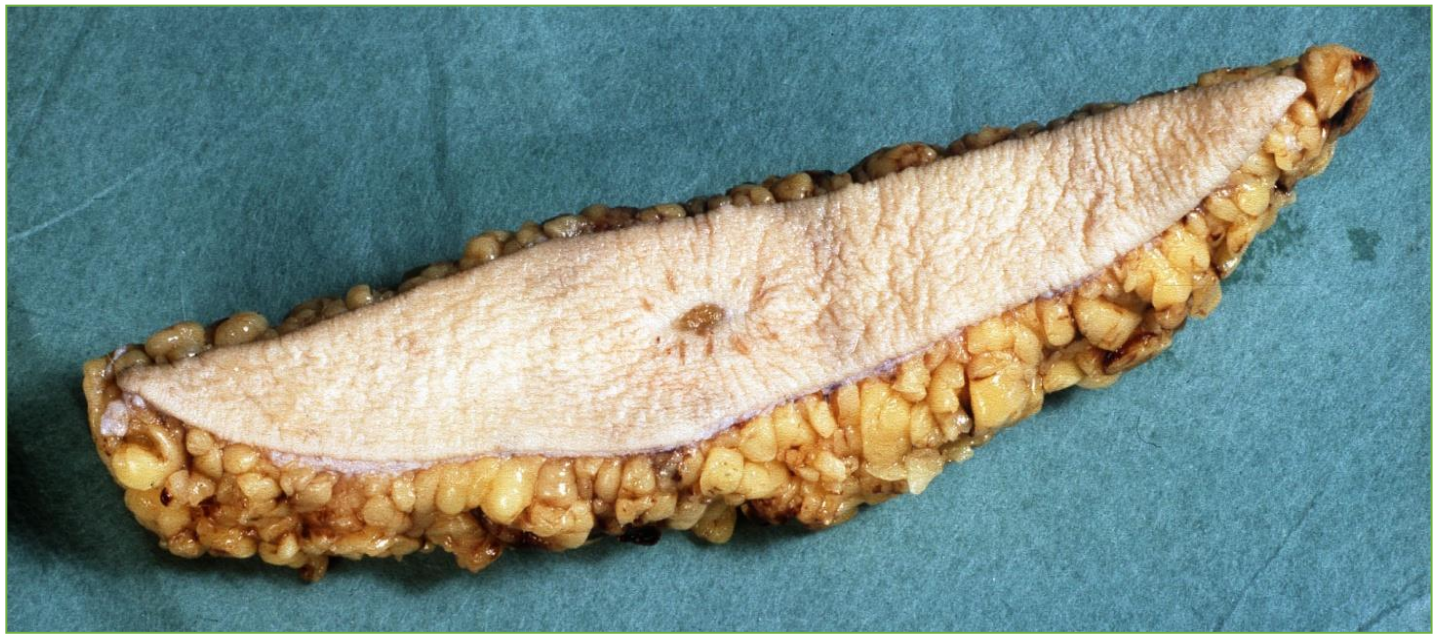
Margins of Excision in Melanoma



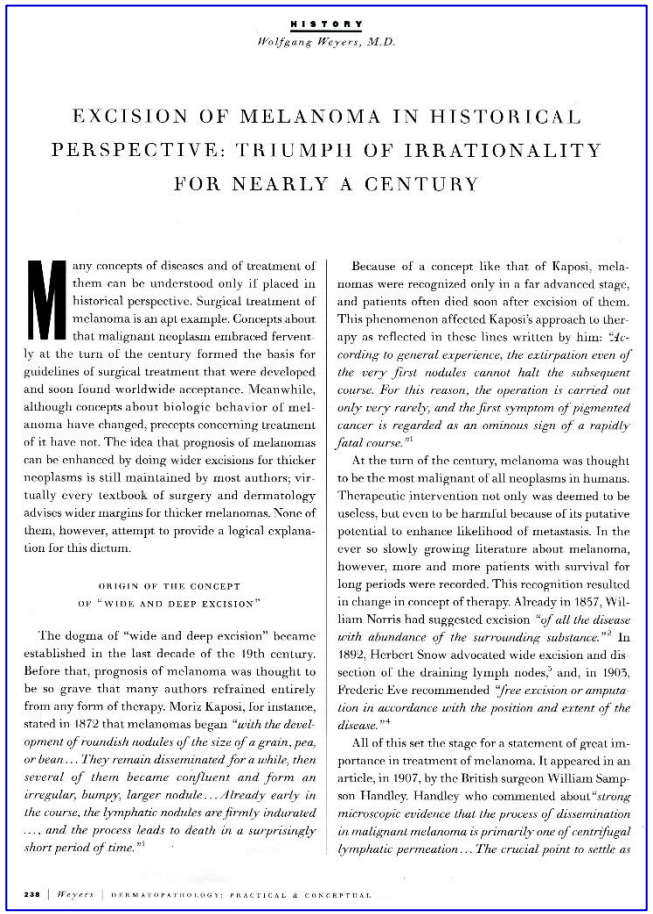
W. Weyers
Center for Dermatopathology Freiburg, Germany

Margins of Excision in Melanoma

73rd Brazilian Congress of Dermatology, Curitiba, September 6-9, 2018

The subject of this lecture is old, and it has been addressed time and again. There are basically no new aspects, and what I am going to say about *"margins of excision in melanoma"* today

Margins of Excision in Melanoma



HISTORY

Wolfgang Weyers, M.D.

EXCISION OF MELANOMA IN HISTORICAL PERSPECTIVE: TRIUMPH OF IRRATIONALITY FOR NEARLY A CENTURY

Many concepts of diseases and of treatment of them can be understood only if placed in historical perspective. Surgical treatment of melanoma is an apt example. Concepts about that malignant neoplasm embraced fervently at the turn of the century formed the basis for guidelines of surgical treatment that were developed and soon found worldwide acceptance. Meanwhile, although concepts about biologic behavior of melanoma have changed, precepts concerning treatment of it have not. The idea that prognosis of melanomas can be enhanced by doing wider excisions for thicker neoplasms is still maintained by most authors; virtually every textbook of surgery and dermatology advises wider margins for thicker melanomas. None of them, however, attempt to provide a logical explanation for this dictum.

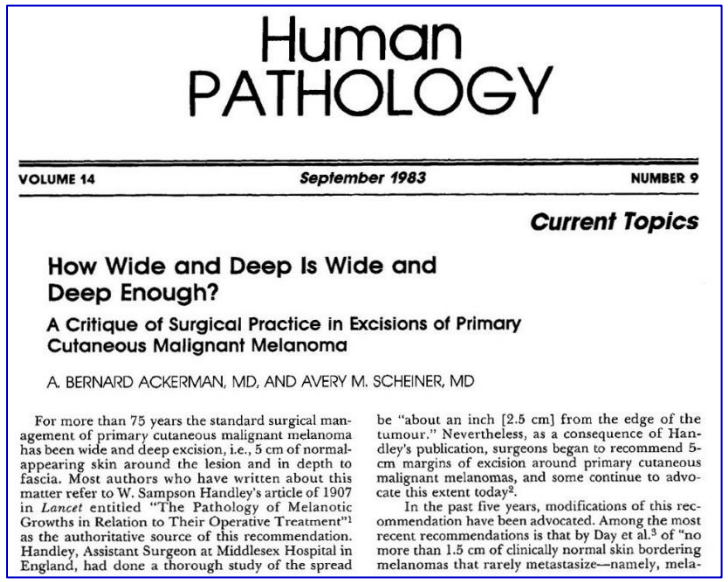
ORIGIN OF THE CONCEPT OF "WIDE AND DEEP EXCISION"

The dogma of "wide and deep excision" became established in the last decade of the 19th century. Before that, prognosis of melanoma was thought to be so grave that many authors refrained entirely from any form of therapy. Moriz Kaposi, for instance, stated in 1872 that melanomas began *"with the development of roundish nodules of the size of a grain, pea, or bean… They remain disseminated for a while, then several of them became confluent and form an irregular, bumpy, larger nodule… Already early in the course, the lymphatic nodules are firmly indurated …, and the process leads to death in a surprisingly short period of time."*[1]

Because of a concept like that of Kaposi, melanomas were recognized only in a far advanced stage, and patients often died soon after excision of them. This phenomenon affected Kaposi's approach to therapy as reflected in these lines written by him: *"According to general experience, the extirpation even of the very first nodules cannot halt the subsequent course. For this reason, the operation is carried out only very rarely, and the first symptom of pigmented cancer is regarded as an ominous sign of a rapidly fatal course."*[1]

At the turn of the century, melanoma was thought to be the most malignant of all neoplasms in humans. Therapeutic intervention not only was deemed to be useless, but even to be harmful because of its putative potential to enhance likelihood of metastasis. In the ever so slowly growing literature about melanoma, however, more and more patients with survival for long periods were recorded. This recognition resulted in change in concept of therapy. Already in 1857, William Norris had suggested excision *"of all the disease with abundance of the surrounding substance."*[2] In 1892, Herbert Snow advocated wide excision and dissection of the draining lymph nodes,[3] and, in 1905, Frederic Eve recommended *"free excision or amputation in accordance with the position and extent of the disease."*[4]

All of this set the stage for a statement of great importance in treatment of melanoma. It appeared in an article, in 1907, by the British surgeon William Sampson Handley. Handley who commented about *"strong microscopic evidence that the process of dissemination in malignant melanoma is primarily one of centrifugal lymphatic permeation… The crucial point to settle as*



Human PATHOLOGY

VOLUME 14 | September 1983 | NUMBER 9

Current Topics

How Wide and Deep Is Wide and Deep Enough?

A Critique of Surgical Practice in Excisions of Primary Cutaneous Malignant Melanoma

A. BERNARD ACKERMAN, MD, AND AVERY M. SCHEINER, MD

For more than 75 years the standard surgical management of primary cutaneous malignant melanoma has been wide and deep excision, i.e., 5 cm of normal-appearing skin around the lesion and in depth to fascia. Most authors who have written about this matter refer to W. Sampson Handley's article of 1907 in *Lancet* entitled "The Pathology of Melanotic Growths in Relation to Their Operative Treatment"[1] as the authoritative source of this recommendation. Handley, Assistant Surgeon at Middlesex Hospital in England, had done a thorough study of the spread be "about an inch [2.5 cm] from the edge of the tumour." Nevertheless, as a consequence of Handley's publication, surgeons began to recommend 5-cm margins of excision around primary cutaneous malignant melanomas, and some continue to advocate this extent today[2].

In the past five years, modifications of this recommendation have been advocated. Among the most recent recommendations is that by Day et al.[3] of "no more than 1.5 cm of clinically normal skin bordering melanomas that rarely metastasize—namely, mela-

Arbeitsgemeinschaft Dermatologische Onkologie ADO

24. Deutscher Hautkrebskongress

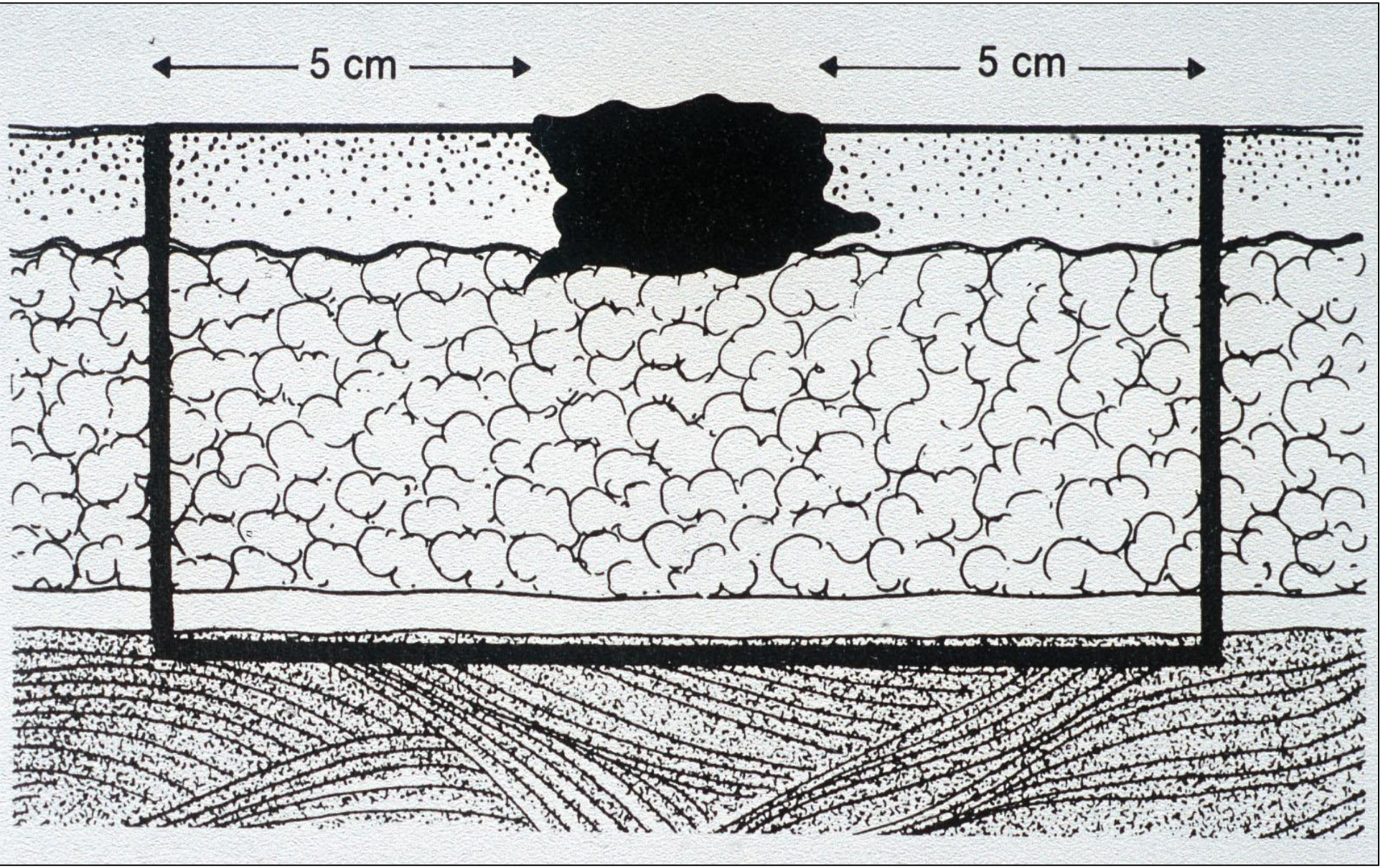
ADO-Jahrestagung

11.–13. September 2014 FRANKFURT AM MAIN

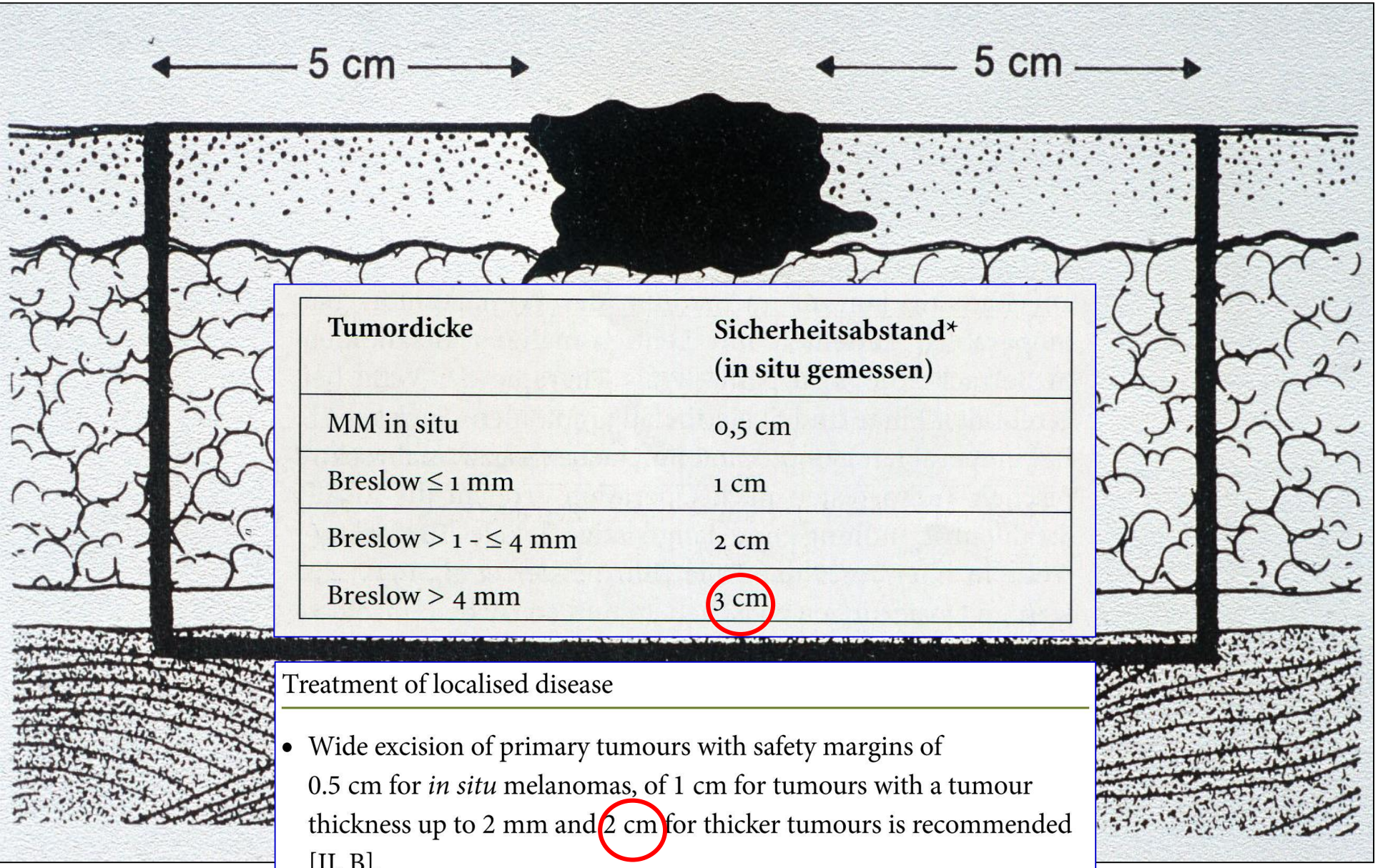
Eine Veranstaltung der Arbeitsgemeinschaft Dermatologische Onkologie der Deutschen Krebsgesellschaft und der Deutschen Dermatologischen Gesellschaft

has been pointed out by myself and others repeatedly in the past 20 years, in articles and at congresses. Why speak about it once again?

