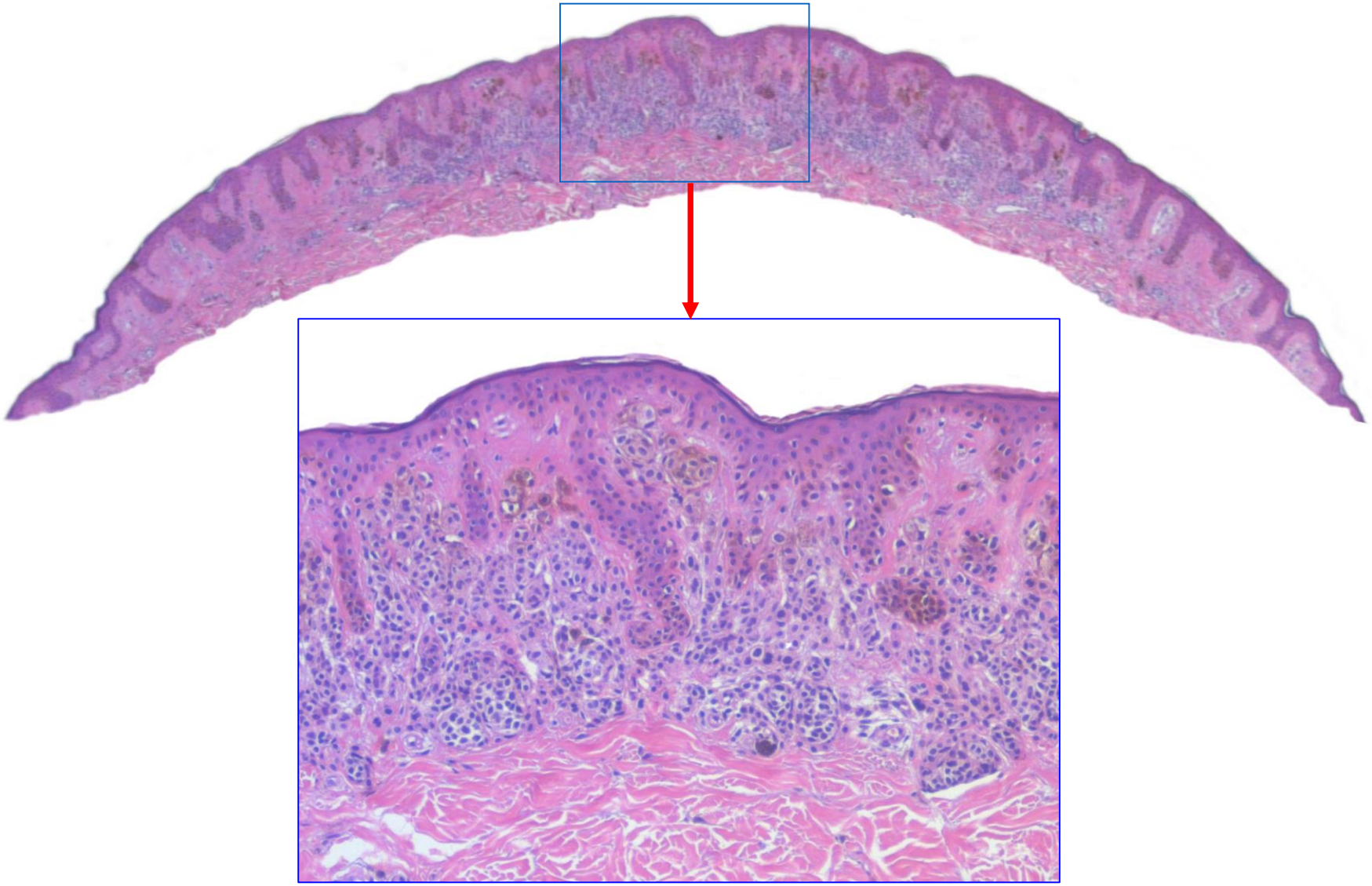
Results: Increased odds of histopathologic misdiagnosis were associated with punch biopsy (OR, 16.6; 95% CI, 10-27) ($P<.001$) and shave biopsy (OR, 2.6; 95% CI, 1.2-5.7) ($P=.02$) compared with excisional biopsy. Punch biopsy was associated with increased odds of misdiagnosis with an adverse outcome (OR, 20; 95% CI, 10-41) ($P<.001$). Other factors associated with increased odds of misdiagnosis included acral lentiginous melanoma (OR, 5.1; 95% CI, 2-13) ($P<.001$), desmoplastic melanoma (OR, 3.8; 95% CI, 1.1-13.0) ($P=.03$), and nevoid melanoma (OR, 28.4; 95% CI, 7-115) ($P<.001$). Punch biopsy (OR, 5.1; 95% CI, 3.4-7.6) ($P<.001$) and shave biopsy (OR, 2.3; 95% CI, 1.5-3.6) ($P<.001$) had increased odds of microstaging inaccuracy over excisional biopsy. Tumor thickness was the most important determinant of microstaging inaccuracy when partial biopsy was used (odds of significant microstaging inaccuracy increased 1.8-fold for every 1 mm increase in tumor thickness; 95% CI, 1.4-2.4) ($P<.001$).

Conclusions: Among melanoma seen at a tertiary referral center, histopathologic misdiagnosis is more common for melanomas that have been assessed with punch and shave biopsy than with excisional biopsy. Regardless of biopsy method, adverse outcomes due to misdiagnosis may occur. However, such adverse events are more commonly associated with punch biopsy than with shave and excisional biopsy. The use of punch and shave biopsy also leads to increased microstaging inaccuracy.

Arch Dermatol. 2010;146(3):234-239

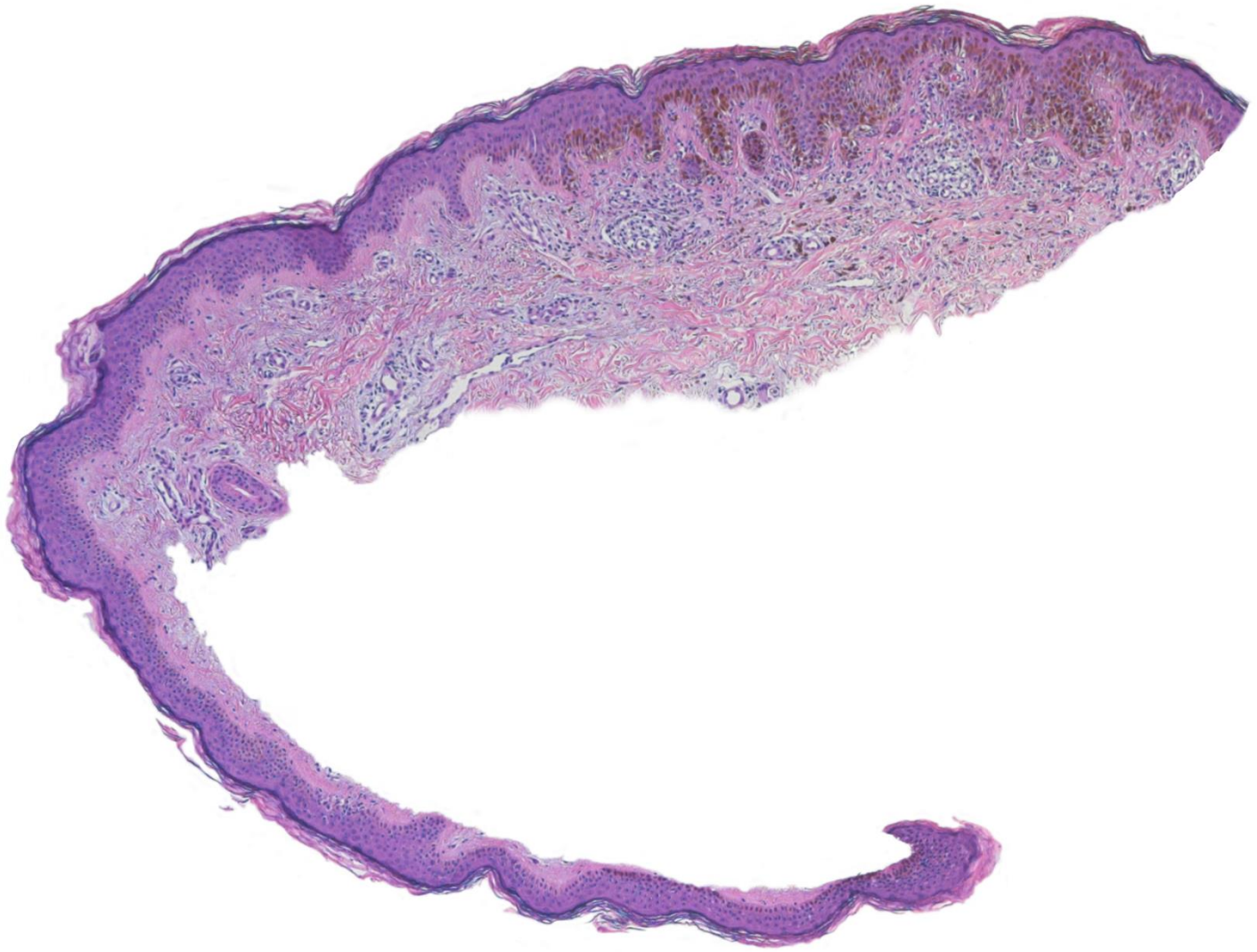
The only *"prospective case series"* concerning *"the impact of partial biopsy on histopathologic diagnosis of cutaneous melanoma"* was published by an Australian group a few years ago and found that *"increased odds of histopathologic misdiagnosis were associated with punch biopsy … and shave biopsy … compared with excisional biopsy."*

The disregard for this important issue is deplorable because the sobering state of diagnostic accuracy could be improved by relatively simple measures.

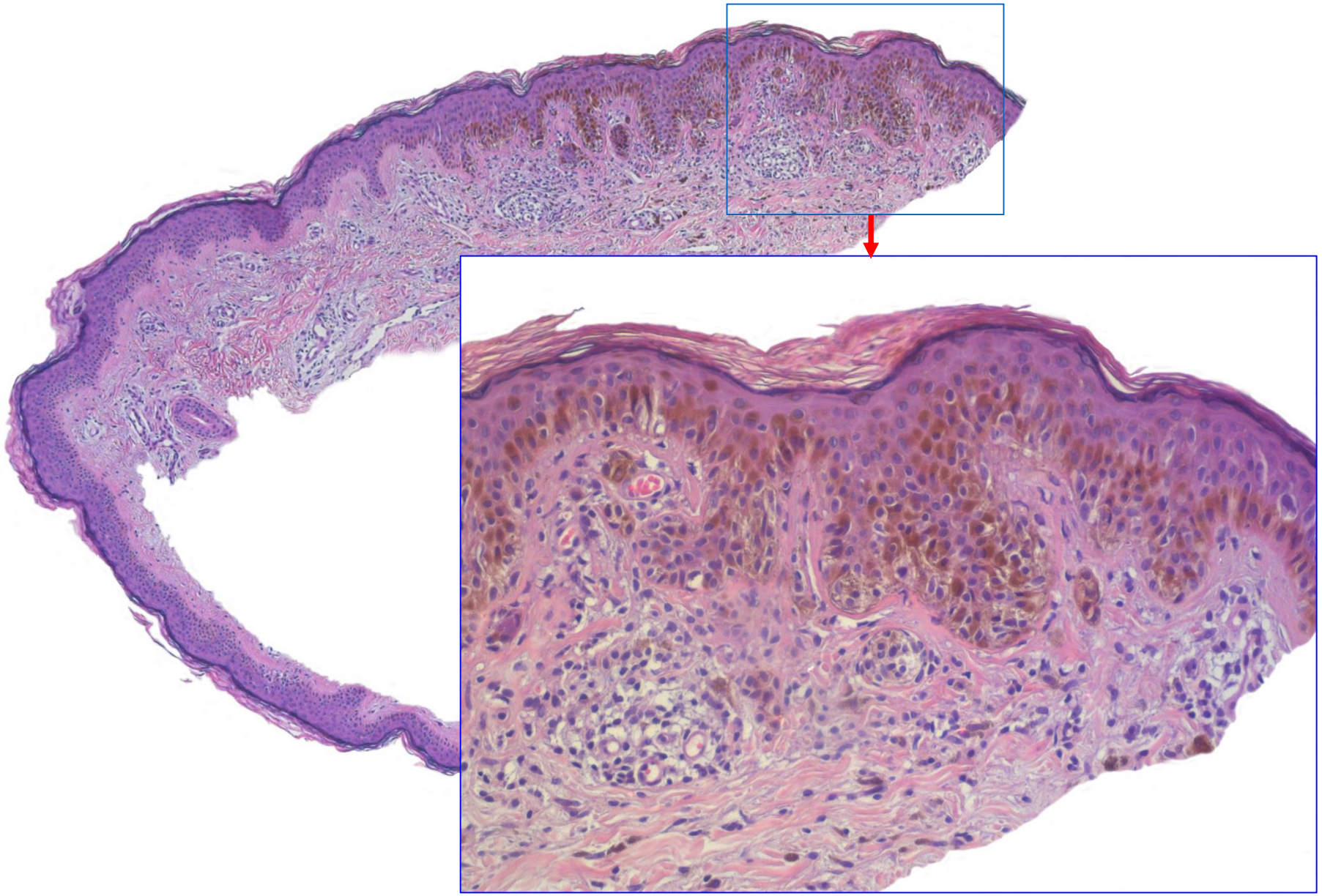


First, if feasible, lesions should be excised completely with a narrow margin of healthy skin. If this is done, diagnosis is not impaired at all by the technique of biopsy, and complete removal is usually easy in small lesions.

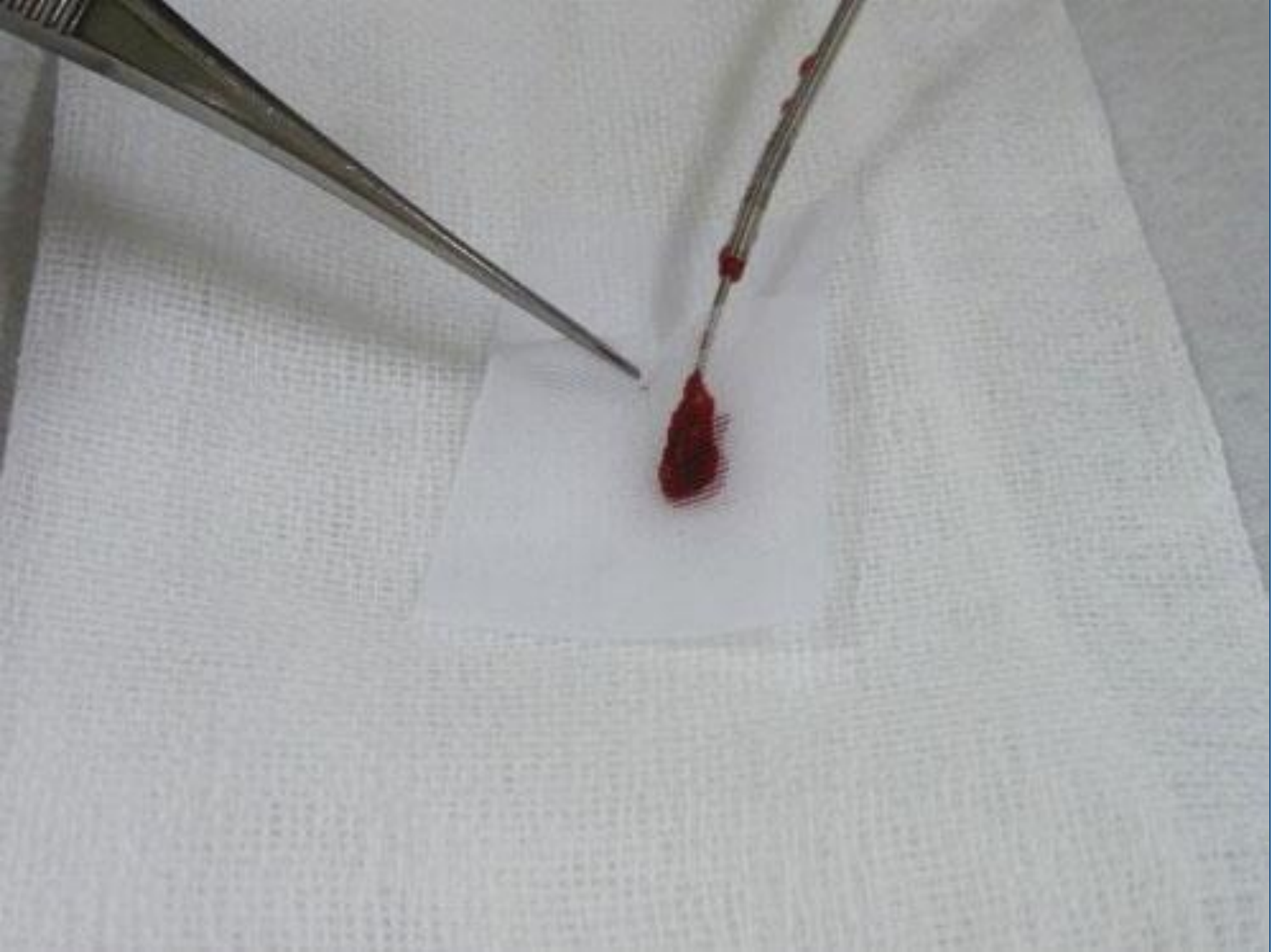
One problem with thin-shaved biopsy specimens is their tendency to curl during fixation because of shrinkage of the dermis. This may result in improper orientation and subsequent tangential sections



that fail to reveal the true surgical margins and compromise the assessment of criteria for diagnosis. In this specimen,



the border cannot be assessed, and without those nests in the dermis, one might be tempted to invoke the diagnosis of melanoma in situ because of some melanocytes above the junction. In order to prevent specimens from curling,



several techniques have been proposed, such as sticking the tissue to filter paper.

AOK | LKK | BKK | IKK | VdAK | AEV | Knappschaft

Name, Vorname des Versicherten [redacted]

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Kassen-Nr. | Versicherten-Nr. | Status

Vertragsarzt-Nr. | VK gültig bis | Datum [redacted]

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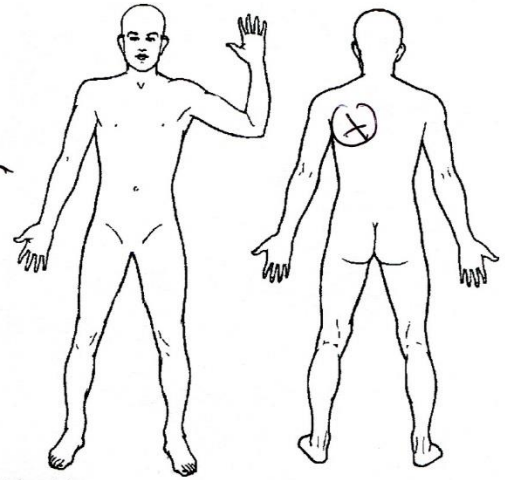
Naevus vs. Melanom



Lokalisation

Vorbehandlung

seit 2 Jahren Veränderungen

Ø 2 cm

- ☐ Ausschluss von Malignität
- ☐ Schnittrandkontrolle
- ☐ Komplette Randschnittdiagnostik
- ☐ Immunfluoreszenz
- ☐ Molekulare Diagnostik (PCR/FISH)
- ☐ Zusatzinformationen (Literatur etc.)
- ☐ Nachrichtlich an: _____

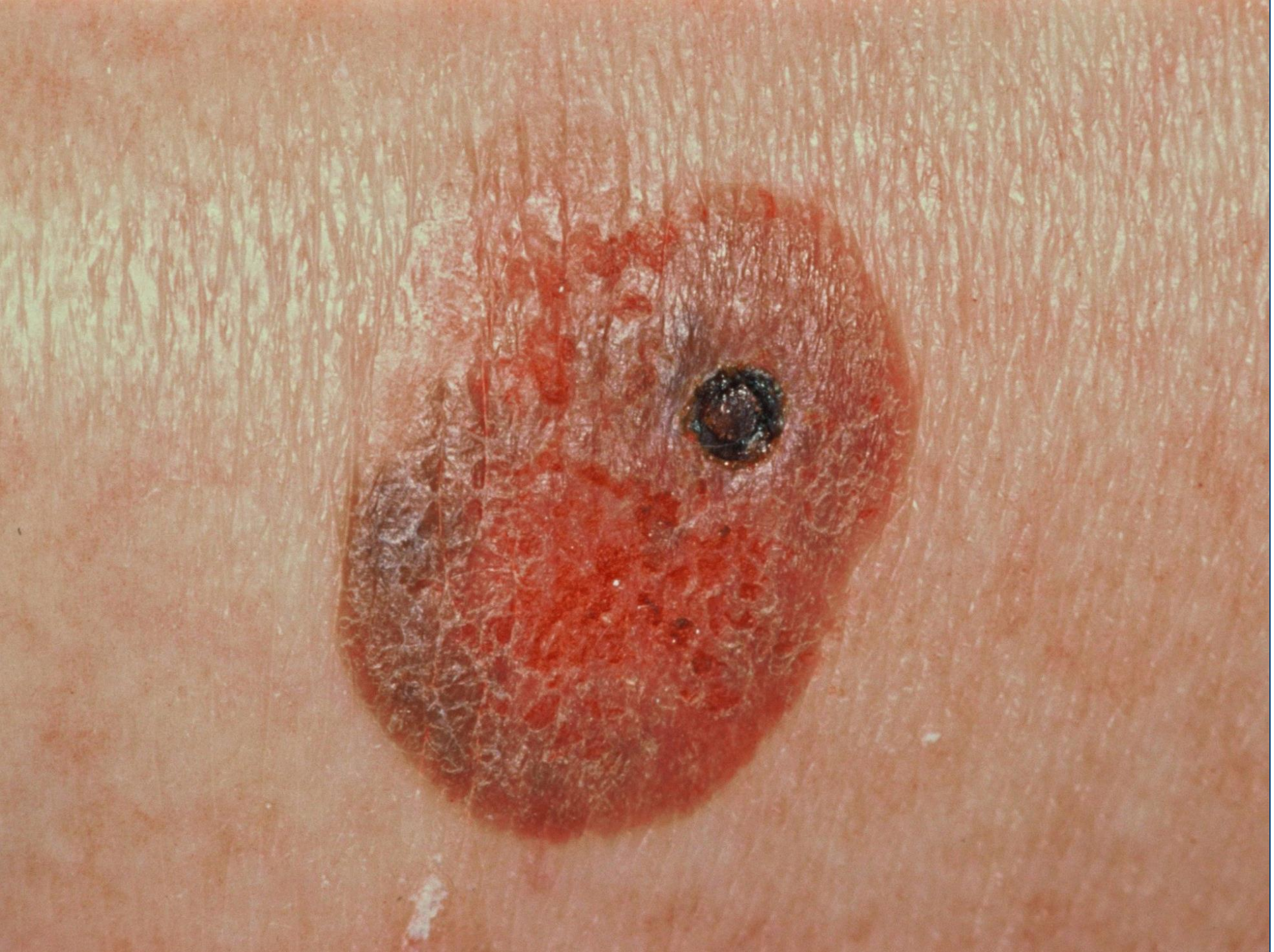
- ☐ Totalexzision
- ☐ Teilexzision
- ☒ PE
- ☐ Shave
- ☐ Kürettage
- ☐ Kauter