Because little has changed, and because recommendations concerning margins of excision in melanoma are among the most shameful chapters in the history of dermatology, a *"triumph of irrationality for nearly a century."*



It is true that guidelines concerning margins have been modified, from 5 cm



Tumordicke	Sicherheitsabstand* (in situ gemessen)
MM in situ	0,5 cm
Breslow ≤ 1 mm	1 cm
Breslow > 1 - ≤ 4 mm	2 cm
Breslow > 4 mm	3 cm

Treatment of localised disease

- Wide excision of primary tumours with safety margins of 0.5 cm for *in situ* melanomas, of 1 cm for tumours with a tumour thickness up to 2 mm and 2 cm for thicker tumours is recommended [II, B].

to 3 cm, and more recently to 2 cm for thicker tumors, but the principle is still the same, namely,

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v126–v132, 2015
doi:10.1093/annonc/mdv297

Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Dummer[1], A. Hauschild[2], N. Lindenblatt[3], G. Pentheroudakis[4] & U. Keilholz[5], on behalf of the ESMO Guidelines Committee*

[1]Department of Dermatology, University Hospital Zürich, Zürich, Switzerland; [2]Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany; [3]Division of Plastic and Reconstructive Surgery, University Hospital Zürich, Zürich, Switzerland; [4]Ioannina University Hospital, Ioannina, Greece; [5]Charité Comprehensive Cancer Center, Charité-Universitätsmedizin, Berlin, Germany

incidence and epidemiology

The European incidence of malignant melanoma varies from 3 to 5/100 000/year in Mediterranean countries to 12–25 (and rising) in Nordic countries. Incre
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Treatment of localised disease

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The histology report should follow the American Joint Committee on Cancer (AJCC) classification [8], and include: information on the maximum thickness in millimetres (Breslow), information on mitotic rate in case of a tumour thickness below
e and extent of regression
[II, A]. In addition, infor-
xtra-cutaneous sites, such
sun damage is necessary.
ype (superficial spreading
, acral lentiginous melan-
n rare situations, melano-
mas may derive from dermal melanocytes (melanoma arising

to adjust the horizontal margin, the width of excision, not to the horizontal, but to the vertical extent of the neoplasm, to *"tumour thickness,"*

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as if trousers needed to be wider, the taller somebody is.

Treatment of localised disease

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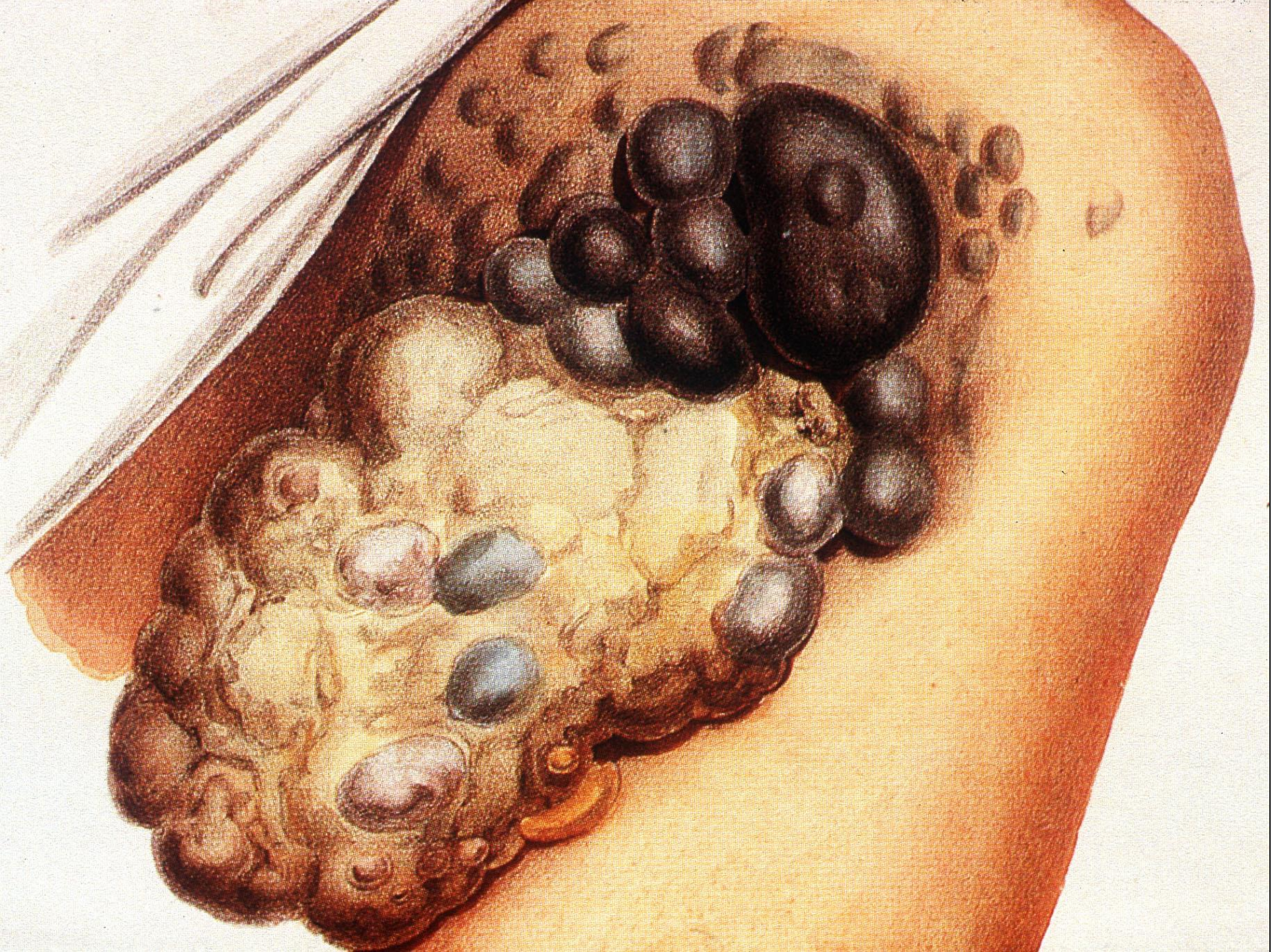
Just image an architect who needs a deep fundament for a skyscraper and tries to reach his goal by expanding the horizontal extent of his construction pit, rather than the vertical one.

Treatment of localised disease

- Wide excision of primary tumours with safety margins of 0.5 cm for *in situ* melanomas, of 1 cm for tumours with a tumour thickness up to 2 mm and 2 cm for thicker tumours is recommended [II, B].

I do not think that you would like to have an apartment in that building.

The current recommendations concerning margins of excision in melanoma violate common sense, and whenever this is the case, one is well advised to look for historical reasons.



A hundred years ago, diagnosis of melanoma was still equated with a death sentence. Melanomas were recognized late and prognosis was terrible. As a consequence, some authors refrained from any treatment.

According to general experience, the exstirpation even of the very first nodules cannot halt the subsequent course. For this reason, the operation is carried out only very rarely, and the first symptom of pigmented cancer is regarded as an ominous sign of a rapidly fatal course.

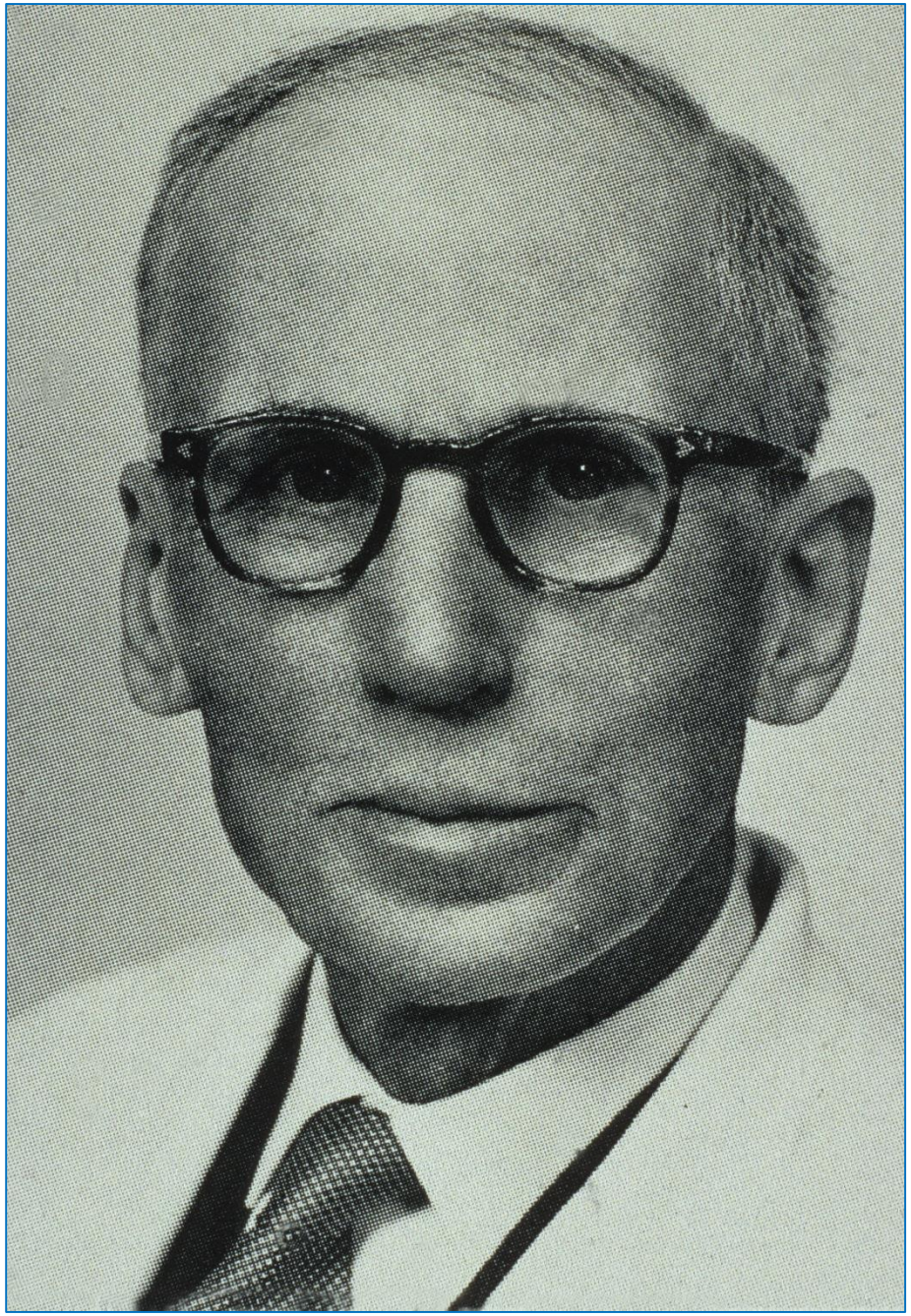
Moriz Kaposi, 1872

Among them was Moriz Kaposi who stated in 1872: *"According to general experience, the exstirpation even of the very first nodules cannot halt the subsequent course. For this reason, the operation is carried out only very rarely, and the first symptom of pigmented cancer is regarded as an ominous sign of a rapidly fatal course."*

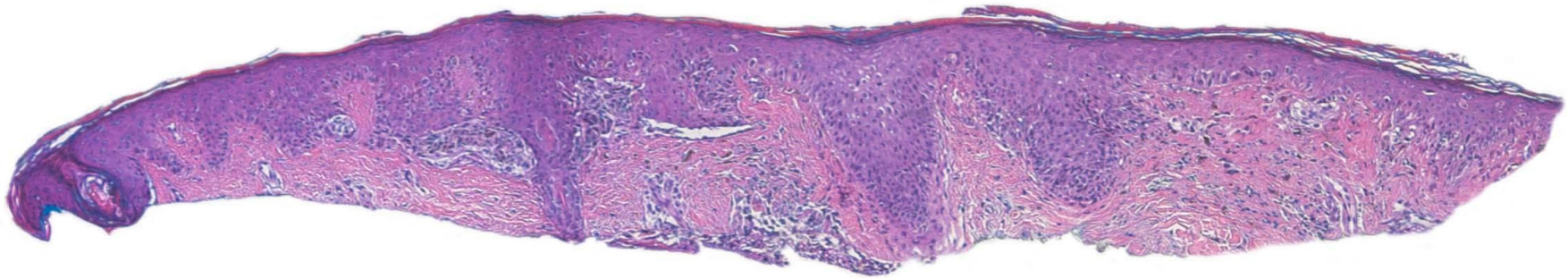
Despite some success in individual cases, surgical procedures were even considered to be detrimental.

Surgical treatment is being abandoned increasingly at least for primary tumors because the danger of dissemination is doubtlessly greatest in them, and cases with acute exacerbation following the procedure have been observed repeatedly.