Stempel

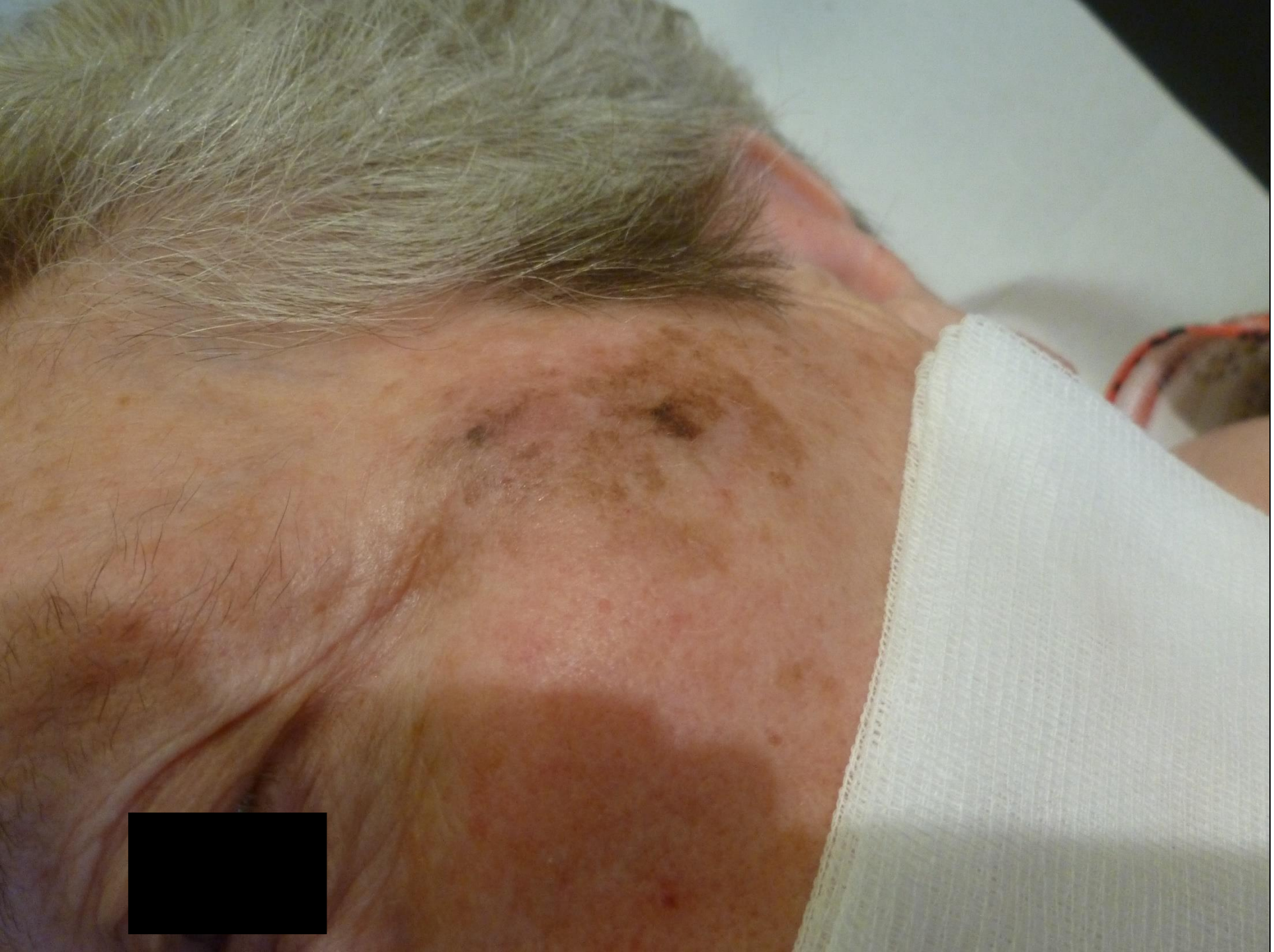
Antrag auf histologisches Gutachten

Unterschrift des überweisenden Arztes

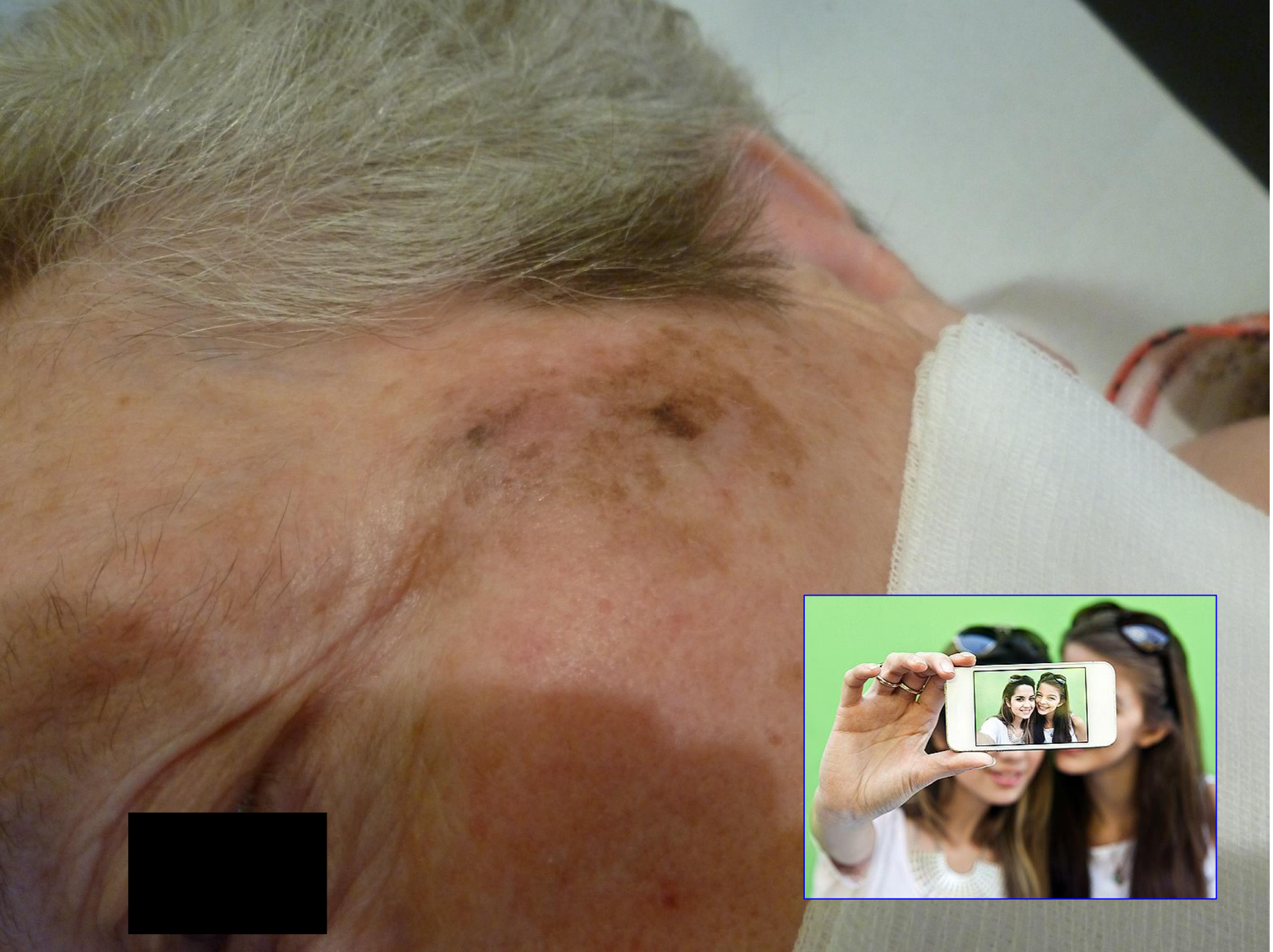
If lesions cannot be excised completely, the sacrifice of diagnostic criteria should be compensated for by describing the lesion on the request slip, especially its size. It makes a big difference



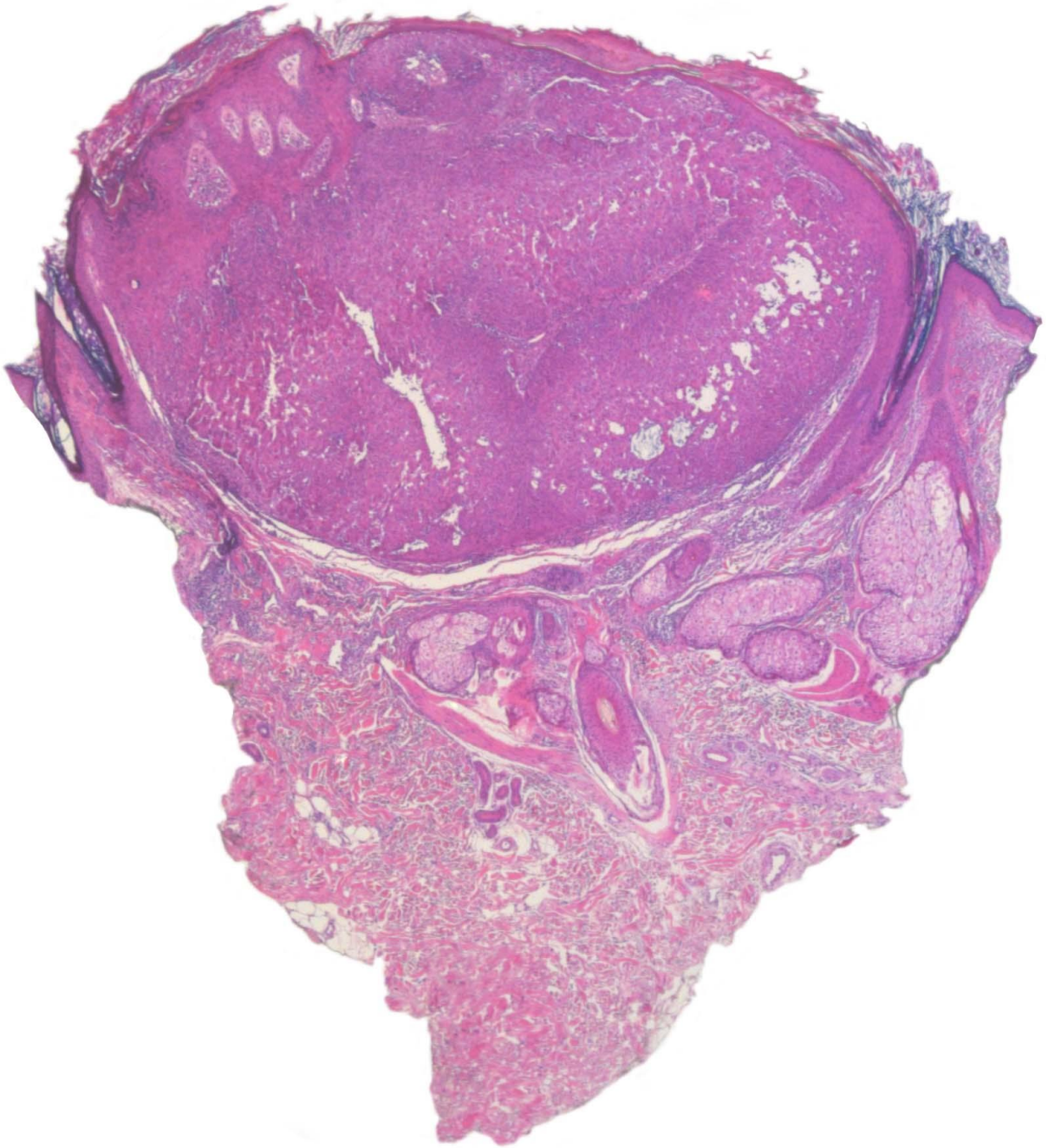
whether a punch biopsy specimen comes from a lesion measuring 4 mm or 3 cm in diameter.



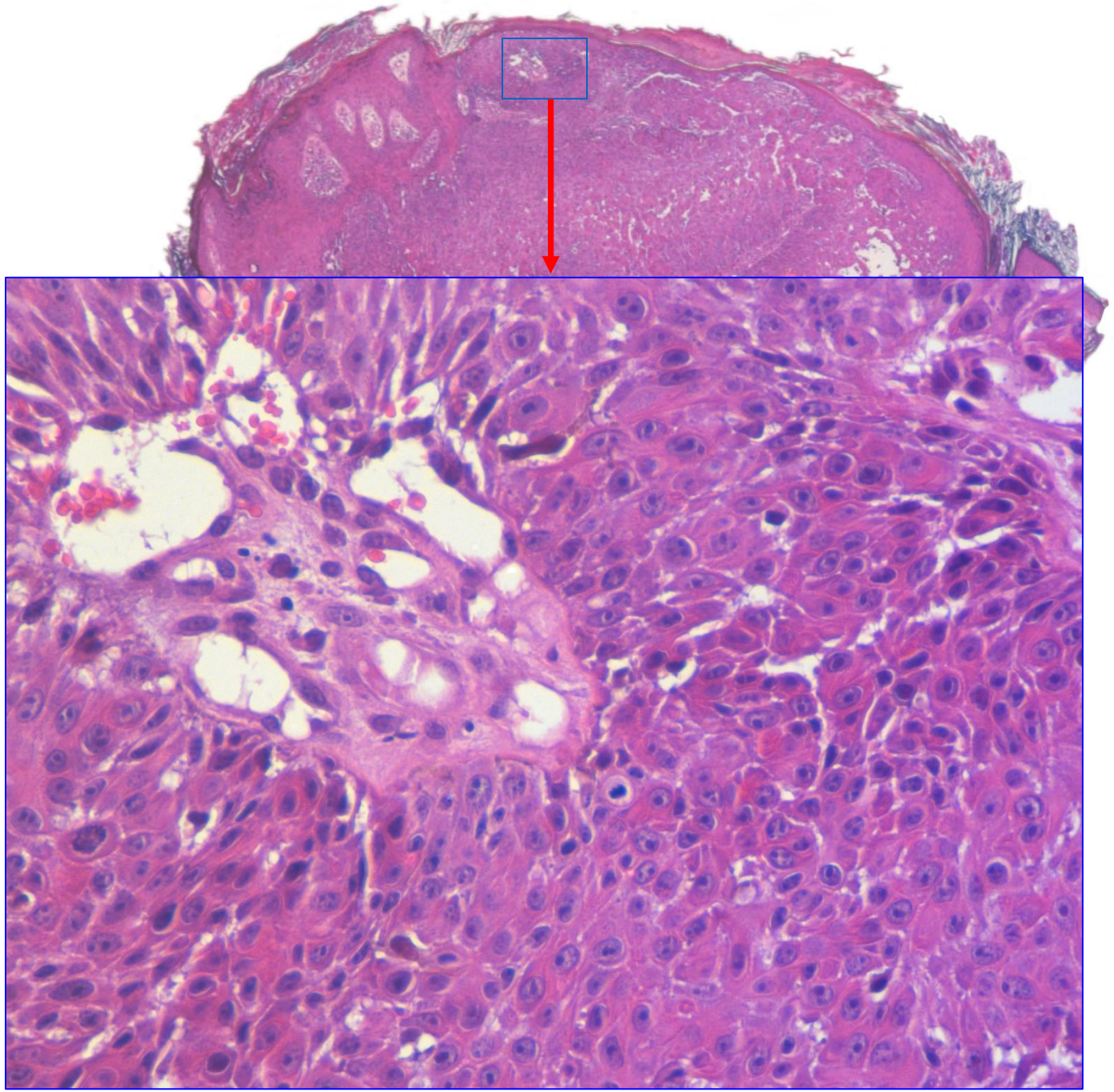
If possible, a clinical picture should be provided.



In the era of smartphones and selfies, it should not cause insurmountable problems to send a clinical picture for every incisional biopsy specimen.



A major problem complicating histopathologic diagnosis is irritation of lesions. As in this wart,



irritation may result in considerable nuclear atypia and mitotic figures, and in superficial biopsy specimens, those changes may cause overdiagnosis as squamous cell carcinoma.

The American Journal of Dermatopathology 17(1): 1–6, 1995

UV-Irradiated Melanocytic Nevi Simulating Melanoma In Situ

Michael Tronnier, M.D., and Helmut H. Wolff, M.D.

A causative role of UV light in the development of melanocytic neoplasms has often been suggested. In order to investigate the short-term effects of UV light on melanocytic nevi, the morphological and immunohistochemical changes in nevi after a single UV irradiation are studied in 12 nevi from 10 patients and compared with the nonirradiated part of the same nevus. After irradiation more melanocytes above the dermal-epidermal junction are observed in seven nevi, simulating a melanoma in situ in three nevi. Moreover, a marked increase in the expression of HMB-45 is found after irradiation in all investigated nevi, indicating an activation of the melanocytes and active melanosome formation. The metabolic activity correlates with the ultrastructural findings, which show a large cytoplasm, hypertrophic Golgi apparatus, abundant mitochondria, and an increased number of melanosomes of different stages. One week after irradiation, no increase in the proliferative activity of the melanocytes is found. The morphological and immunohistochemical changes after one low dose of UV irradiation should be considered in the differential diagnosis of pigmented skin lesions. The UV-irradiated nevus should be added to the list of so-called simulators of malignant melanoma.
Key Words: UV irradiation—Melanocytic nevus—Simulators of melanoma—Ultrastructure—Immunohistochemistry.

Whereas most melanocytic lesions can be easily differentiated by histomorphological criteria, in some conditions melanocytic nevi display morphological changes that simulate melanomas. Those benign simulators of melanoma (e.g., recurrent nevi, genital nevi, and nevi of the newborn) have been summarized as "pseudomelanomas" (1). To consider those simulators as a differential diagnosis, it is necessary to know their histopathological features, and it is helpful to have the exact clinical data of the patients.

Histological investigations of a large number of nevi have shown seasonal variations in their morphological features (2,3). Those findings have indicated an influence of the sunlight on nevi. Because of the possible causative role of UV light in the induction and promotion of melanocytic tumors (4,5), we investigated the short-term effect of UV irradiation on benign melanocytic nevi. The purpose of this article is to report the morphological changes in nevi that may appear after a single irradiation with UV light.

Irritation of melanocytic lesions is an even greater problem. For example, brief ultraviolet irradiation has been shown