Guido Miescher, 1933



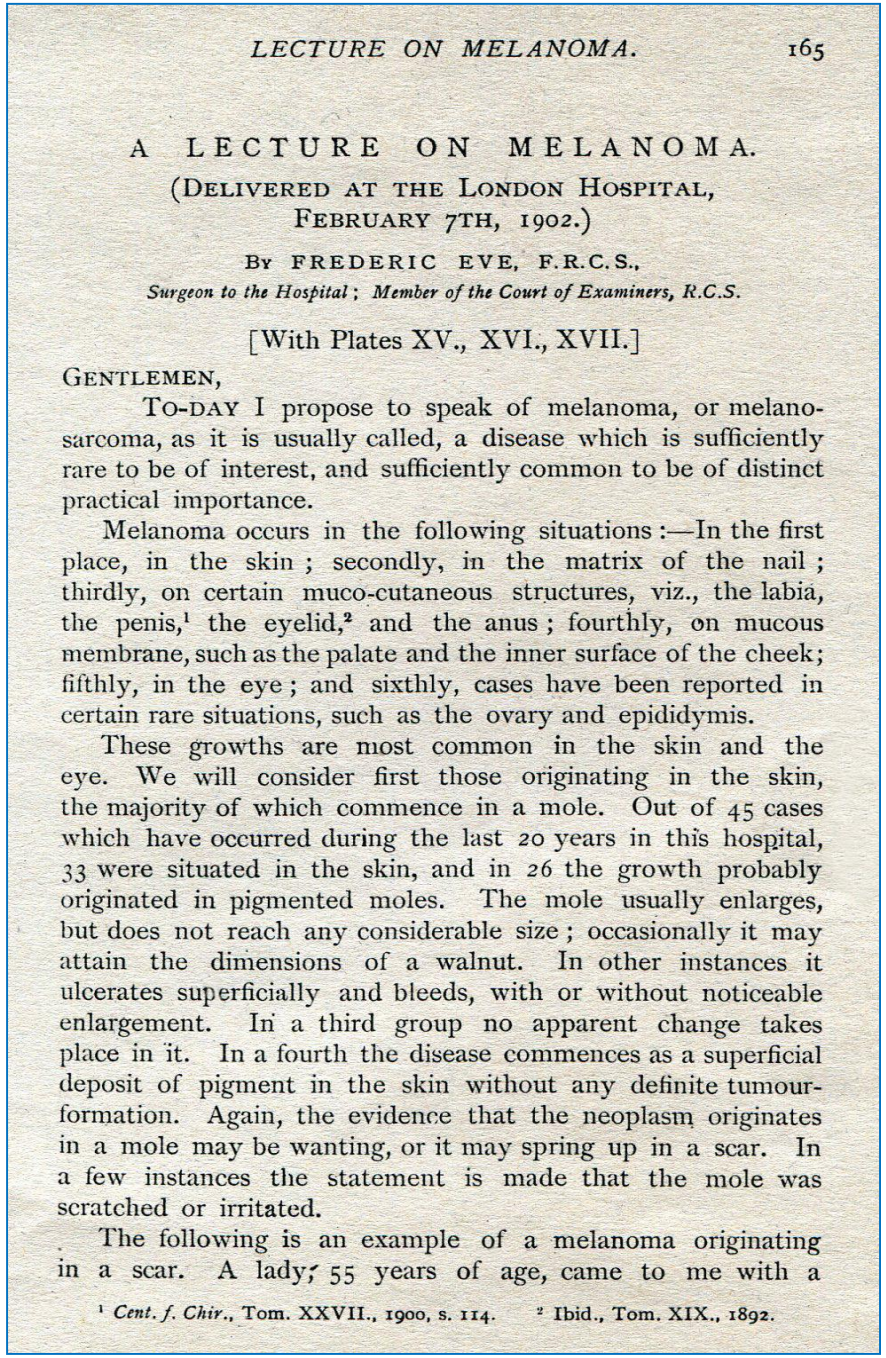
As late as in 1933, Guido Miescher noted in Jadassohn's Handbook: *"Surgical treatment is being abandoned increasingly at least for primary tumors because the danger of dissemination is doubtlessly greatest in them, and cases with acute exacerbation following the procedure have been observed repeatedly."*



Today it is well known that even incisional biopsies have no impact on prognosis of melanoma, but at that time, fear of displacing tumor cells through the surgical procedure was appalling. Therefore, surgical procedures, if done at all, were radical.

The treatment of melanoma of the skin can be given in few words, i.e., free excision or amputation ...

Frederic Eve,
Practitioner, 1903



A LECTURE ON MELANOMA.

(DELIVERED AT THE LONDON HOSPITAL, FEBRUARY 7TH, 1902.)

BY FREDERIC EVE, F.R.C.S.,
Surgeon to the Hospital; Member of the Court of Examiners, R.C.S.

[With Plates XV., XVI., XVII.]

GENTLEMEN,

TO-DAY I propose to speak of melanoma, or melano-sarcoma, as it is usually called, a disease which is sufficiently rare to be of interest, and sufficiently common to be of distinct practical importance.

Melanoma occurs in the following situations:—In the first place, in the skin; secondly, in the matrix of the nail; thirdly, on certain muco-cutaneous structures, viz., the labia, the penis,[1] the eyelid,[2] and the anus; fourthly, on mucous membrane, such as the palate and the inner surface of the cheek; fifthly, in the eye; and sixthly, cases have been reported in certain rare situations, such as the ovary and epididymis.

These growths are most common in the skin and the eye. We will consider first those originating in the skin, the majority of which commence in a mole. Out of 45 cases which have occurred during the last 20 years in this hospital, 33 were situated in the skin, and in 26 the growth probably originated in pigmented moles. The mole usually enlarges, but does not reach any considerable size; occasionally it may attain the dimensions of a walnut. In other instances it ulcerates superficially and bleeds, with or without noticeable enlargement. In a third group no apparent change takes place in it. In a fourth the disease commences as a superficial deposit of pigment in the skin without any definite tumour-formation. Again, the evidence that the neoplasm originates in a mole may be wanting, or it may spring up in a scar. In a few instances the statement is made that the mole was scratched or irritated.

The following is an example of a melanoma originating in a scar. A lady, 55 years of age, came to me with a

[1] *Cent. f. Chir.*, Tom. XXVII., 1900, s. 114. [2] Ibid., Tom. XIX., 1892.

For example, Frederic Eve stated in 1903: *"The treatment of melanoma of the skin can be given in few words, i.e., free excision or amputation..."*

MALIGNANT MELANOMA*

MIMS GAGE, M.D., AND WILLIAM DAWSON, M.D.
NEW ORLEANS, LOUISIANA

FROM THE DEPARTMENTS OF SURGERY, OCHSNER CLINIC AND TULANE UNIVERSITY OF LOUISIANA, SCHOOL OF MEDICINE, NEW ORLEANS

Ann Surg 1951; 133: 772-782

THE MOST COMMON LESION of the skin is the pigmented nevus or mole. There are few human beings who do not have one or mo... a are n... de- as the... to lieves... for would... ma Of... no melar... ith carcin... ate is wit... on- and n... es[1] incide... at- gical treatment. Pack and associates[1] reported recurrence following operation elsewhere in 64 per cent of 552 cases of malig-

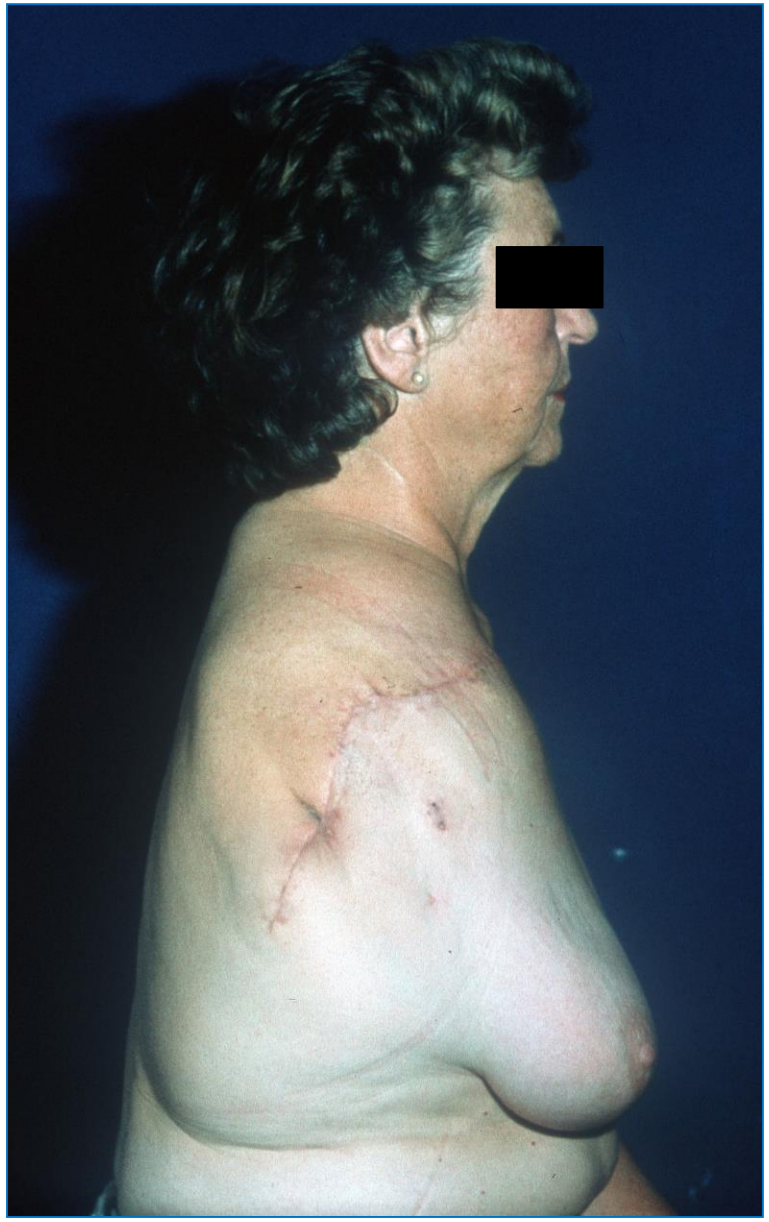
the Ochsner Clinic over a period of seven and three quarters years.

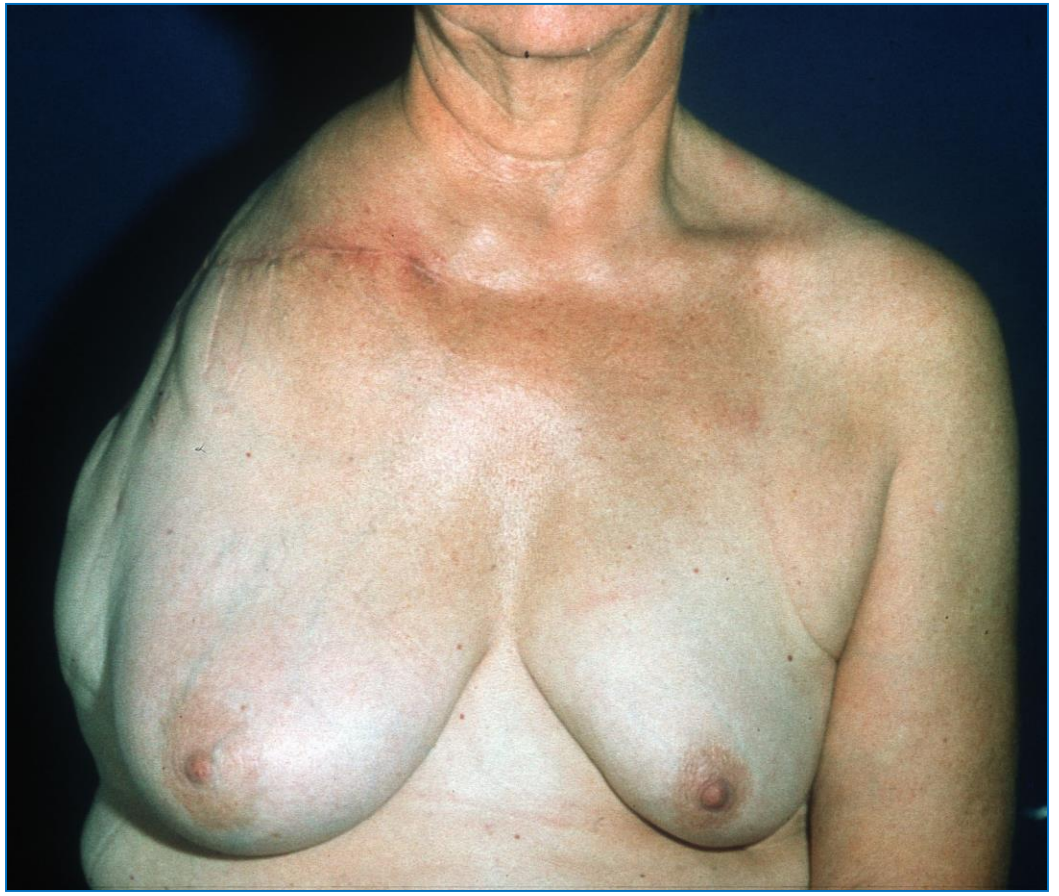
Even though these growths are compar-

ment only 38.4 per cent survive three years, and 17.7 per cent of those with localized melanoma live five years.

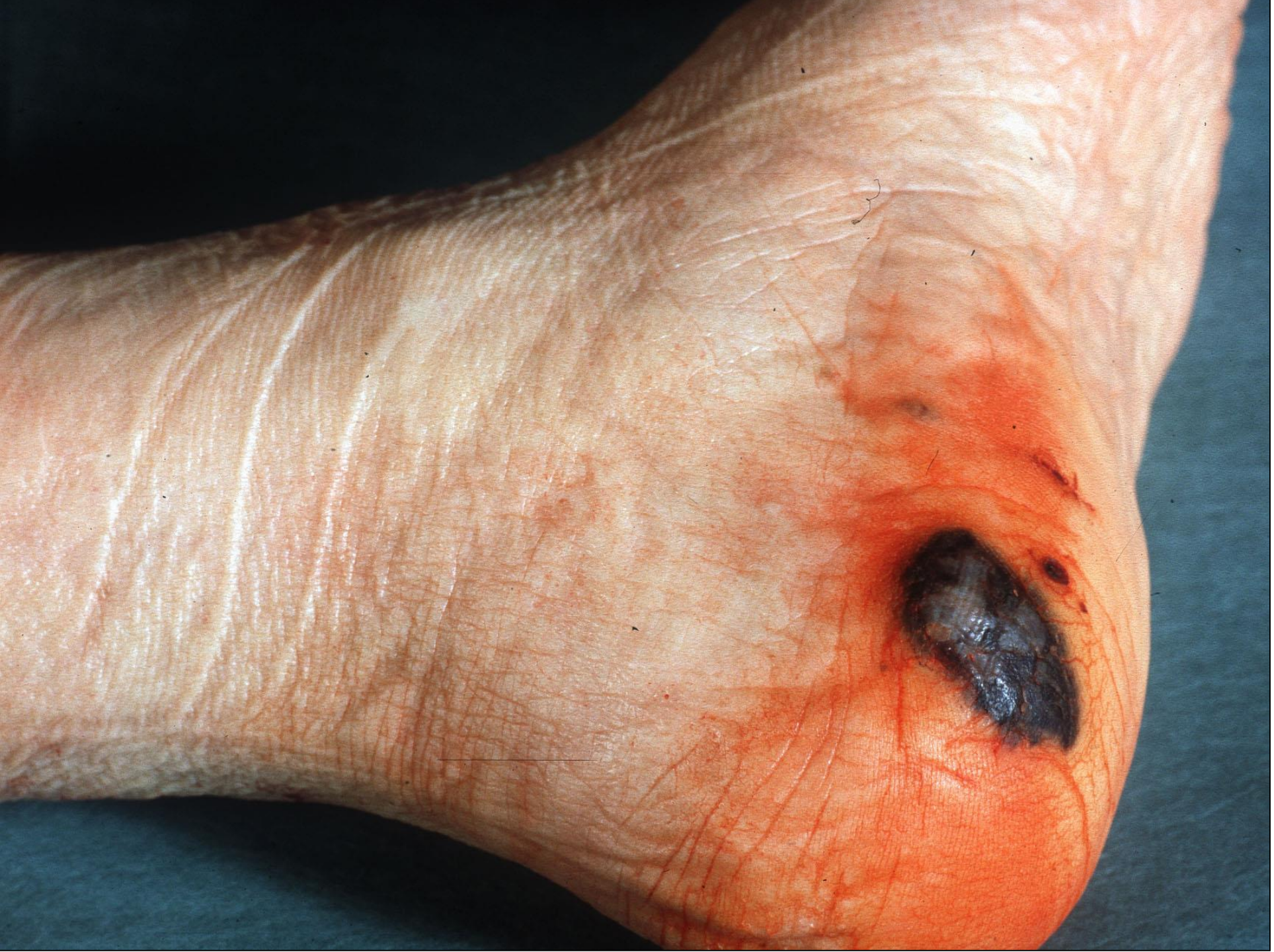
For malignant melanomas as radical a procedure as the patient's condition will permit is indicated. There should be no hesitancy in performing forequarter or hindquarter amputations on patients with malignant melanomata located on or in the extremities.