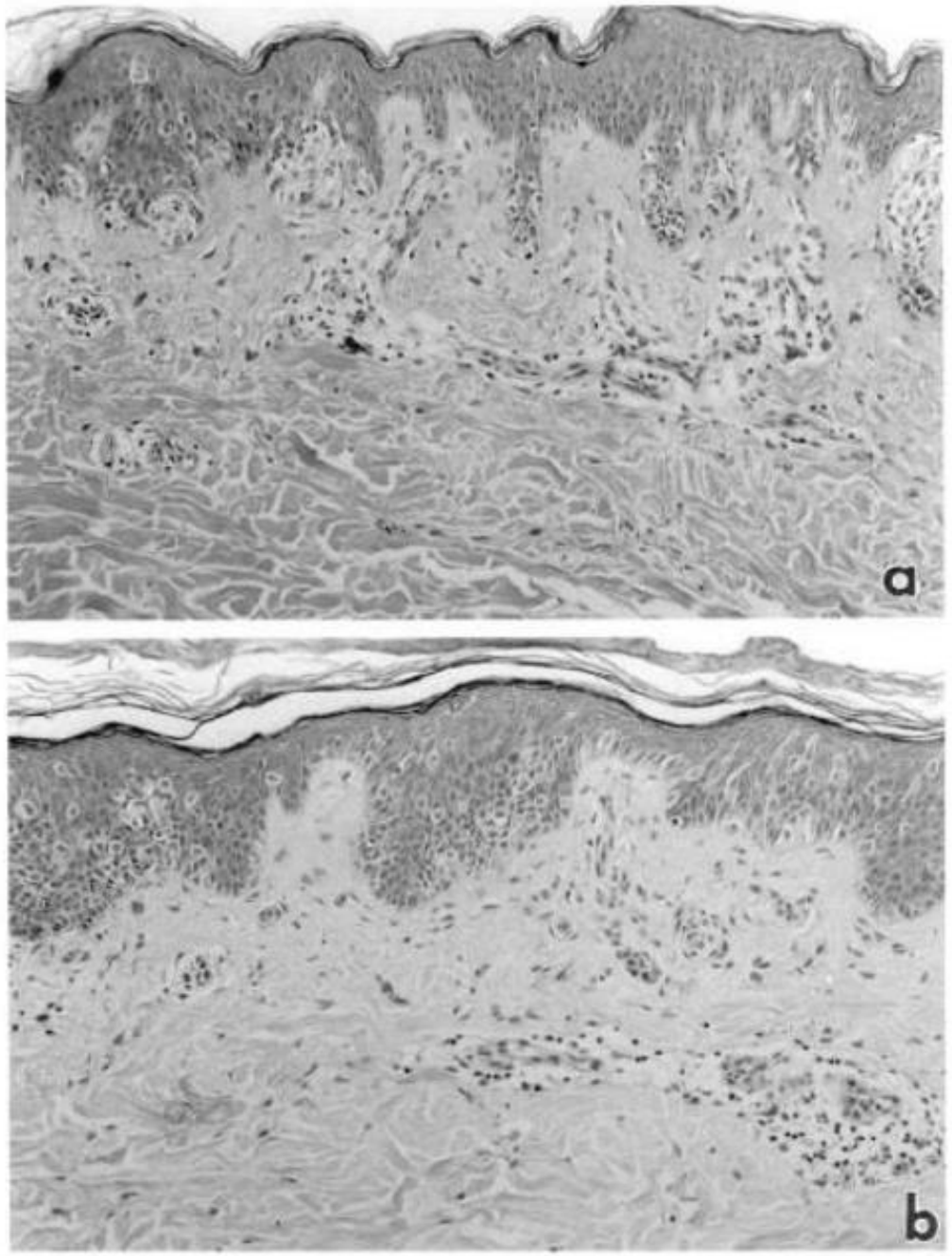
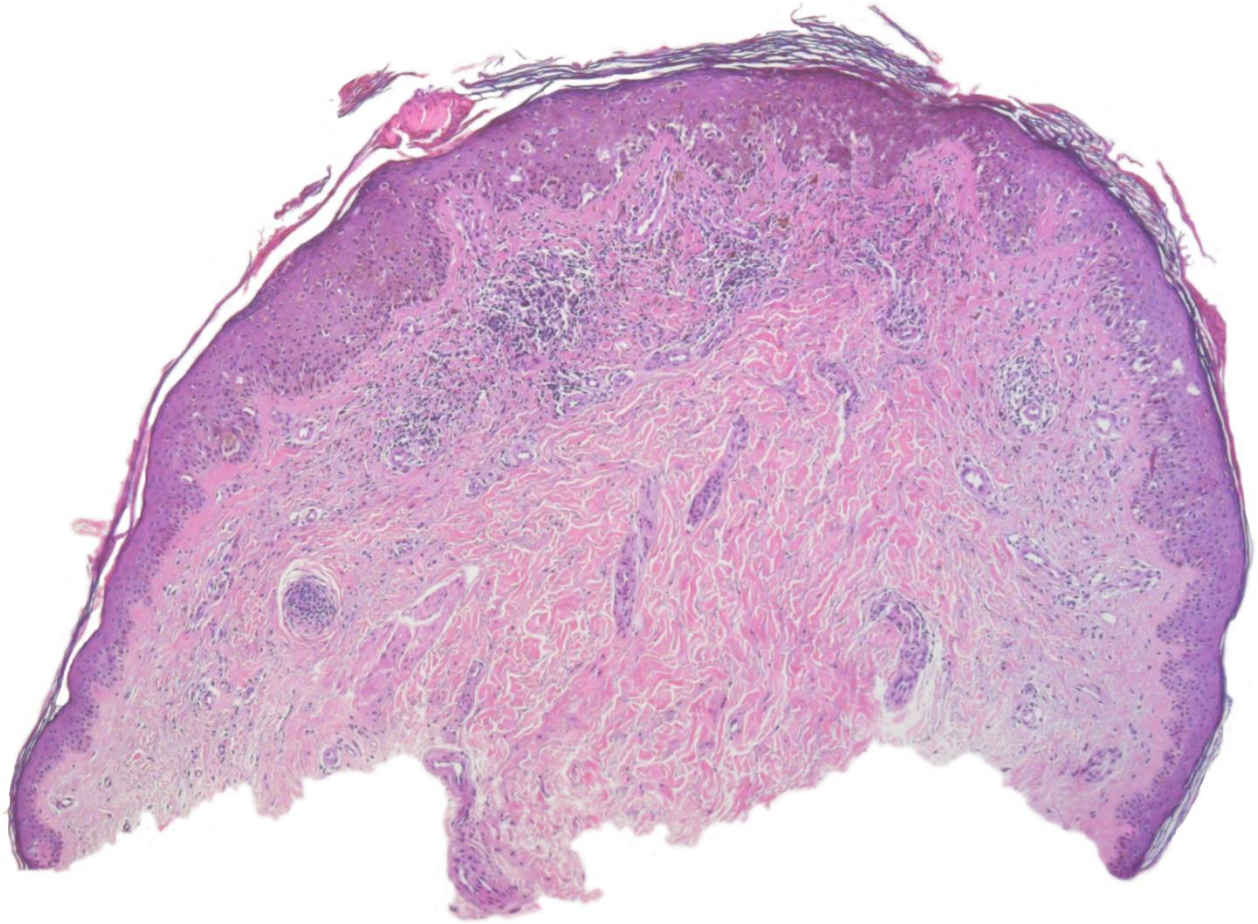
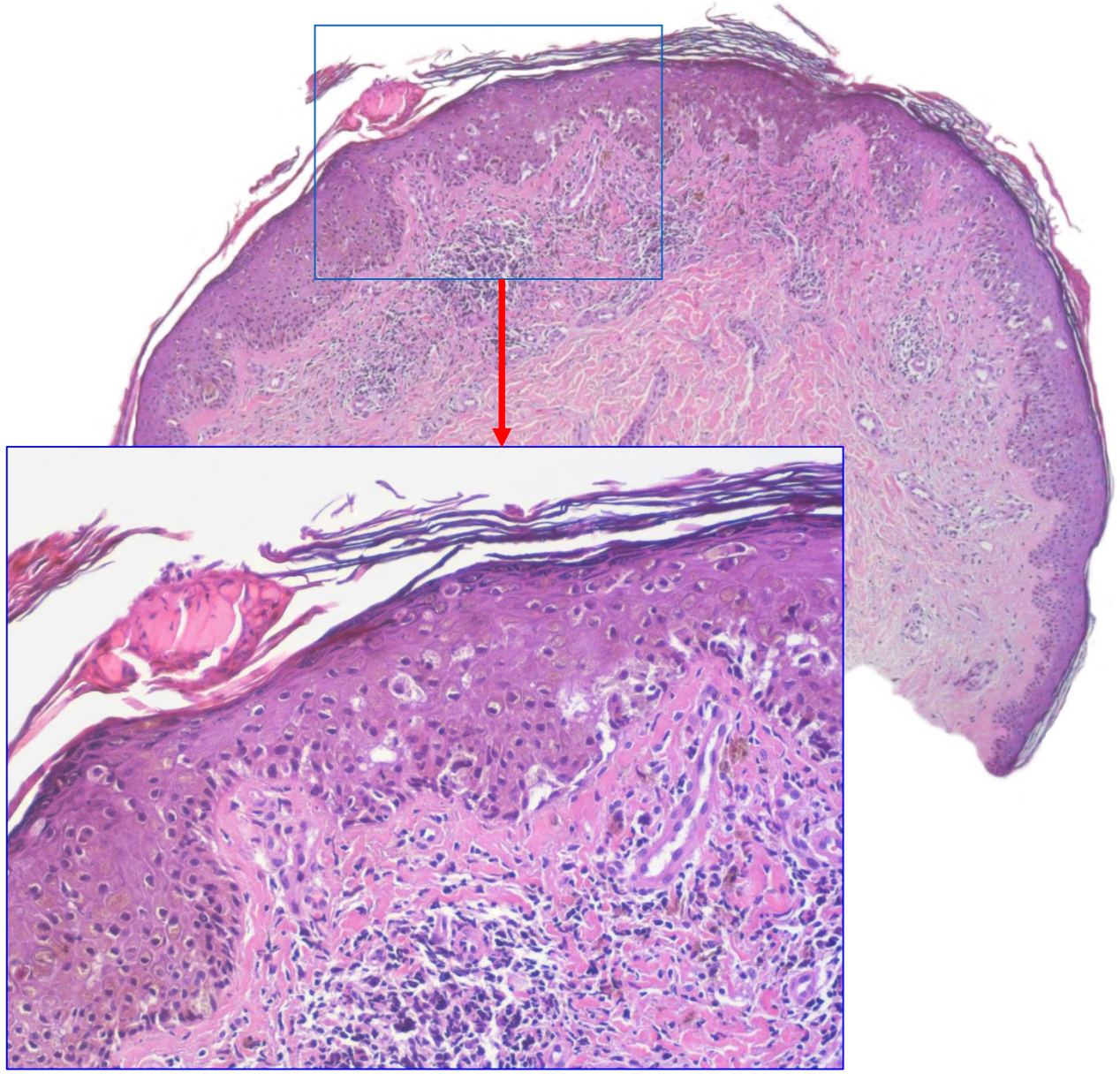


FIG. 1. (a) MN/nUV. Single and nested melanocytes at the dermal-epidermal junction. **(b)** MN/+UV. Same nevus. Many, mostly single melanocytes are seen above the dermal-epidermal junction, simulating a melanoma in situ. Parakeratosis is evident above the regular basket-weave horny layer. There is a slightly pronounced perivascular inflammatory infiltrate.

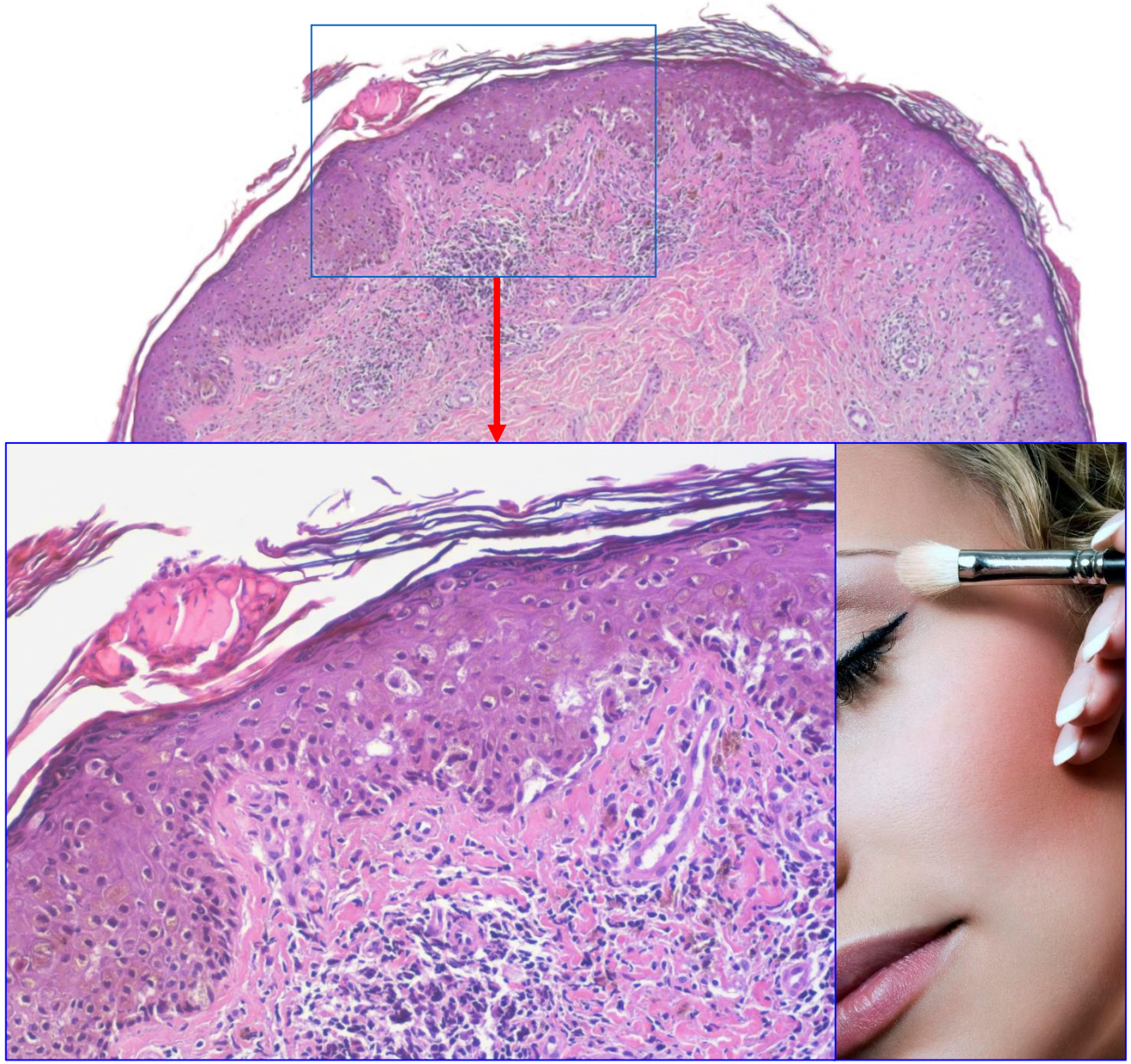
to evoke changes reminiscent of melanoma in situ in banal melanocytic nevi, as demonstrated by pictures of the protected and the irradiated half of a nevus. So much for the grading of nevi and for the claim that it has any biological significance. Of course, the biologic potential of a lesion is not changed by a few hours in the sun,