Half a century later, Gage and Dawson declared: *"For malignant melanomas as radical a procedure as the patient's condition will permit is indicated. There should be no hesitancy in performing forequarter or hindquarter amputations on patients with malignant melanomata located on or in the extremities."*

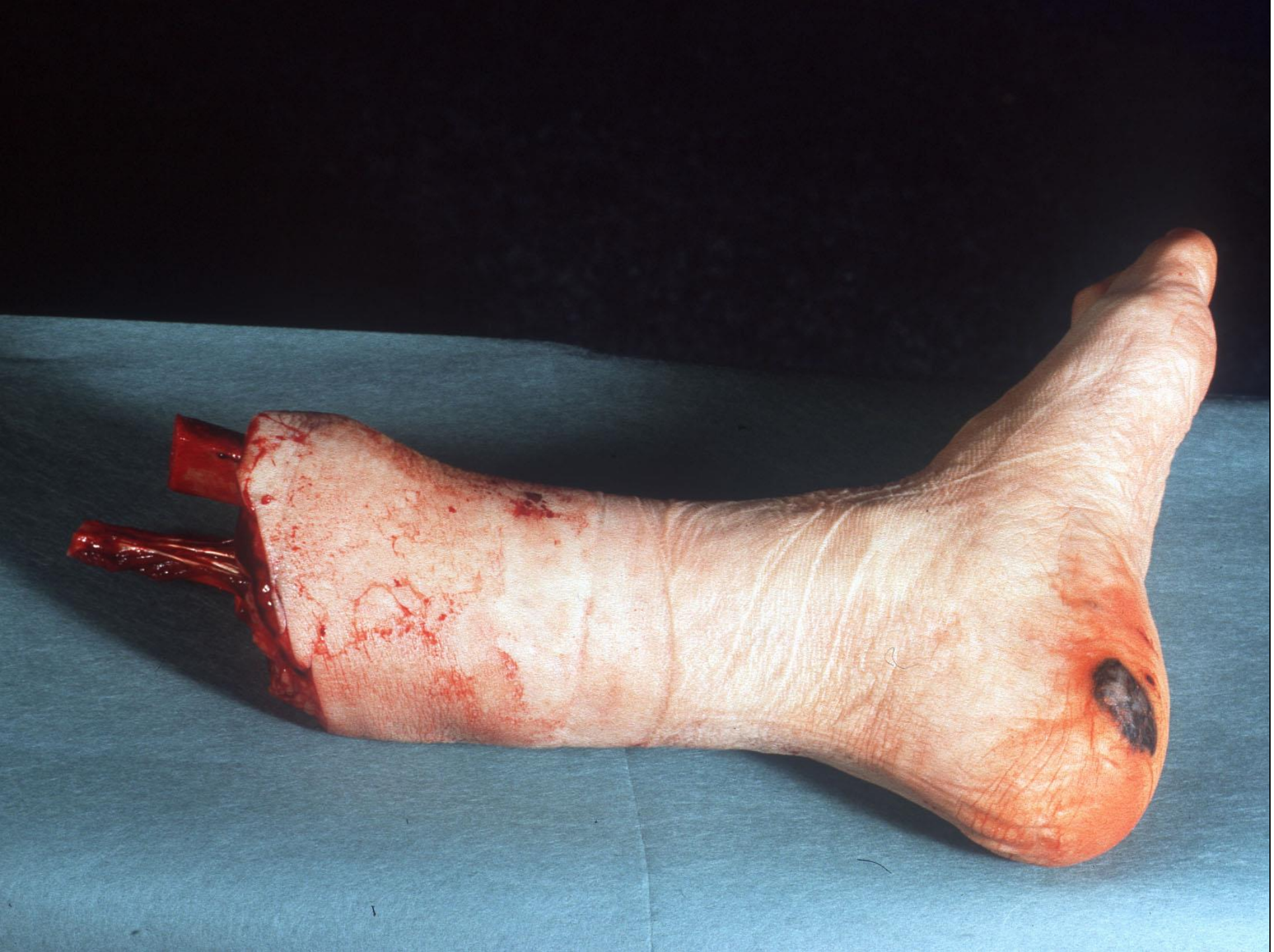




This is an example of a hindquarter amputation, a procedure carried out for years until it became apparent that it did not improve survival.



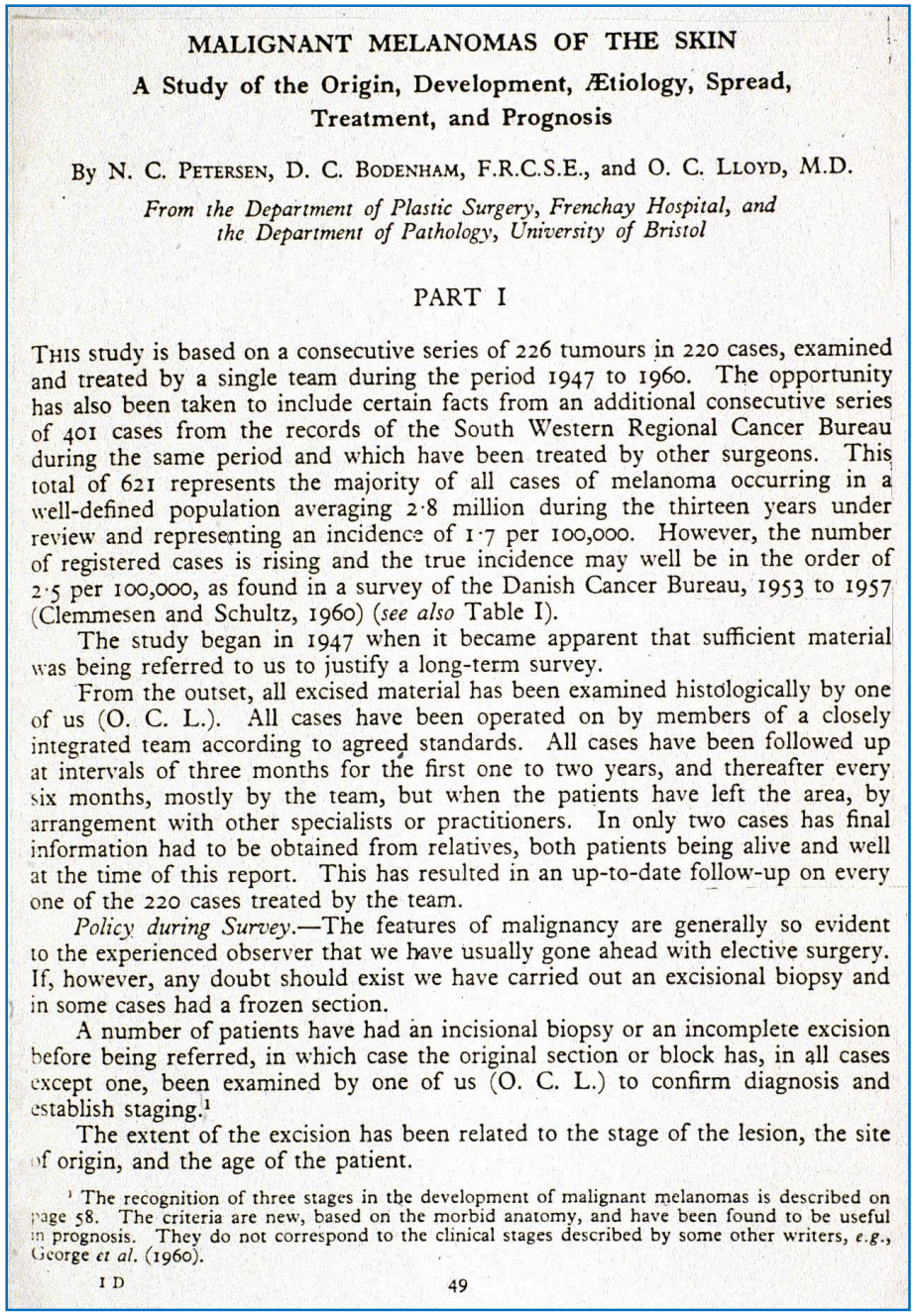
For acral melanomas such as this one,



amputations were advocated well into the 1980s. And if amputation was omitted, the margins of excision were excessive.

Even the most extensive excisions compare favourably in results ... with those following extensive burns and traffic accidents where large areas of skin have been lost.

N.C. Petersen et al.,
Br J Plast Surg 1962



MALIGNANT MELANOMAS OF THE SKIN

A Study of the Origin, Development, Ætiology, Spread, Treatment, and Prognosis

By N. C. PETERSEN, D. C. BODENHAM, F.R.C.S.E., and O. C. LLOYD, M.D.

From the Department of Plastic Surgery, Frenchay Hospital, and the Department of Pathology, University of Bristol

PART I

THIS study is based on a consecutive series of 226 tumours in 220 cases, examined and treated by a single team during the period 1947 to 1960. The opportunity has also been taken to include certain facts from an additional consecutive series of 401 cases from the records of the South Western Regional Cancer Bureau during the same period and which have been treated by other surgeons. This total of 621 represents the majority of all cases of melanoma occurring in a well-defined population averaging 2·8 million during the thirteen years under review and representing an incidence of 1·7 per 100,000. However, the number of registered cases is rising and the true incidence may well be in the order of 2·5 per 100,000, as found in a survey of the Danish Cancer Bureau, 1953 to 1957 (Clemmesen and Schultz, 1960) (*see also* Table I).

The study began in 1947 when it became apparent that sufficient material was being referred to us to justify a long-term survey.

From the outset, all excised material has been examined histologically by one of us (O. C. L.). All cases have been operated on by members of a closely integrated team according to agreed standards. All cases have been followed up at intervals of three months for the first one to two years, and thereafter every six months, mostly by the team, but when the patients have left the area, by arrangement with other specialists or practitioners. In only two cases has final information had to be obtained from relatives, both patients being alive and well at the time of this report. This has resulted in an up-to-date follow-up on every one of the 220 cases treated by the team.

Policy during Survey.—The features of malignancy are generally so evident to the experienced observer that we have usually gone ahead with elective surgery. If, however, any doubt should exist we have carried out an excisional biopsy and in some cases had a frozen section.

A number of patients have had an incisional biopsy or an incomplete excision before being referred, in which case the original section or block has, in all cases except one, been examined by one of us (O. C. L.) to confirm diagnosis and establish staging.[1]

The extent of the excision has been related to the stage of the lesion, the site of origin, and the age of the patient.

[1] The recognition of three stages in the development of malignant melanomas is described on page 58. The criteria are new, based on the morbid anatomy, and have been found to be useful in prognosis. They do not correspond to the clinical stages described by some other writers, *e.g.*, George *et al.* (1960).

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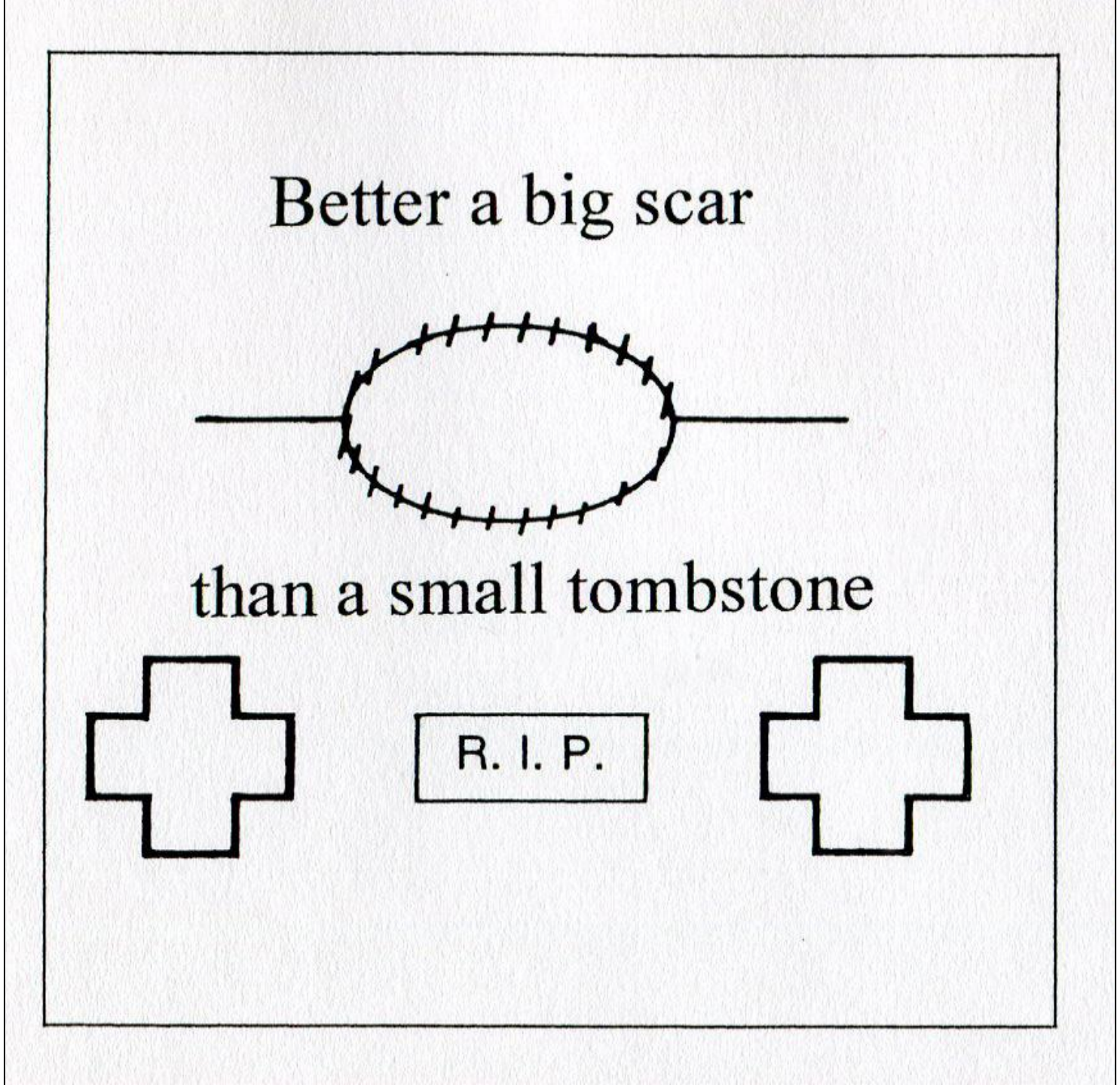
They were defended by arguing that *"even the most extensive excisions compare favourably in results ... with those following extensive burns and traffic accidents where large areas of skin have been lost,"*



or by the notion, *“better a big scar than a small tombstone.”*

There is a long tradition among surgeons to trivialze the consequences of their procedures, and that tradition continues.

Systematic or Meta-analysis Studies

Surgical excision margins in primary cutaneous melanoma: A meta-analysis and Bayesian probability evaluation

Keith Wheatley [a], Jayne S. Wilson [a], Piers Gaunt [a], Jerry R. Marsden [b,*]

[a] Cancer Research UK Clinical Trials Unit, Institute of Cancer & Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom
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ABSTRACT

Background: Surgery is the only curative treatment for primary cutaneous melanoma, therefore it is important to determine excision margins that minimise risk of local recurrence, distant recurrence and death.
Methods: MEDLINE, EMBASE and Cochrane CENTRAL were searched from 2009 to 2015. Inclusion criteria were: population/setting – patients with primary melanoma; comparison – narrow versus wide margins; outcomes – overall survival, melanoma-specific survival, recurrence-free survival, and loco-regional recurrence; design – randomized controlled trials (RCTs). Results were pooled using meta-analysis and data explored using likelihood Bayesian probability plots.
Results: Six RCTs with 4233 patients were included. Narrow margins were defined as 1 or 2 cm of clinically normal skin around the melanoma; wide margins as 3, 4 or 5 cm. Hazard ratios (HR) were as follows (HR > 1 indicates wide margin better): overall survival 1.09 (95% CI 0.98–1.22; $p = 0.1$); melanoma-specific survival 1.17 (CI 1.03–1.34; $p = 0.02$); recurrence-free survival 1.08 (CI 0.97–1.20; $p = 0.2$); loco-regional recurrence 1.10 (CI 0.96–1.26; $p = 0.2$), with no evidence of heterogeneity between trials for any end point or within subgroup analyses. There was an 94% probability that overall survival was worse with a narrow margin and a 43% probability that it was more than 10% worse in proportional terms (i.e. HR > 1.1). Probabilities that narrow margins were worse were 99%, 92% and 92% for melanoma-specific survival, recurrence-free survival and loco-regional recurrence respectively.
Conclusions: Contrary to recommendations in several national guidelines that narrow margins are safe, this systematic review and meta-analysis provides evidence that a narrow margin may lead to a worse outcome than a wide margin.

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For example, a recent meta-analyses comparing margins of up to 2 cm and up to 5 cm with one another came to the result that *"a narrow margin may lead to a worse outcome than a wide margin."*

Systematic or Meta-analysis Studies

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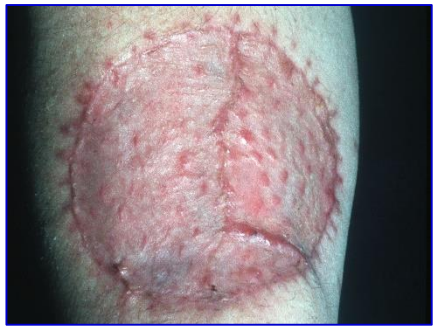

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Background: Surgery is the only curative treatment for primary cutaneous melanoma, therefore it is important to determine excision margins that minimise risk of local recurrence, distant recurrence and death.

Methods: MEDLINE, EMBASE and Cochrane CENTRAL were searched from 2009 to 2015. Inclusion criteria were: population/setting – patients with primary melanoma; comparison – narrow versus wide margins; outcomes – overall survival, melanoma-specific survival, recurrence-free survival, and loco-regional recurrence; design – randomized controlled trials (RCTs). Results were pooled using meta-analysis and data explored using likelihood Bayesian probability plots.

Results: Six RCTs with 4233 patients were included. Narrow margins were defined as 1 or 2 cm of clinically normal skin around the melanoma; wide margins as 3, 4 or 5 cm. Hazard ratios (HR) were as follows (HR > 1 indicates wide margin better): overall survival 1.09 (95% CI 0.98–1.22; $p = 0.1$); melanoma-specific survival 1.17 (CI 1.03–1.34; $p = 0.02$); recurrence-free survival 1.08 (CI 0.97–1.20; $p = 0.2$); loco-regional recurrence 1.10 (CI 0.96–1.26; $p = 0.2$), with no evidence of heterogeneity between trials for any end point or within subgroup analyses. There was an 94% probability that overall survival was worse with a narrow margin and a 43% probability that it was more than 10% worse in proportional terms (i.e. HR > 1.1). Probabilities that narrow margins were worse were 99%, 92% and 92% for melanoma-specific survival, recurrence-free survival and loco-regional recurrence respectively.

Conclusions: Contrary to recommendations in several national guidelines that narrow margins are safe, this systematic review and meta-analysis provides evidence that a narrow margin may lead to a worse outcome than a wide margin.

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The probabilities were minimal, and they were obtained on the basis of flawed material, pooled from many studies in which only clinical margins were considered. Moreover, none of those studies had a control group which is a prerequisite in all drug trials. With surgical procedures, a control group would not be ethically feasible but, of course, some placebo effect must be taken into account and, in all likelihood, it could also be achieved by less drastic means than the production of big scars. The minimal difference found in their statistical work-up prompted the authors to recommend margins of up to 5 cm,

Systematic or Meta-analysis Studies

Surgical excision margins in primary cutaneous melanoma: A meta-analysis and Bayesian probability evaluation

Keith Wheatley [a], Jayne S. Wilson [a], Piers Gaunt [a], Jerry R. Marsden [b,*]

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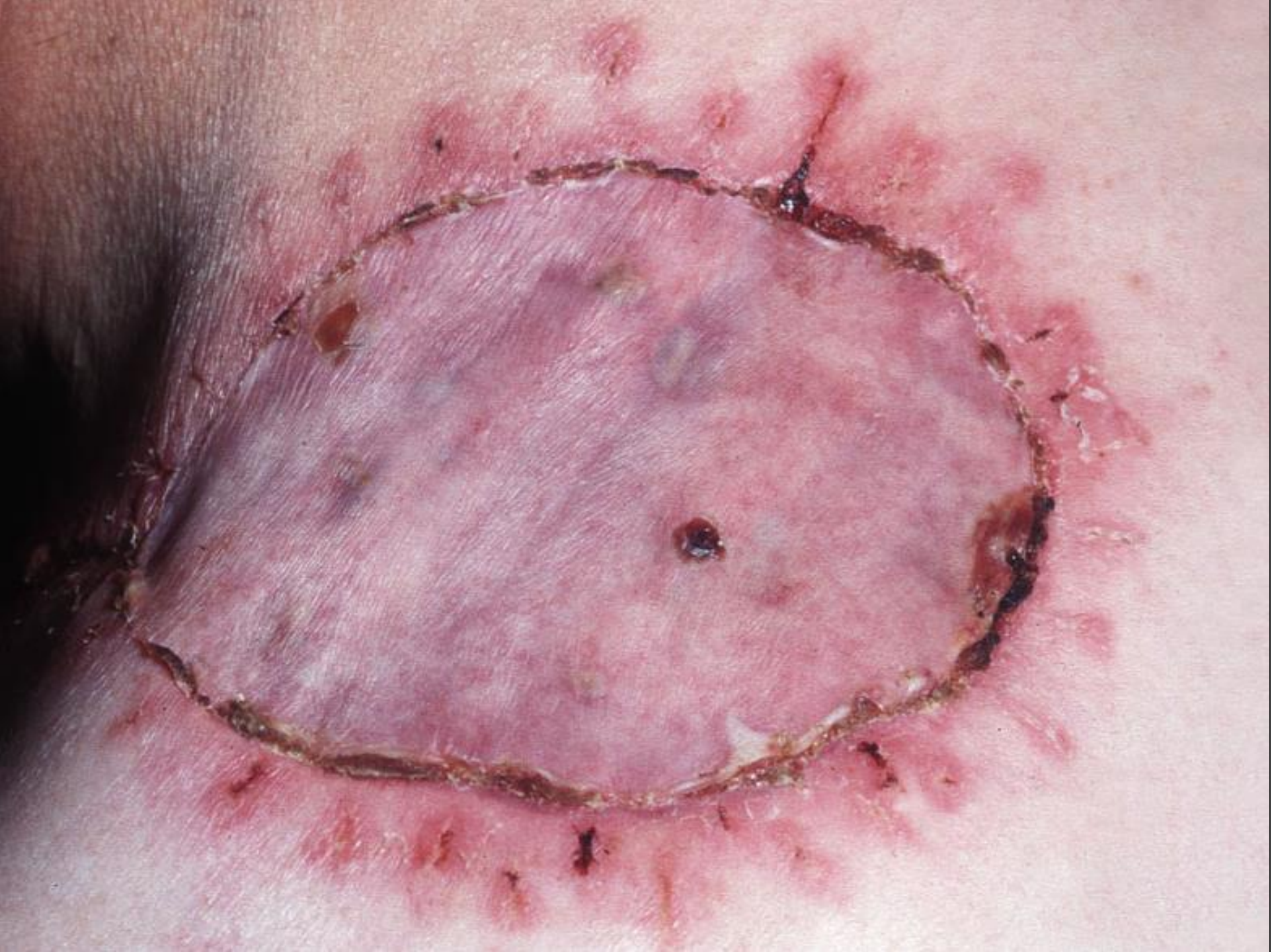
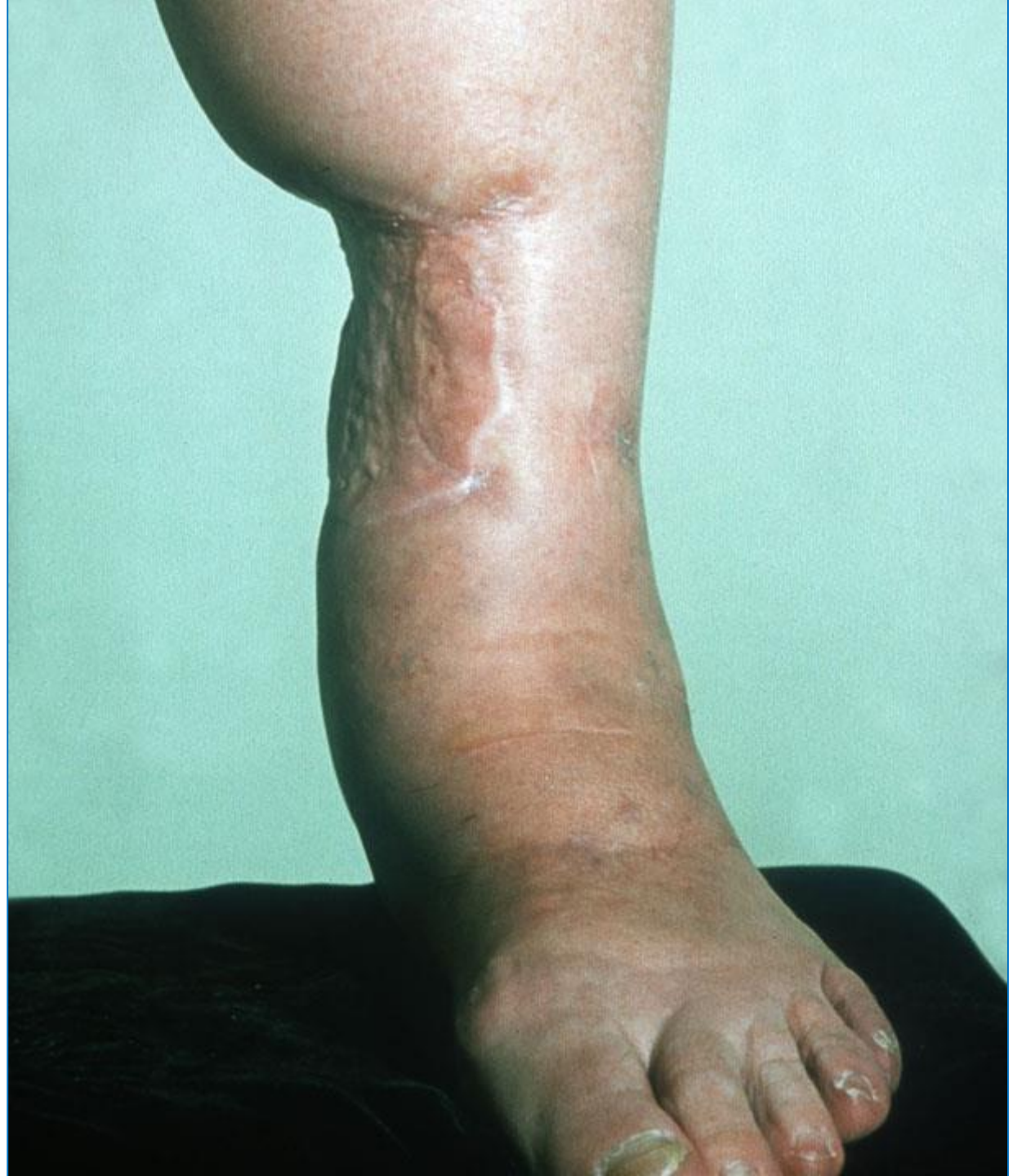
chance of any benefit of a wide margin is perceived by clinicians as small. Patients may not share this view. A small survey of patients' views on surgical margins was presented at a UK melanoma meeting in 2011; the clear message was that minimising relapse risk was their principal concern, with cosmesis being much less important (S. Brothwell, pers. comm.). This is congruent with data showing that patients are willing to tolerate substantial toxicity and morbidity for only small survival benefits [30] and by quality of life data showing that the cosmetic and functional adverse effects of wider margin surgery only have a transient affect and by 6 months are no longer measurable [31,32]. The optimum

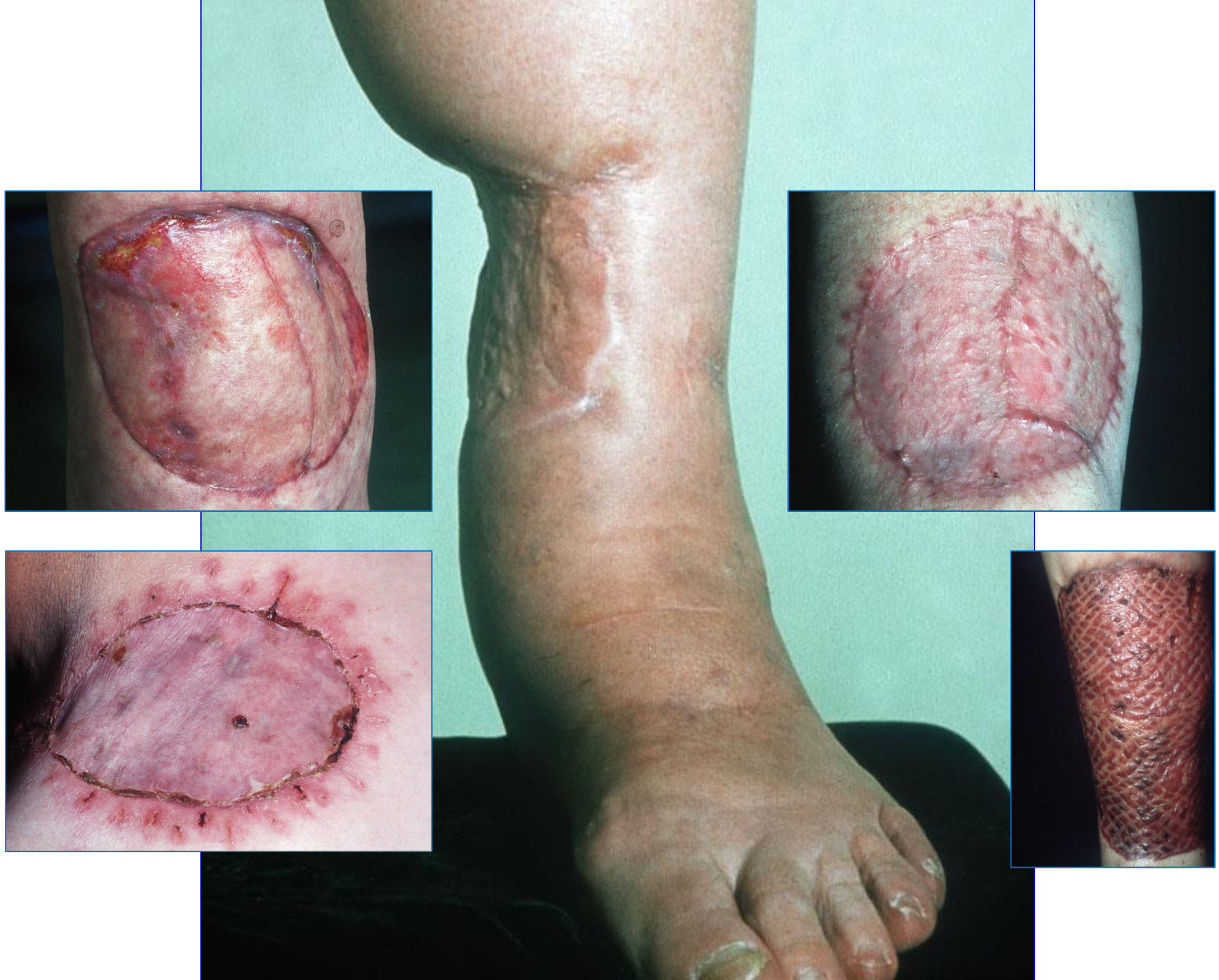
arguing that, for patients, *"minimising relapse risks"* was the *"principal concern, with cosmesis being much less important,"* that *"patients are willing to tolerate substantial toxicity and morbidity for only small survival benefits,"* and that *"cosmetic and functional adverse effects of wider margin surgery only have a transient affect and by 6 months are no longer measurable."* One may gently suggest that the way benefits and risks are explained to patients may have a profound effect on how much toxicity and morbidity they are willing to tolerate.



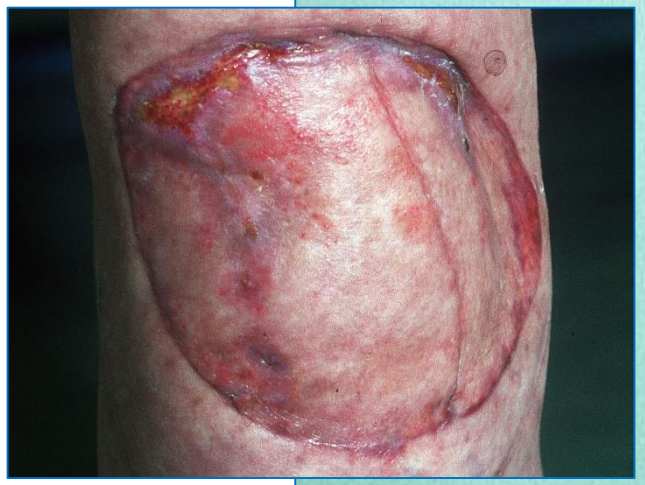
Moreover, the notion that *“wider margin surgery”* has only a *“transient affect”* is not really convincing. Margins of up to 5 cm require skin grafting, possible complications ranging from infection and loss of the graft

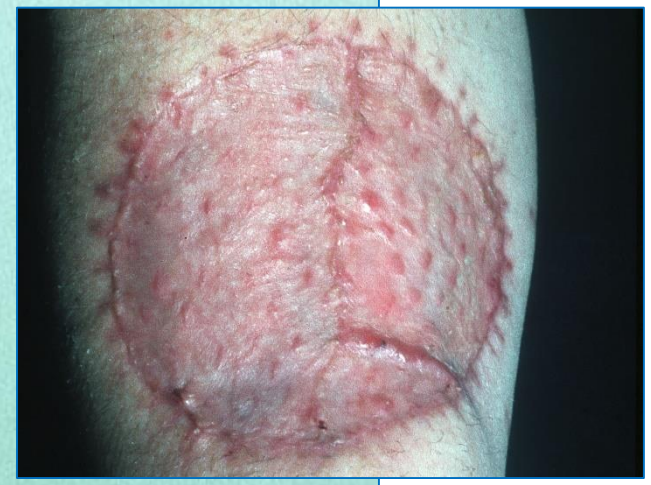


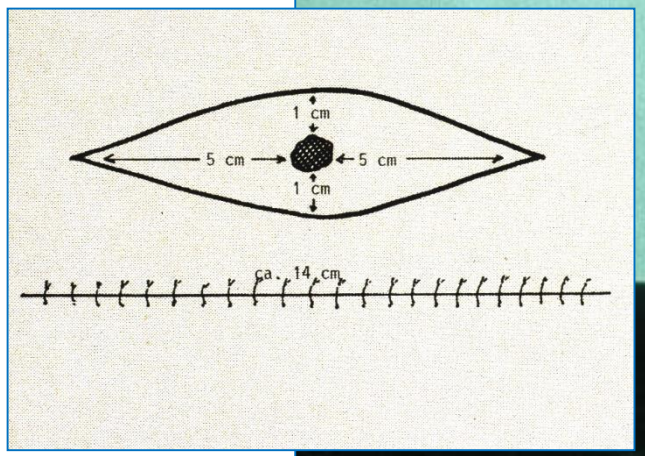
to lymphedema, and the effects of surgery last far longer than 6 months;

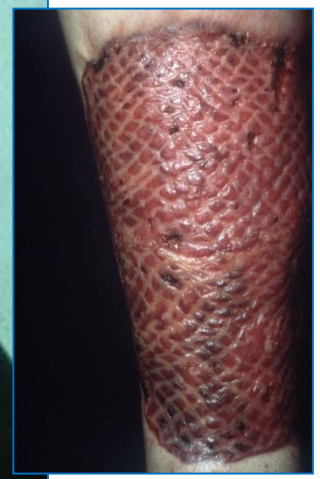


those scars are stigmatizing, burdensome psychologically, and remain for a lifetime.