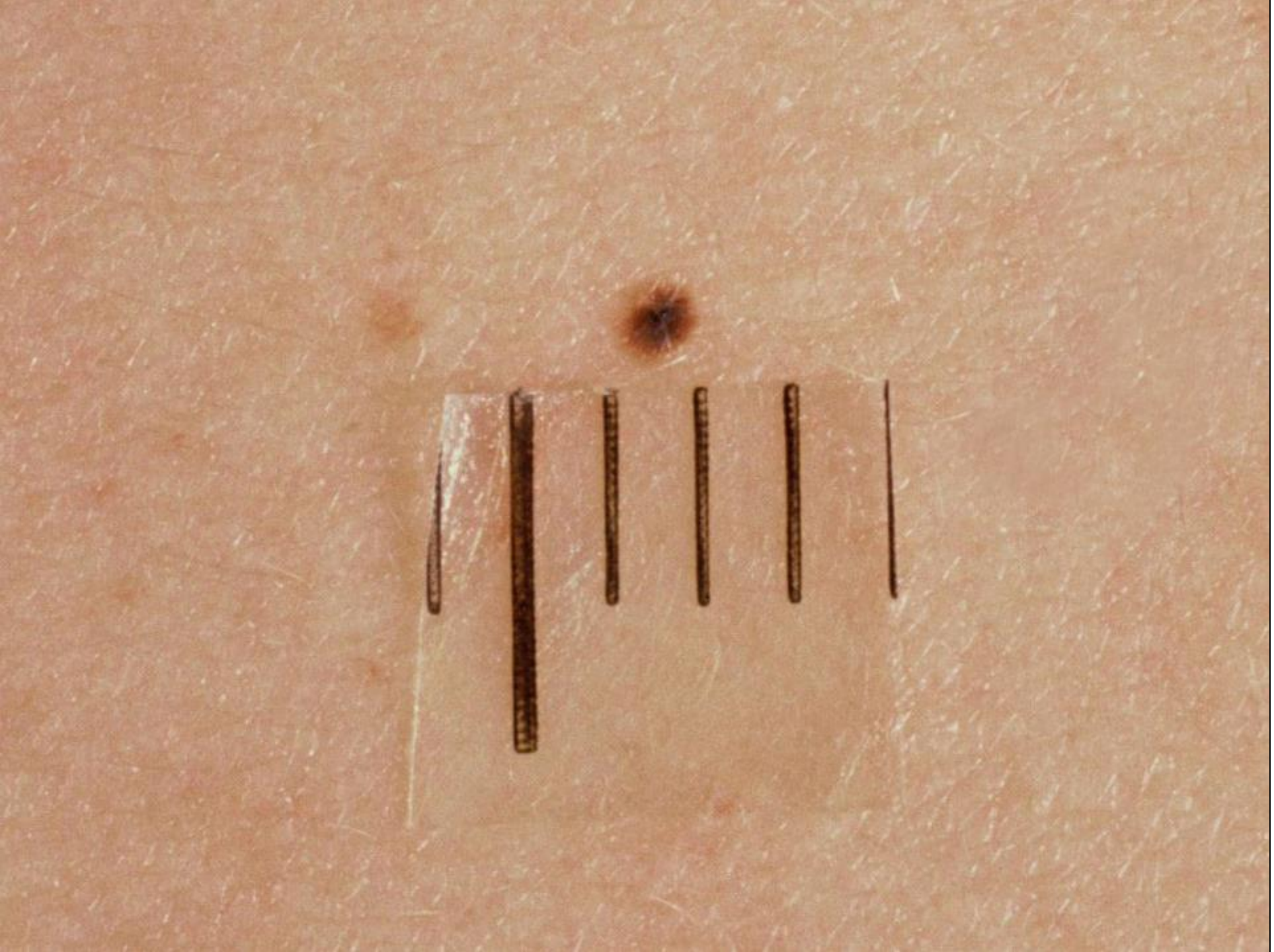
but its presentation may be, and sometimes dramatically so. In this irritated nevus covered by a scale crust,



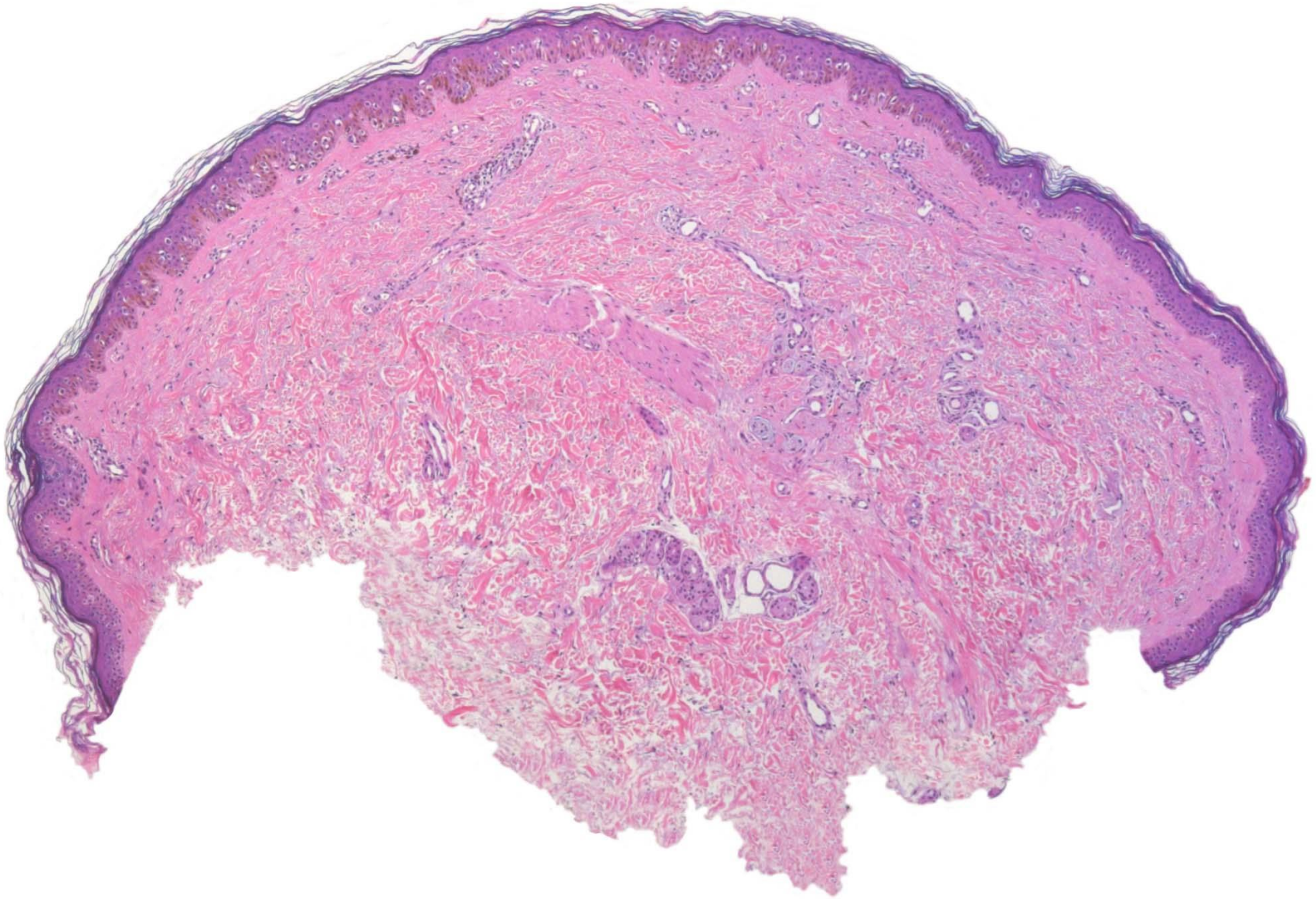
there are many largish melanocytes in all reaches of the epidermis, and the diagnosis of melanoma in situ would be made were it not for its small size, symmetry, and sharp circumscription. Because of those problems,



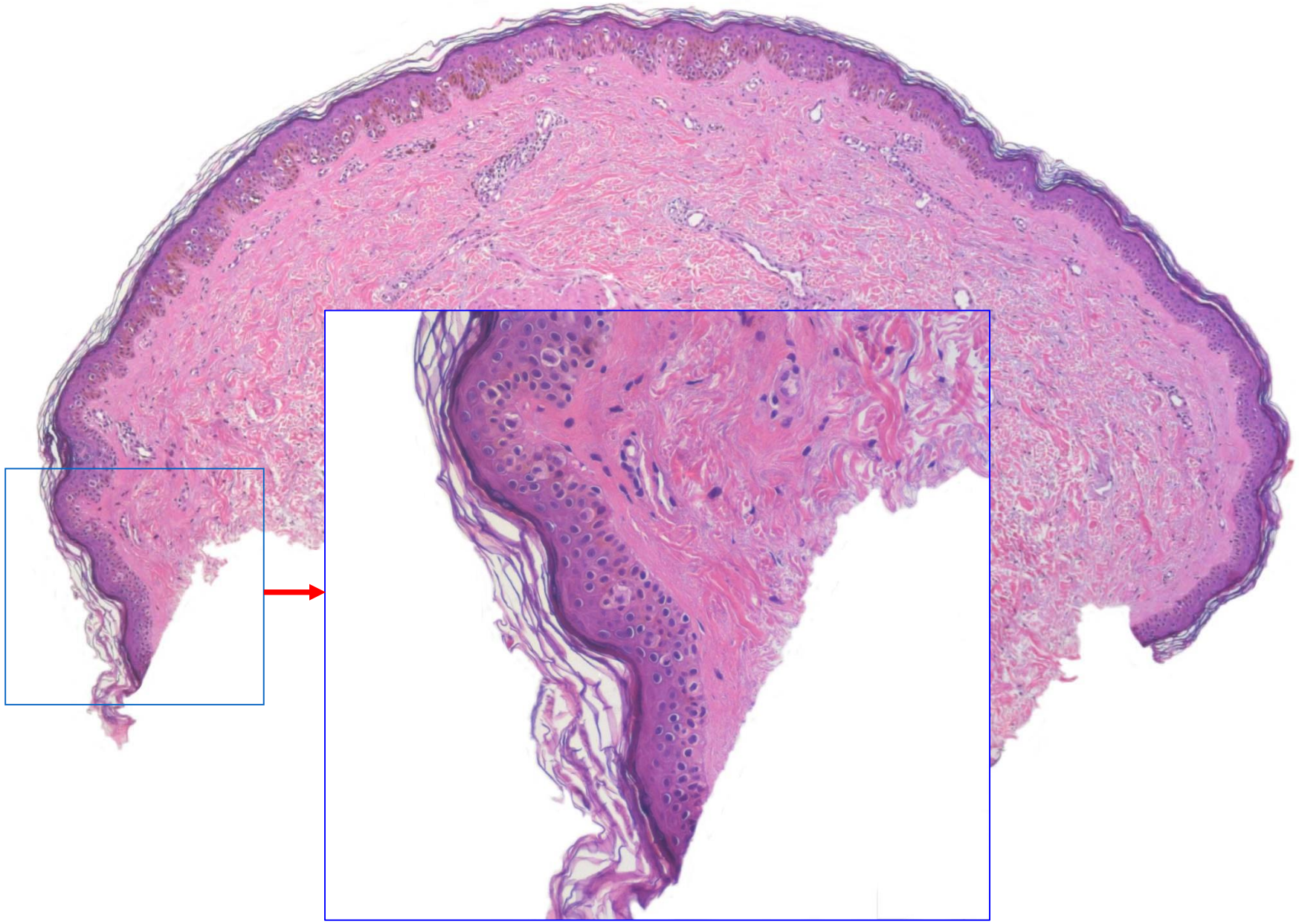
irritated lesions should be granted a make-up before being biopsied. If they are covered for two weeks and treated with some antimicrobial or antiphlogistic cream, problems in diagnosis can be evaded.