Even a relatively narrow margin of only 1 cm implies that long scars are produced.

Nonetheless, the trivializing comments in the meta-analysis were not pure confabulation. They represent intentionally misleading quotations from a study

A Quality-of-Life Study in High-Risk (Thickness ⩾ 2 mm) Cutaneous Melanoma Patients in a Randomized Trial of 1-cm versus 3-cm Surgical Excision Margins

Julia A. Newton-Bishop, Clarissa Nolan, Faye Turner, Margaret McCabe, Candida Boxer,*
J. Meirion Thomas,† Gill Coombes,‡ Roger P. A'Hern,† and Jennifer H. Barrett
Division of Genetic Epidemiology, Cancer Research UK Clinical Center in Leeds, St. James's University Hospital, Beckett Street, Leeds; *Frimley Park Hospital, Camberley; †Royal Marsden NHS Trust and ‡Institute of Cancer Research, Sutton, UK

A quality-of-life study was carried out to test the hypothesis that melanoma patients treated with a 3-cm margin of excision suffer greater impairment of their quality of life than those treated with a 1-cm margin. The secondary aim was to determine the predictors of a poor patient perception of their excision scar. A postal questionnaire study was carried out using Hospital Anxiety and Depression (HAD), Psychosocial Adjustment of Illness Scale–Self-Report (PAIS-SR), Medical Outcomes Survey–Short Form 36 (MOS-SF36), and the Cassileth Scar questionnaires. Data were collected from 426 of the 537 patients who were mailed the questionnaires (response rate 79%). Fourteen percent had clinically significant anxiety and 5% had significant depression. A poor attitude toward quality of health care was associated with youth. Patients treated with a 3-cm margin excision had significantly poorer mental and physical function 1 mo after surgery, which disappeared within 6 mo. The greater difficulties experienced by the 3-cm margin group were particularly in their domestic, sexual, and social roles. Women, younger patients, those with poor physical and mental function after surgery, and those treated by a 3-cm margin were more likely to report a poorer perception of their scar. The poorer scar perception of patients in the 3-cm group persisted throughout the study period. Use of a 3-cm margin of excision for melanoma is associated with significantly more morbidity than use of a 1-cm margin, but this effect disappears in 6 mo. Patients treated by 3-cm excision were more likely, however, to have a persistent poor view of their scar. Youth and being female were also predictors of poor perception of the scar.

Key words: scar/HAD/PAIS-SR/MOS-SF36
J Investig Dermatol Symp Proc 9:152–159, 2004

concerning the quality-of-life in melanoma patients. Although some effects associated with wider margins disappeared within 6 months, the majority persisted. *"The greater difficulties experienced by the 3-cm margin group were particularly in their domestic, sexual, and social roles. Women, younger patients, those with poor physical and mental function after surgery, and those treated by a 3-cm margin were more likely to report a poorer perception of their scar. The poorer scar perception of patients in the 3-cm group persisted throughout the study period."*

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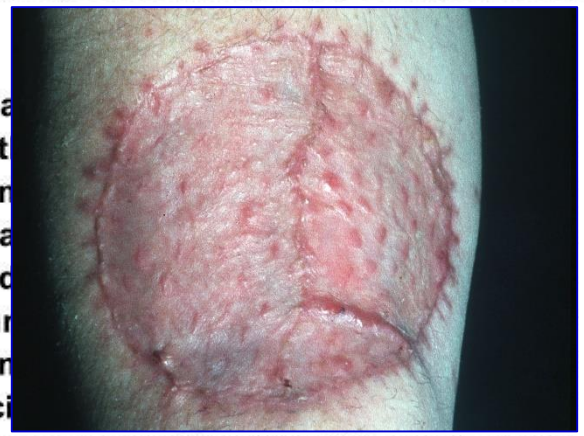

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No wonder.

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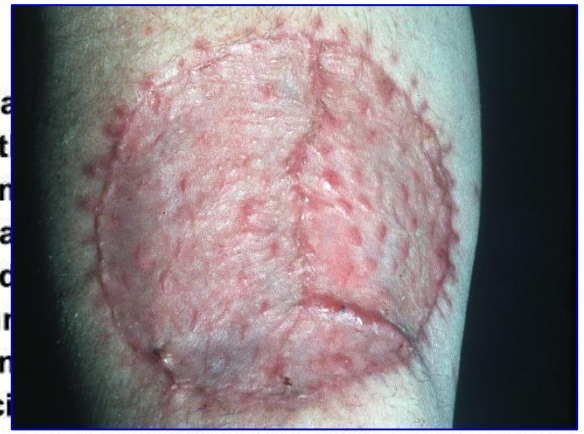
Even the most extensive excisions compare favourably in results ... with those following extensive burns and traffic accidents …

N.C. Petersen et al., Br J Plast Surg, 1962



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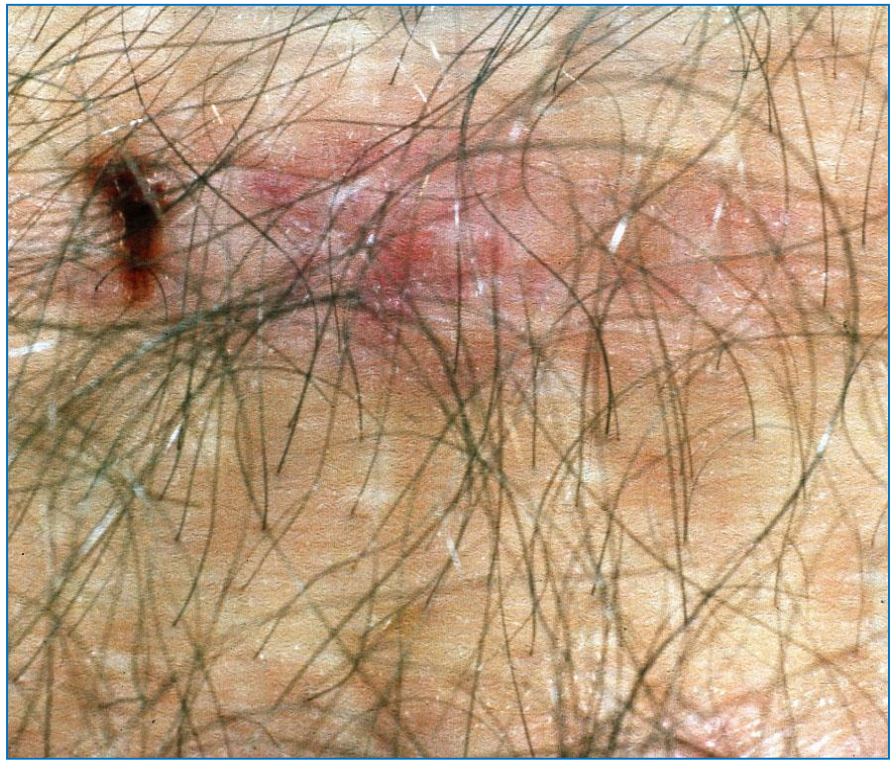
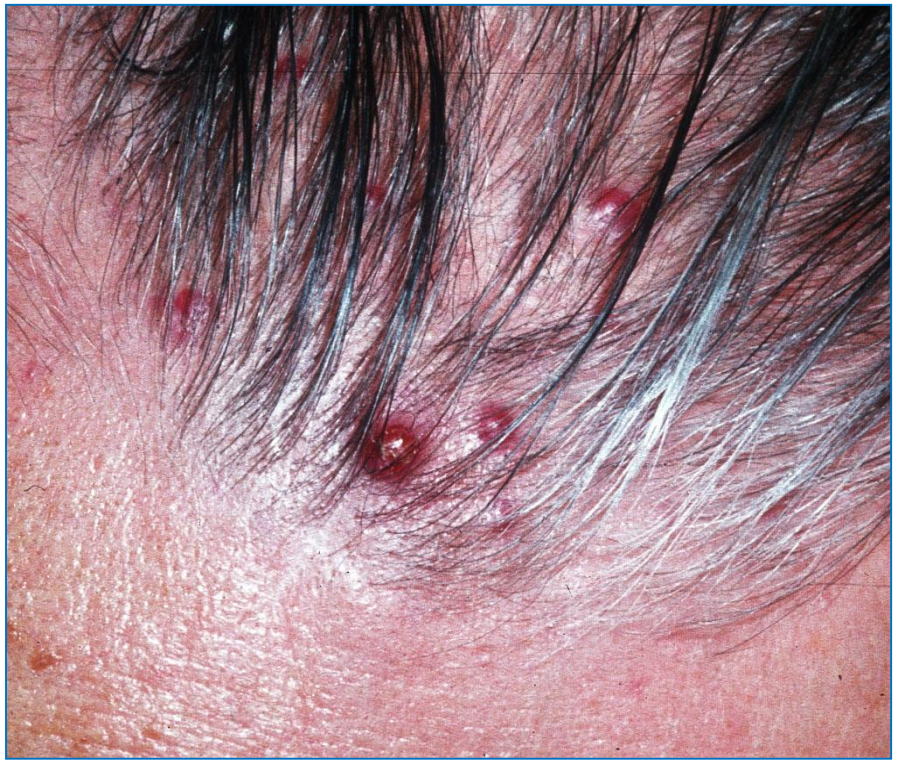
Of course, it is true that *"even the most extensive excisions compare favourably in results ... with those following extensive burns and traffic accidents,"* but nobody submits himself to burns or accidents voluntarily. For the voluntary decision to accept disfiguring procedures, one must have very good reasons.

What reasons might justify such radical excisions?

rationale for deep and wide excisions



prevention of persistence of the primary melanoma



removal of clinically inapparent satellite metastases

There are only two: first, to prevent incomplete excision, persistence, and re-growth of the primary melanoma, and second, to remove existing, but clinically inapparent, metastases in the immediate vicinity of it. Let us first examine the second of those reasons.

The Hunterian Lectures

ON

THE PATHOLOGY OF MELANOTIC GROWTHS IN RELATION TO THEIR OPERATIVE TREATMENT.

Delivered before the Royal College of Surgeons of England on Feb. 25th and 27th, 1907,

BY W. SAMPSON HANDLEY, M.S. LOND., F.R.C.S. ENG.,

HUNTERIAN PROFESSOR; ASSISTANT SURGEON TO THE MIDDLESEX HOSPITAL.

LECTURE I.

Delivered on Feb. 25th.

MR. PRESIDENT AND GENTLEMEN,—The subject of these lectures attracted me on account of the very unfavourable results of operation in melanotic growths, and the belief that these results are capable of improvement is my principal excuse for claiming your attention. I shall deal almost exclusively with those pigmented growths which arise in the skin. My work on the subject was mainly carried out in the Middlesex Hospital Cancer Research Laboratories during my tenure of the "Richard Hollins" Cancer Research Scholarship. To the Cancer Investigation Committee and to the director of the laboratories, Dr. W. S. Lazarus-Barlow, my best thanks are due for the facilities afforded me and for permission to reproduce certain illustrations from the Archives of the Middlesex Hospital.

Many scientific men have held that the pursuit of useful knowledge, as distinct from the pursuit of knowledge for its own sake, degrades both the research and the student below sides upon the same problem. Experimental work and morbid anatomy are the two eyes of cancer research, and to deny the use of either is to forfeit the advantages of binocular vision.

For the sake of convenience it is necessary to depart from the logical order of my subject and to reserve for my second lecture certain problems as to the etiology and nature of malignant melanotic growths and the consideration of their surgical treatment. The present lecture will be concerned with a study of their mode of spread, chiefly based upon the following case.

ABSTRACT OF NECROPSY.

Necropsy No. 186, the Middlesex Hospital, 1905. The body is that of an emaciated woman, aged 34 years. At the insertion of the right tendo Achillis is a small healthy linear scar, where the primary melanotic sarcoma was excised. In Scarpa's triangle on the right side is a considerable mass in the situation of the femoral glands. Beneath the skin over and around this mass are very numerous discrete black nodular growths, occupying an area roughly circular in shape and perhaps eight inches in diameter. (See Fig. 1.) The growths become smaller in all directions the further they are situated from the femoral glands, until apparently healthy skin is reached. On the back, at the level of the tenth dorsal vertebra, there is a patch three inches square studded with similar cutaneous growths. The right breast shows enormous enlargement, and in the skin over the breast are many similar growths. The left breast, though smaller, is in a like condition. Scattered over the front of the thorax and the abdomen are numerous subcutaneous nodules, and there is one on the face in the left malar region. There is far more growth on the right side of the body than on the left. No deposits are present in the skin and subcutaneous tissue of the left leg below the level of the symphysis pubis. There are numerous deposits in the calvaria; a few small nodules are present in the brain and in the thyroid body. Several deposits are found on the

The idea that surgical treatment of melanoma should be directed at removing occult "satellite" metastases was spawn by British surgeon William Sampson Handley. In a "Hunterian Lecture" in 1907, he spoke about *"the pathology of melanotic growth in relation to their operative treatment,"* although he acknowledged that he had never treated a primary melanoma himself. On the basis of microscopic studies of lymph node metastases in but a single patient,

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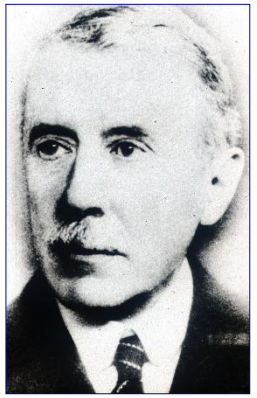
Many scientific men have held that the pursuit of useful knowledge, as distinct from the pursuit of knowledge for its own sake, degrades both the research and the student below

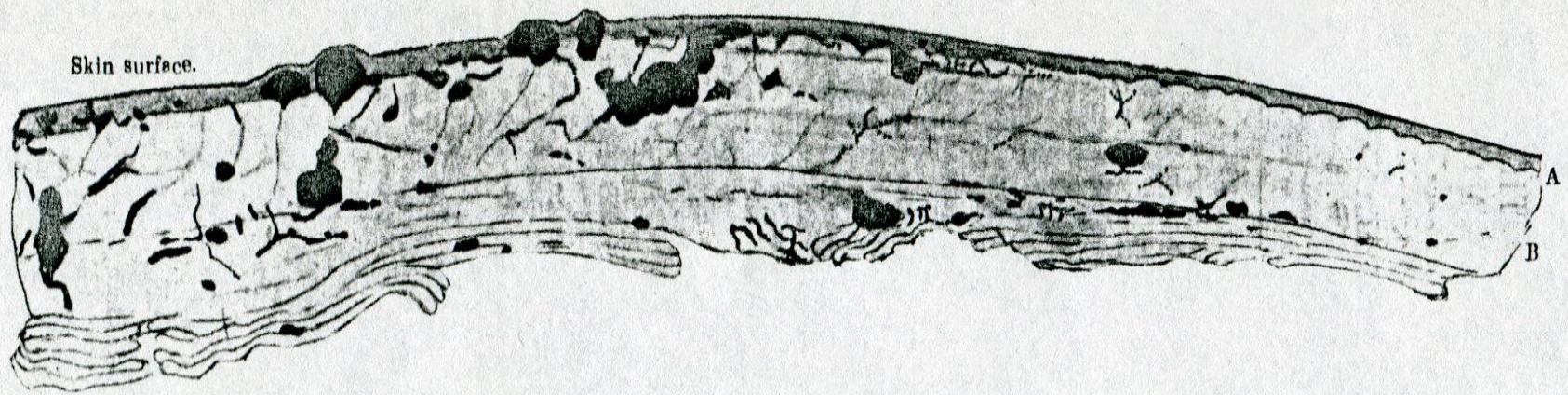
The process of dissemination in malignant melanoma is primarily one of centrifugal lymphatic permeation. ... Fortunately it would appear that as a general rule blood invasion does not take place at an early stage.



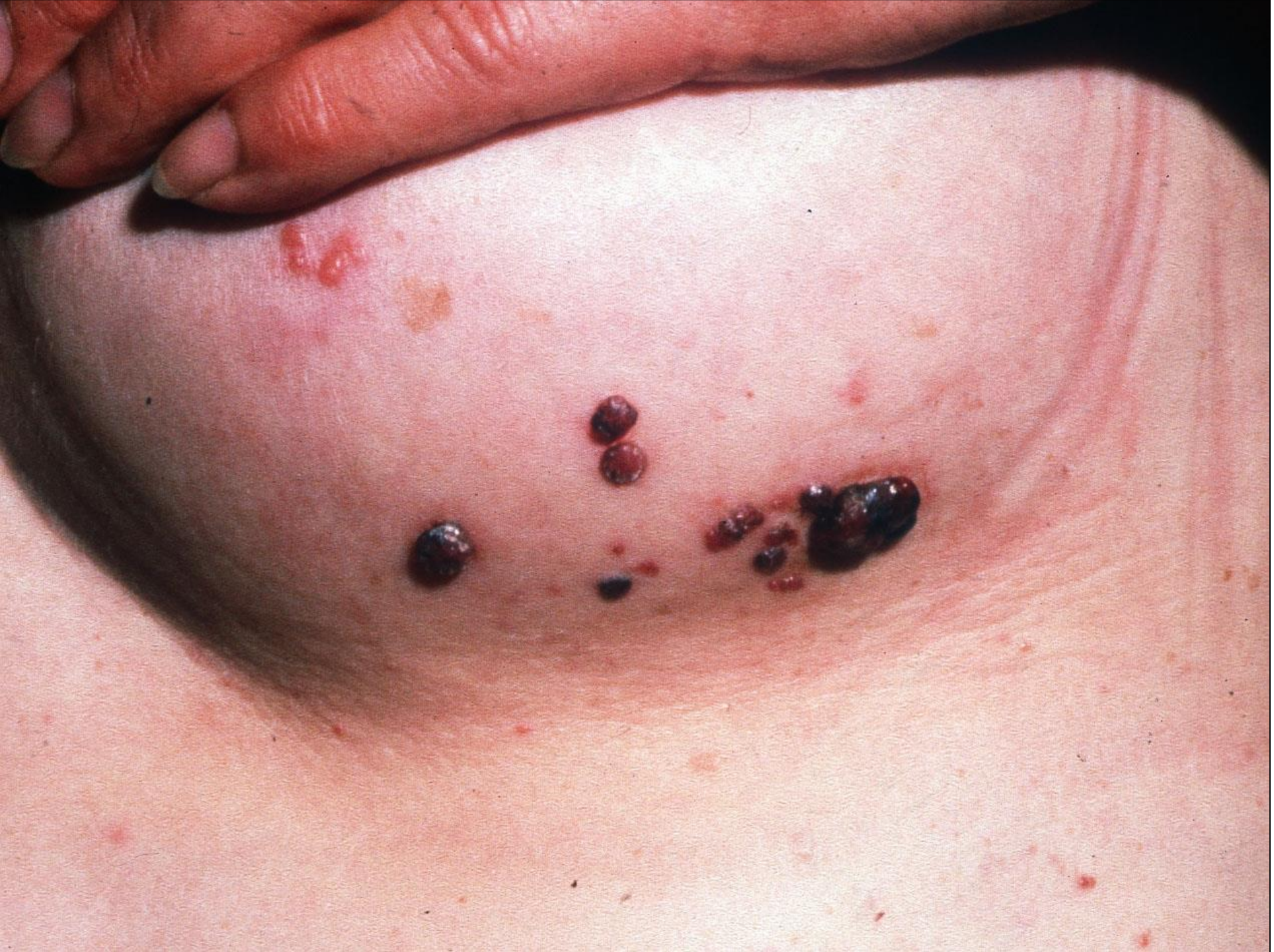
Handley asserted that *"the process of dissemination in malignant melanoma is primarily one of centrifugal lymphatic permeation. ... Fortunately it would appear that as a general rule blood invasion does not take place at an early stage."*

Because of this concept, Handley advised that surgical excision of melanoma be expanded in order to remove potential aggregations of neoplastic cells in adjacent lymphatic vessels.

FIG. 2.



Reproduction of drawing, natural size, of a translucent strip of the skin and underlying tissues taken in a radial direction from the mass of growth in the situation of the inguinal glands to demonstrate the centrifugal spread of permeation. Note that the growth extends much further along the deep fascia than along the skin or in the muscle. A, Skin. B, Subcutaneous fat, separated by the deep fascia from C, a thin layer of muscle.



Handley’s concept of lymphogenic spread was supported by occurrence of cutaneous metastases in the vicinity of melanomas that were sometimes arranged in linear fashion, seemingly following lymphatic vessels.

MALIGNANT MELANOMAS OF THE SKIN

A Study of the Origin, Development, Ætiology, Spread, Treatment, and Prognosis

By N. C. Petersen, D. C. Bodenham, F.R.C.S.E., and O. C. Lloyd, M.D.

From the Department of Plastic Surgery, Frenchay Hospital, and the Department of Pathology, University of Bristol

PART I

This study is based on a consecutive series of 226 tumours in 220 cases, examined and treated by a single team during the period 1947 to 1960. The opportunity has also been taken to include certain facts from an additional consecutive series of 401 cases from the records of the South Western Regional Cancer Bureau during the same period and which have been treated by other surgeons. This total of 621 represents the majority of all cases of melanoma occurring in a well-defined population averaging 2·8 million during the thirteen years under review and representing an incidence of 1·7 per 100,000. However, the number of registered cases is rising and the true incidence may well be in the order of 2·5 per 100,000, as found in a survey of the Danish Cancer Bureau, 1953 to 1957 (Clemmesen and Schultz, 1960) (*see also* Table I).

The study began in 1947 when it became apparent that sufficient material was being referred to us to justify a long-term survey.

From [redacted] lly by one of us (O. [redacted] a closely integrated [redacted] llowed up at intervals [redacted] fter every six months, mostly by the team, but when the patients have left the area, by arrangement with other specialists or practitioners. In only two cases has final information had to be obtained from relatives, both patients being alive and well at the time of this report. This has resulted in an up-to-date follow-up on every one of the 220 cases treated by the team.

"chain formation"

Policy during Survey.—The features of malignancy are generally so evident to the experienced observer that we have usually gone ahead with elective surgery. If, however, any doubt should exist we have carried out an excisional biopsy and in some cases had a frozen section.

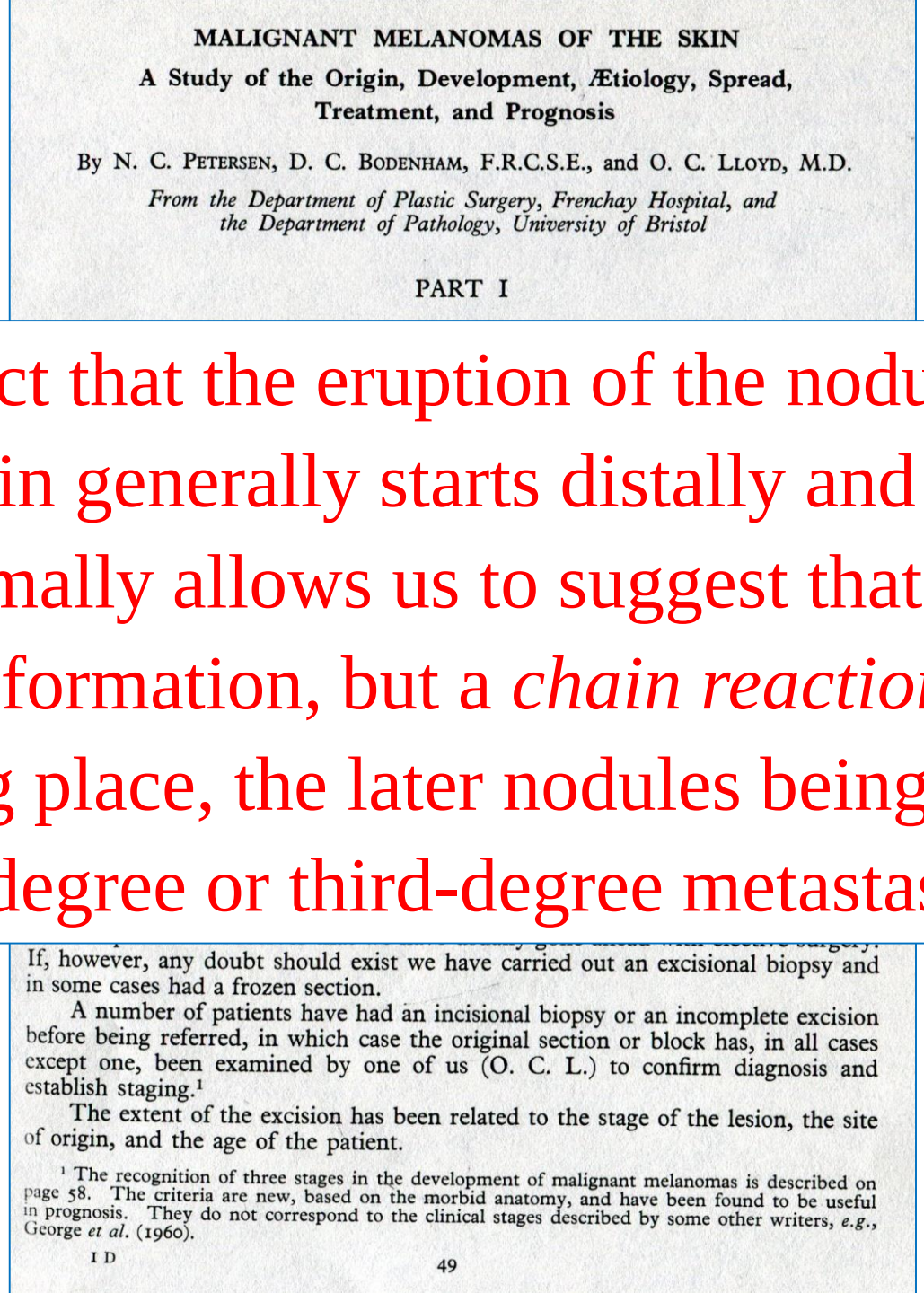
A number of patients have had an incisional biopsy or an incomplete excision before being referred, in which case the original section or block has, in all cases except one, been examined by one of us (O. C. L.) to confirm diagnosis and establish staging.[1]

The extent of the excision has been related to the stage of the lesion, the site of origin, and the age of the patient.

[1] The recognition of three stages in the development of malignant melanomas is described on page 58. The criteria are new, based on the morbid anatomy, and have been found to be useful in prognosis. They do not correspond to the clinical stages described by some other writers, *e.g.*, George *et al.* (1960).

In 1962, Petersen and co-workers referred to that phenomenon as "chain formation" and continued as follows:

Br J Plast Surg,
1962; 15: 49-116



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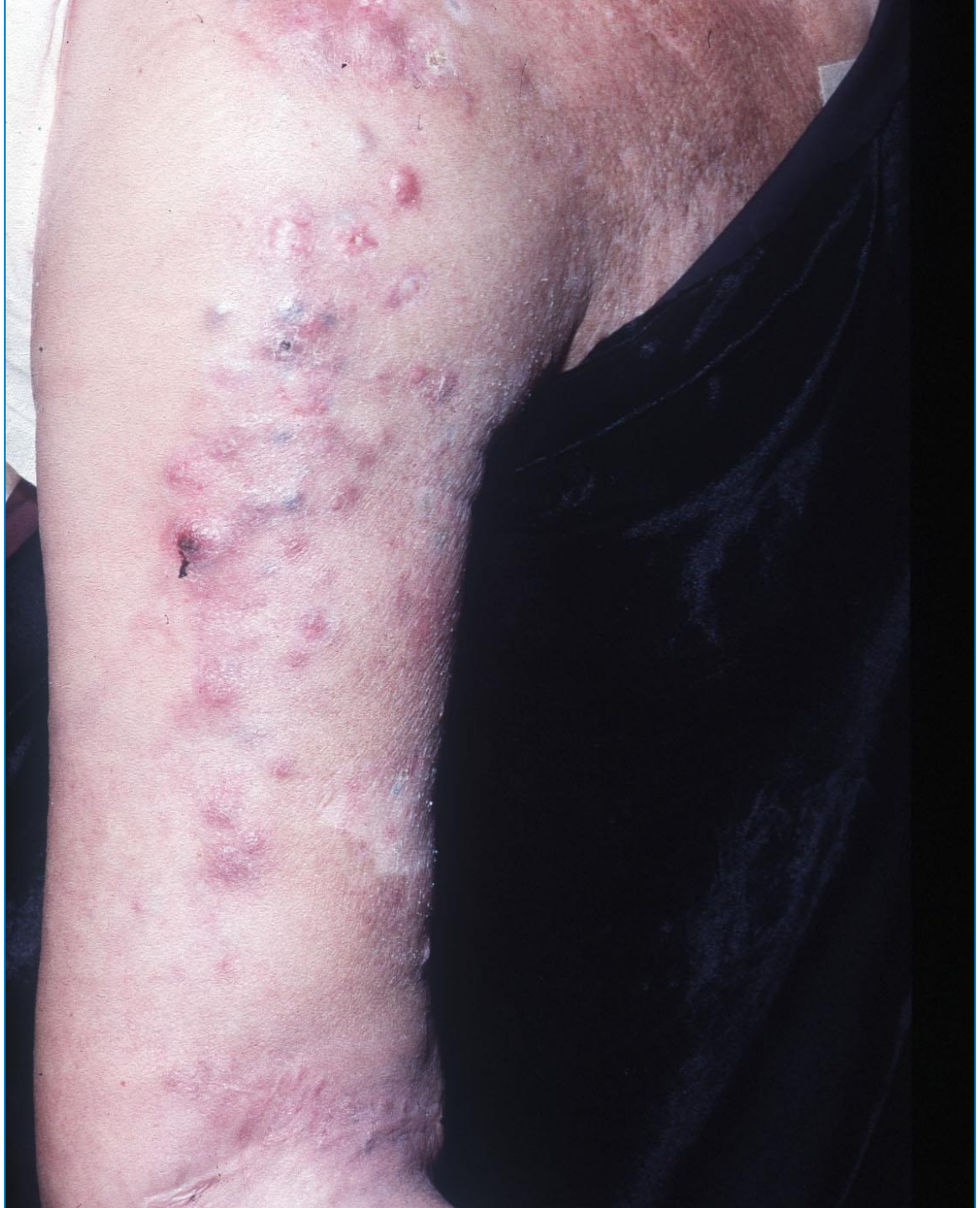
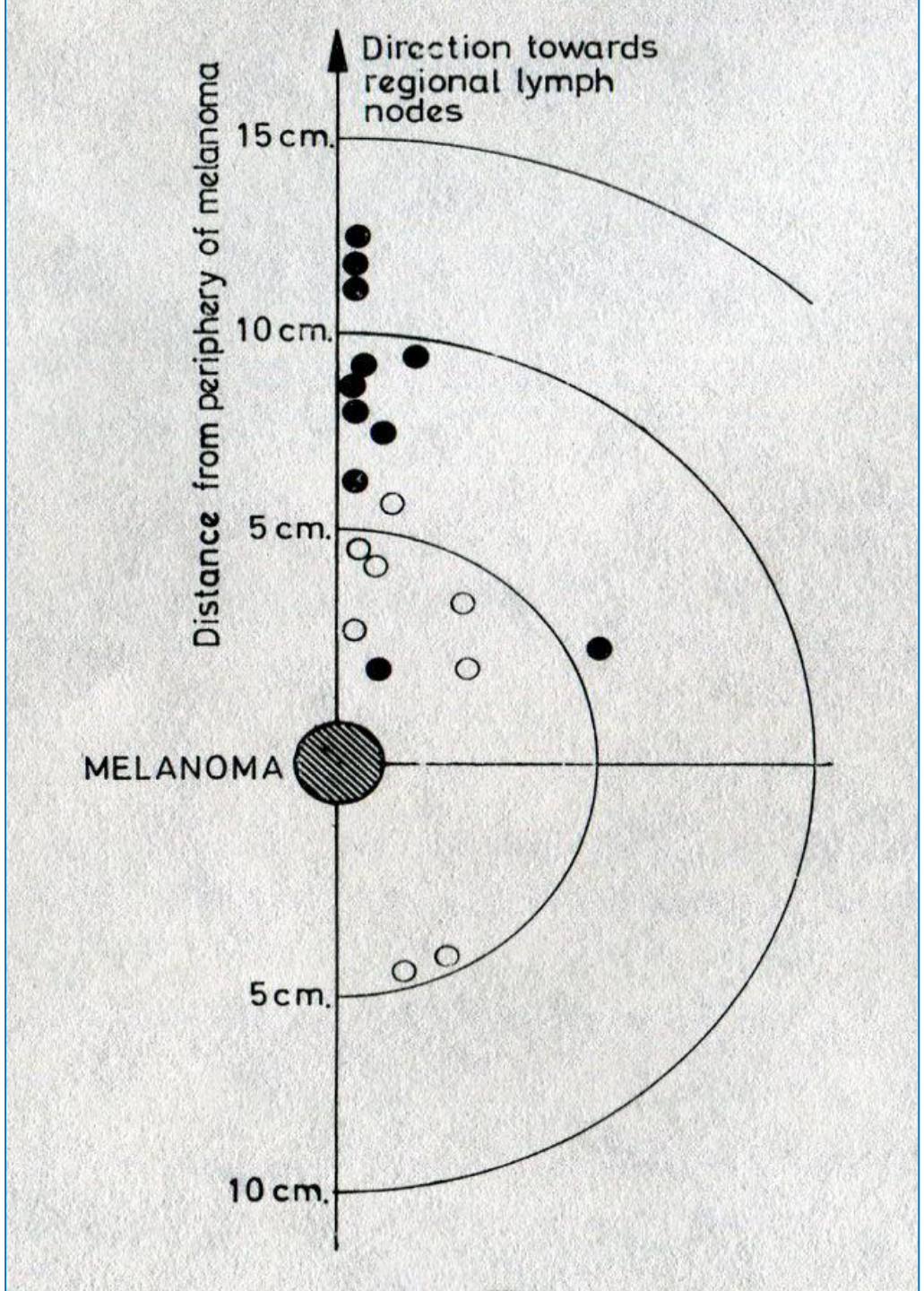
The fact that the eruption of the nodules in the chain generally starts distally and works proximally allows us to suggest that not only chain formation, but a *chain reaction* may be taking place, the later nodules being second-degree or third-degree metastases.