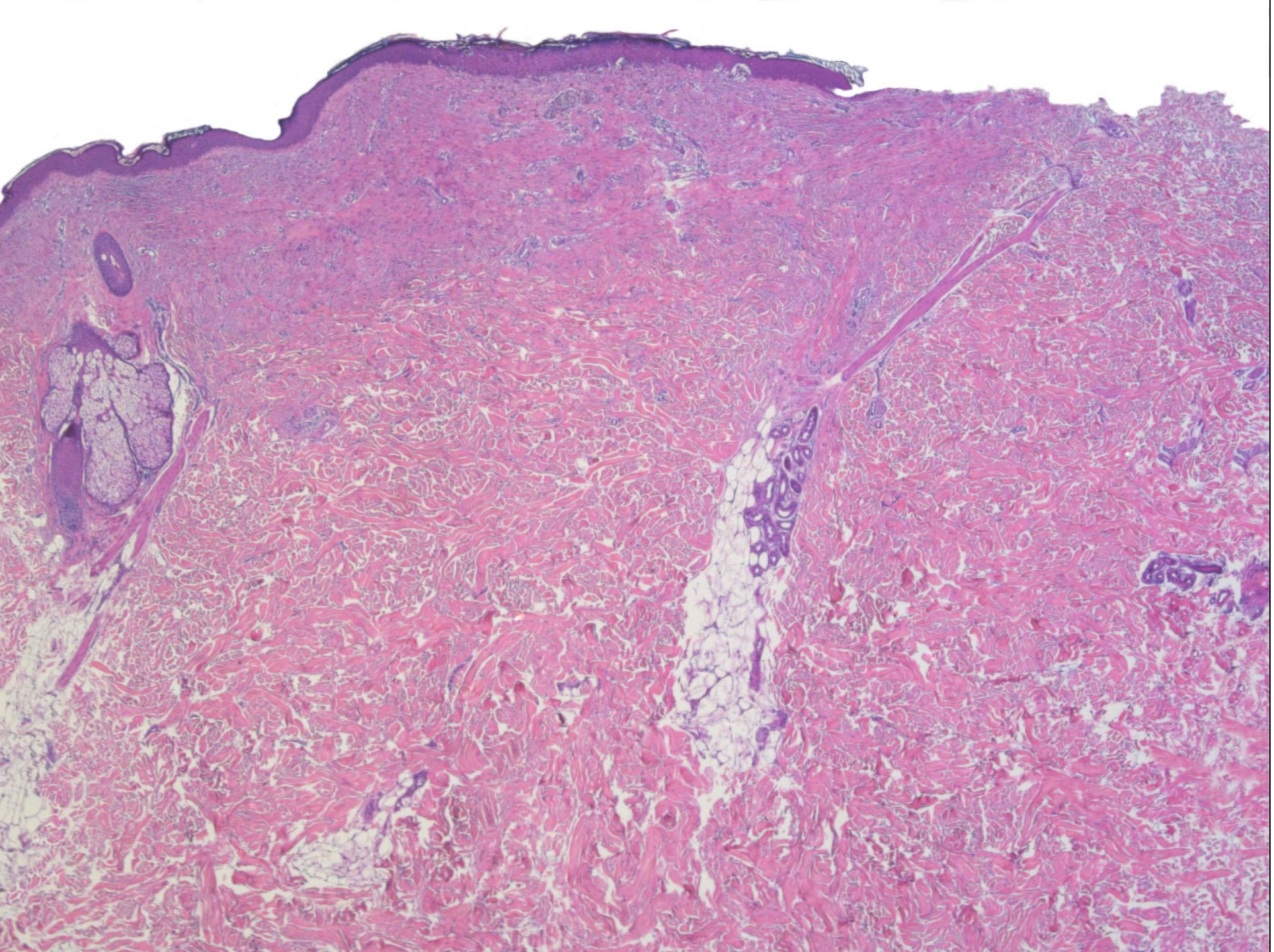
Last, one should refrain from biopsy of very small pigmented lesions. There are two reasons. First, most of them will turn out to be nevi so that the biopsy was unnecessary.



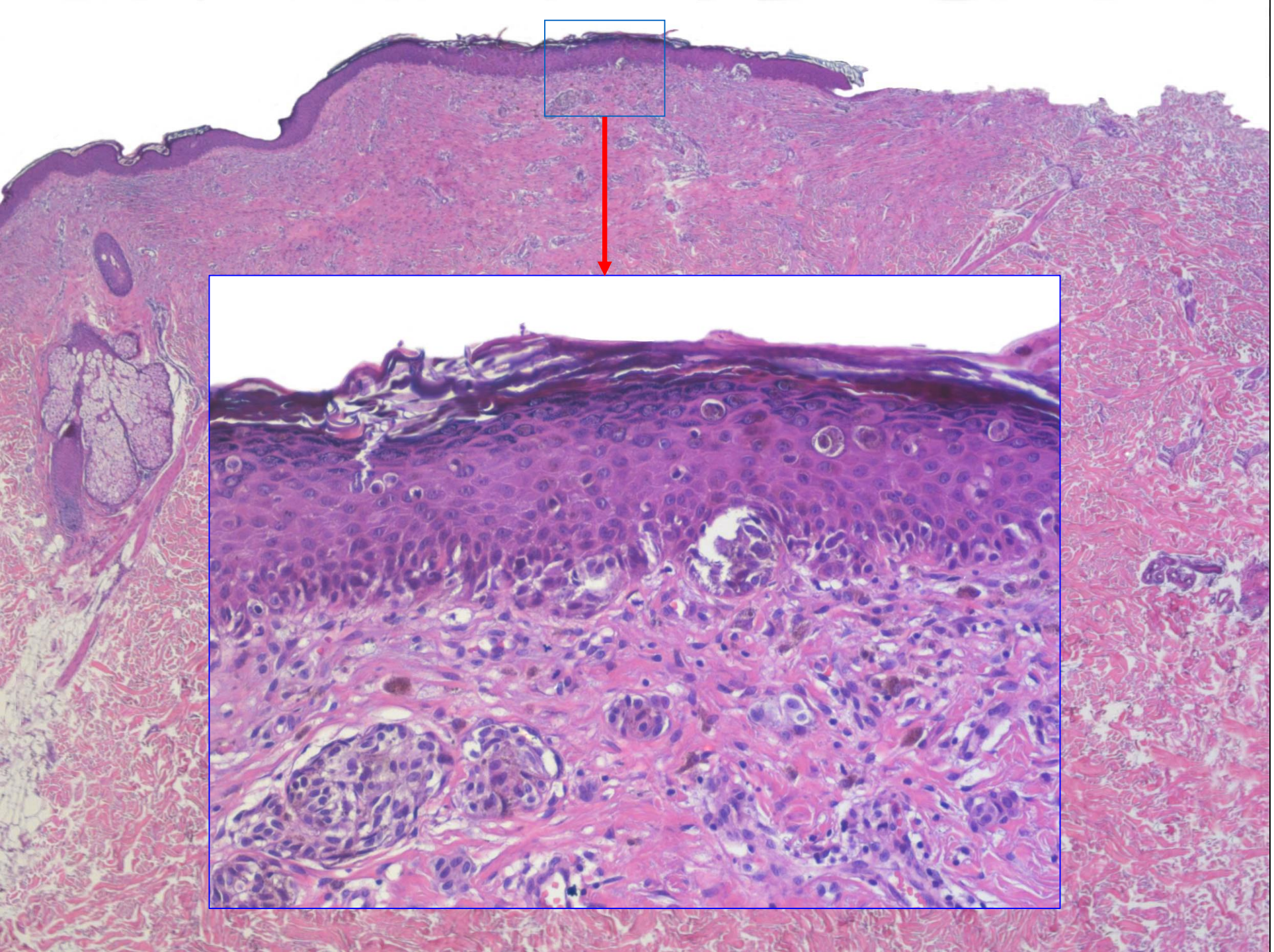
Second, they may not yet exhibit changes that allow a histopathologic diagnosis to be made with confidence, such as discrete nests at the junction in nevi or irregularly distributed melanocytes in melanomas.



If such a lesion extends to lateral margins and an incipient melanoma cannot be excluded, a re-excision will be performed,



and all too often, it does not resolve the conundrum either because nothing or only a small portion of the lesion is left.



In the latter instance, those remnants are often difficult to interpret because of signs of irritation caused by the previous procedure, such as melanocytes in the upper reaches of the epidermis. As a consequence, the patient may have undergone two unnecessary excisions and may carry the false label of possible melanoma for his lifetime.

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.

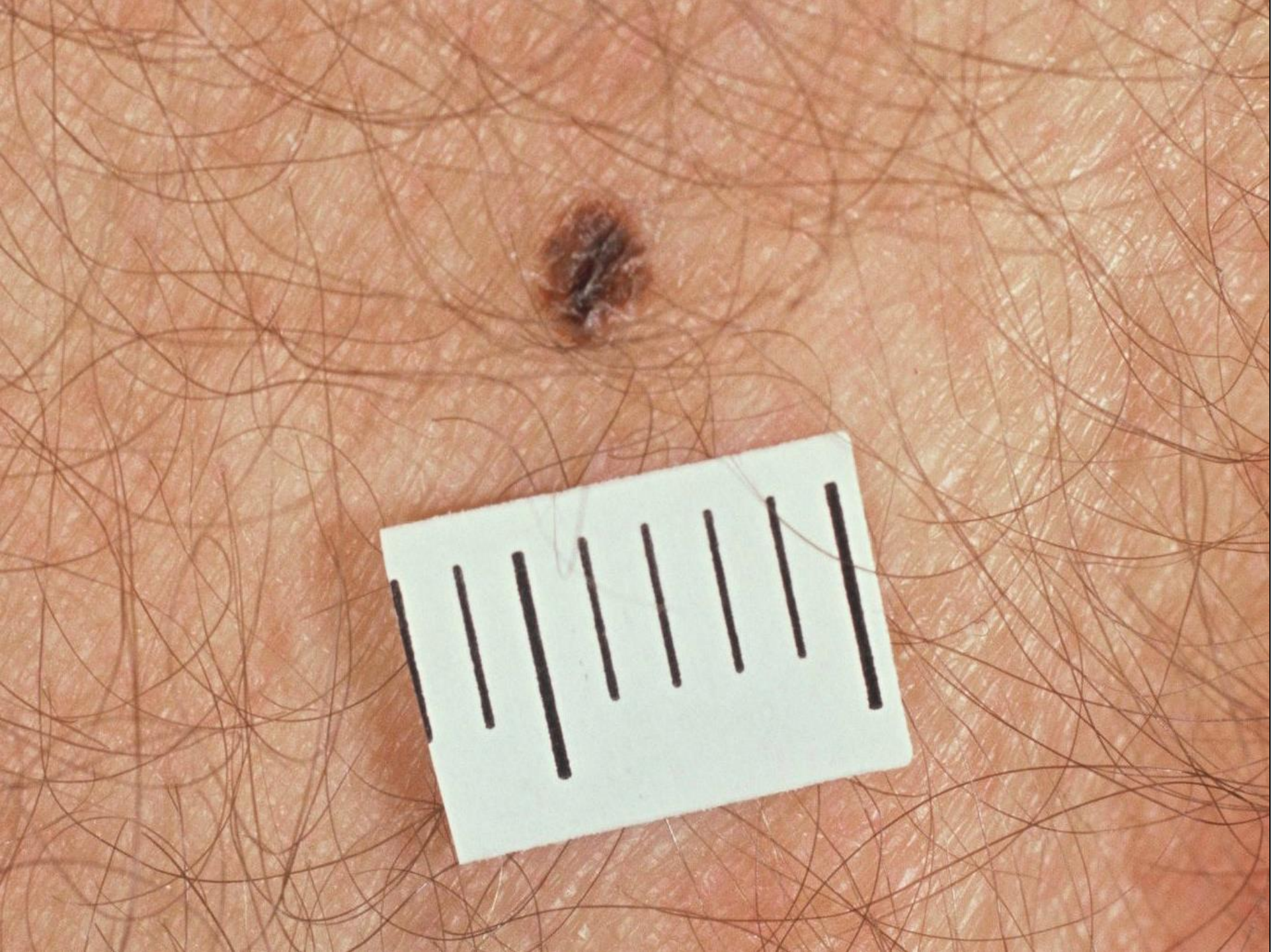
Methods: We searched for all biopsy specimens that were performed because of clinical suspicion of melanoma in 2013. Characteristics of the patient, lesion, and clinician performing the biopsy, and the final pathology diagnosis were recorded.

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%).

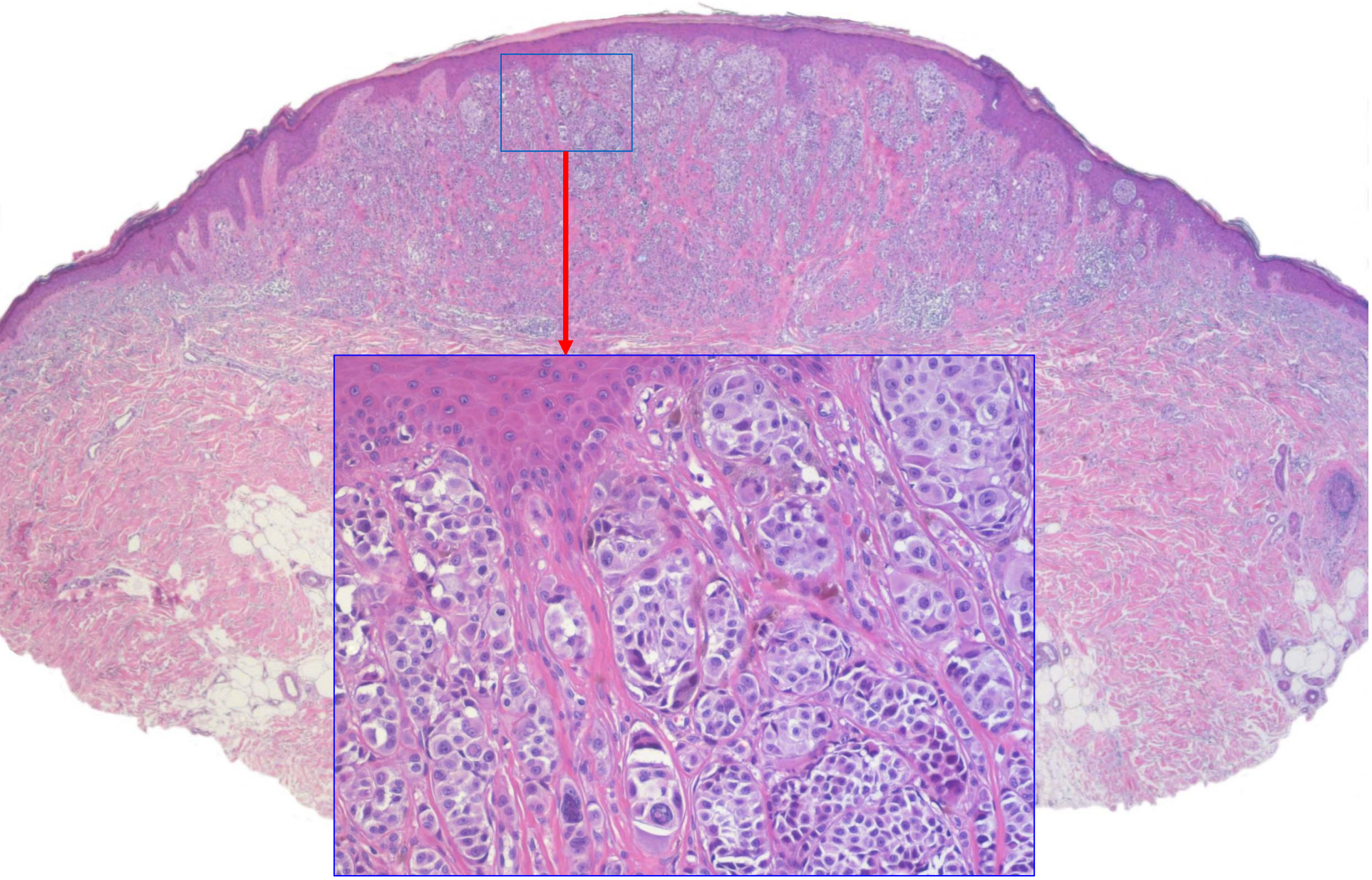
Limitations: Factors influencing the decision to biopsy a lesion may be difficult to evaluate retrospectively.

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.)

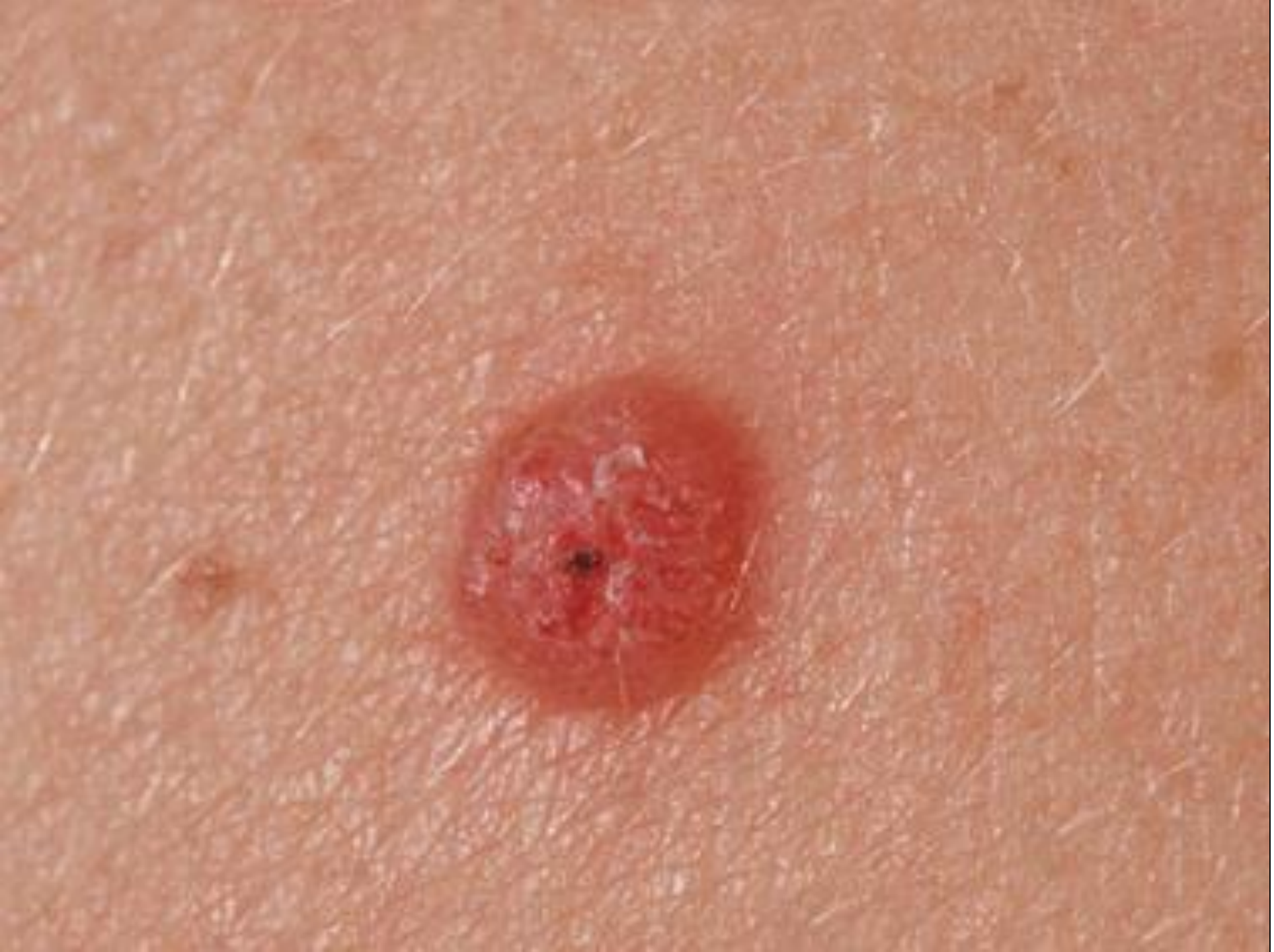
It has recently been suggested to postpone biopsies until lesions have reached a diameter of 6 mm because *"lesions larger than 6mm in size had higher positive predictive value"* but are nearly always thin and cured permanently by simple excision.



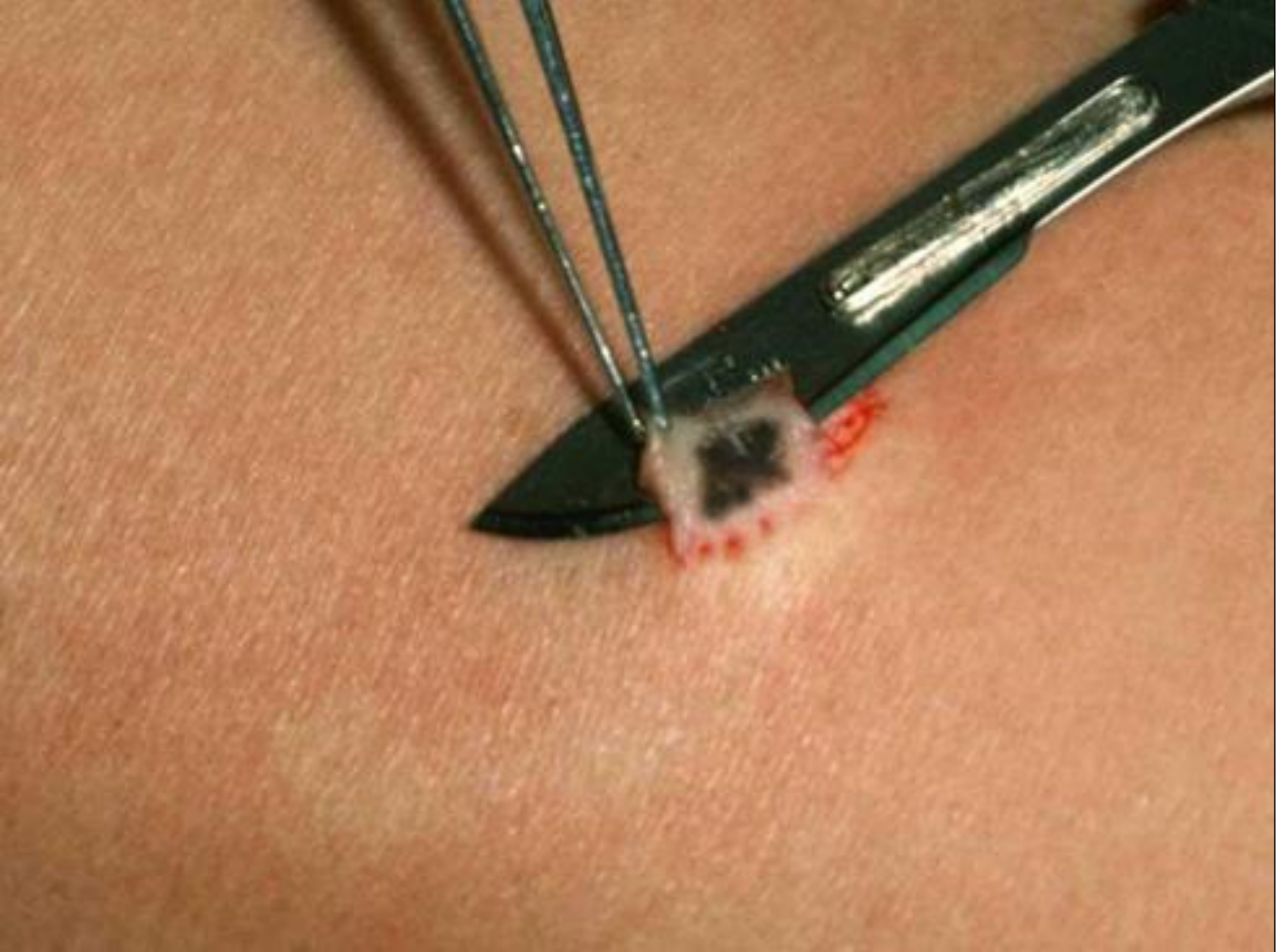
According to that suggestion, lesions like this one would not be biopsied. I acknowledge that clinical diagnosis can be improved by techniques such as dermatoscopy, and if criteria for malignancy are fulfilled clearly by smaller lesions, they should be excised.



I also acknowledge that melanomas with a small diameter may occasionally be life-threatening because they acquire considerable depth early-on.



Those exceptional lesions tend to be domed and scarcely pigmented, and they are the ones to focus on. If there are hints of pigment they should be excised without hesitation.



In general, however, patients would be served by a shift in management to fewer, but better biopsies. This would greatly alleviate the serious problem

Overdiagnosis of Skin Cancer

- Excisional biopsy, if feasible
- Clinical description or clinical picture for incisional biopsies
- No biopsy of irritated lesions
- No biopsy of very small lesions

of overdiagnosis of skin cancer. More specifically, some principles should be observed: perform excisional biopsies, if feasible; provide a clinical description or clinical picture for incisional biopsies; do not biopsy irritated lesions; do not biopsy very small lesions.