"The fact that the eruption of the nodules in the chain generally starts distally and works proximally allows us to suggest that not only chain formation, but a chain reaction may be taking place, the later nodules being second-degree or third-degree metastases."

Br J Plast Surg, 1962; 15: 49-116

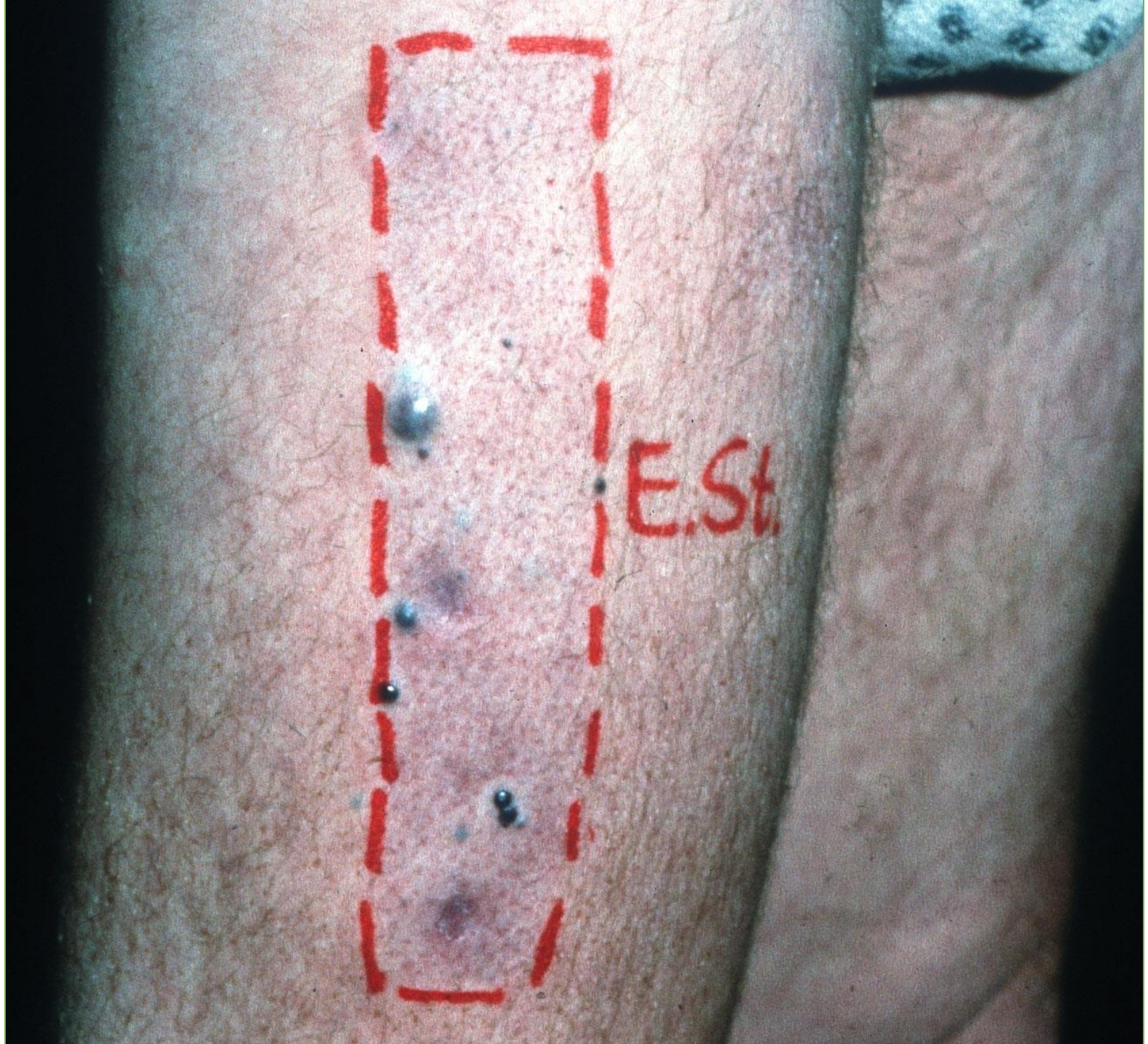


Of course, the concept that early metastases were the site of origin of later metastases, slowly advancing proximally toward lymph nodes and internal organs, made removal of the very first metastases, even occult ones, mandatory. The problem was that the site of occurrence of metastases could not be predicted.



Petersen measured the distance of cutaneous metastases to the site of the primary tumors and, on the basis of his findings, urged margins of excision of up to 15 cm.

Petersen's guidelines for treatment were the logical result of his concept of spread of melanoma. That concept, however, is wrong.



The idea of an orderly progression of metastases – from the vicinity of the primary melanoma to regional lymph nodes and then distant sites – is pure fiction. Even if cutaneous metastases are arranged in a chain, which is rare, there is no evidence of a “chain reaction.” Instead of gradual advancement toward lymph nodes, metastases further away from the primary site often occur earlier and are larger than those in its immediate vicinity. Moreover, there is no evidence that local metastases are the source of distant ones.

British Journal of Dermatology 2002; 147: 62–70.

Clinical and Laboratory Investigations

Metastatic pathways and time courses in the orderly progression of cutaneous melanoma

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Accepted for publication 14 March 2002

Summary

Background It is known that two-thirds of patients who develop clinical metastases following treatment of a primary cutaneous melanoma initially present with locoregional metastases and one-third initially present with distant metastases. However, few reports in the literature give detailed figures on different metastatic pathways in cutaneous melanoma.

Objectives The aim of the present study was to perform a detailed analysis of the different metastatic pathways, the time course of the development of metastases and the factors influencing them.

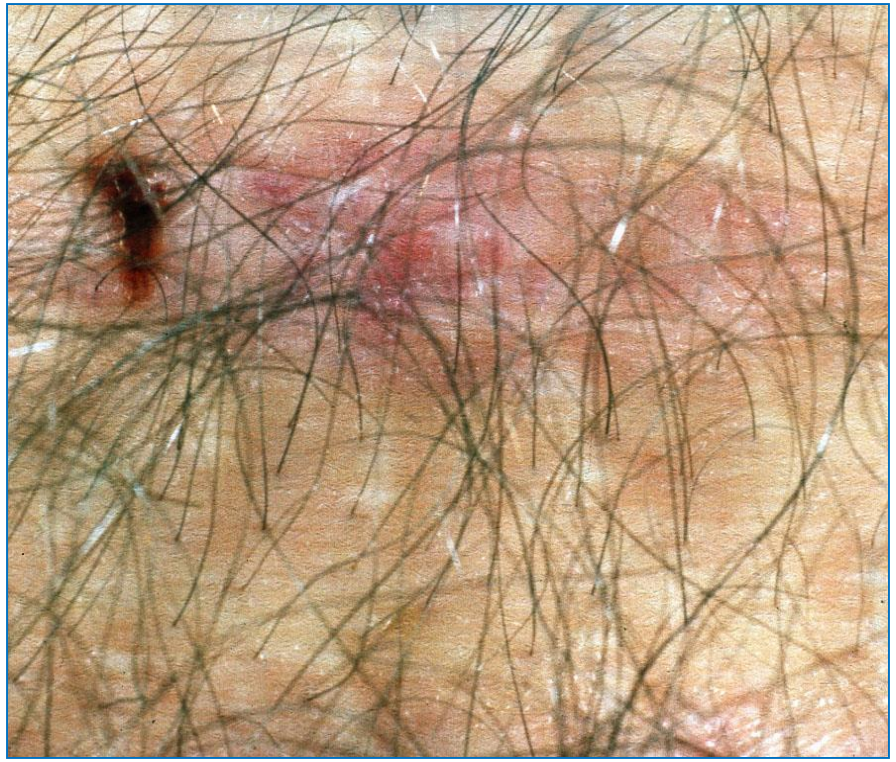
Methods In a series of 3001 patients with primary cutaneous melanoma at first presentation, 466 subsequently developed metastasis and were followed-up over the long term at the University of Tuebingen, Germany between 1976 and 1996. Different pathways of metastatic spread were traced. Associated risk factors for the different pathways were assessed. Differences in survival probabilities were calculated by the Kaplan–Meier method and evaluated by the log-rank test.

Results In 50·2% of the patients the first metastasis after treatment of the primary tumour developed in the regional lymph nodes. In the remaining half of the patient sample the first metastasis developed in the lymphatic drainage area in front of the regional lymph nodes, as satellite or in-transit metastases (21·7%) or as direct distant metastases (28·1%). Anatomical location, sex and tumour thickness were significant risk factors for the development of metastasis by different pathways. The most important risk factor appeared to be the location of the primary tumour. The median intervals elapsing before the first metastasis differed significantly between the different metastatic pathways. The direct distant metastases became manifest after a median period of 25 months, thus later than the direct regional lymph node metastases (median latency period, 16 months) and the direct satellite and in-transit metastases (median latency period, 17 months). In patients who developed distant metastases the period of development was independent of the metastatic route. The time at which the distant metastases developed was roughly the same (between 24 and 30 months after the detection of the primary tumour), irrespective of whether satellite or in-transit metastases, lymph node metastases or distant metastases were the first to occur.

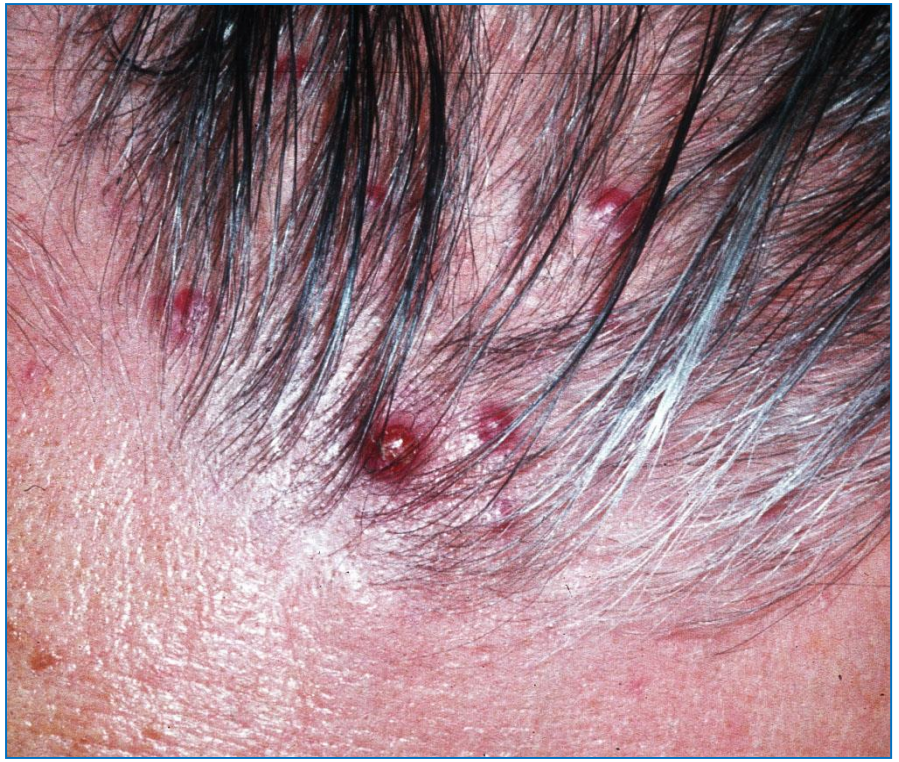
Conclusions The time course of the development of distant metastasis was more or less the same irrespective of the metastatic pathway; this suggests that in patients with in-transit or satellite metastasis or regional lymph node metastasis, haematogenic metastatic spread had already taken place. Thus, the diagnostic value of sentinel lymph node biopsy and the therapeutic benefit of elective lymph node dissection may be limited, as satellite and in-transit metastases or direct distant metastases will not be detected and haematogenous spread may already have taken place when the intervention is performed.

By contrast, a large study about metastatic pathways in melanoma found that *"the time at which the distant metastases developed was roughly the same ..., irrespective of whether satellite or in-transit metastases, lymph node metastases or distant metastases were the first to occur."* The authors concluded that *"in patients with in-transit or satellite metastases or regional lymph node metastases, haematogenic metastatic spread had already taken place."* In other words, satellite metastases do not carry a significant risk of their own; they are not the source, but only an indicator, of hematogenic metastases. Early removal of them, therefore, does not enhance chances for survival.

“local recurrence”



persistent
primary melanoma



satellite
metastases

In former times, prognosis of “satellite metastases” was thought to be relatively favorable. The reason was that they were not distinguished from re-growing primary melanomas that had been excised incompletely. Both phenomena are very different but were referred to by the same name, “local recurrence,” and were lumped together in statistical analyses. As a consequence, prognosis of persistent melanomas was thought to be much poorer and that of “satellite metastases“ much better than it actually is.

Table 17–2 The M. D. Anderson Cancer Center Staging System for Cutaneous Melanoma*

STAGE	CRITERIA
I	Primary melanoma
	IA: Intact primary melanoma
	IB: Primary melanoma, locally excised
	IC: Multiple primaries
II	Local recurrence or local metastases within 3 cm of primary site
III	Regional metastases
	IIIA: Tissues excluding nodes
	IIIB: Node(s)
	IIIAB: Skin etc. plus node(s)
IV	Distant metastases
	IVA: Cutaneous metastases only
	IVB: Any visceral metastases

* From Smith JL: Histopathology and biological behavior of melanoma. In Neoplasms of the Skin and Malignant Melanomas. Chicago, Year Book Medical Publishers, 1976

In old staging systems for cutaneous melanoma, such as the M.D. Anderson classification of 1976, prognosis of local metastases was judged to be more favorable than that of all other types of metastases. But this has changed.

Final Version of 2009 AJCC Melanoma Staging and Classification

Charles M. Balch, Jeffrey E. Gershenwald, Seng-jaw Soong, John F. Thompson, Michael B. Atkins, David R. Byrd, Antonio C. Buzaid, Alistair J. Cochran, Daniel G. Coit, Shouluan Ding, Alexander M. Eggermont, Keith T. Flaherty, Phyllis A. Gimotty, John M. Kirkwood, Kelly M. McMasters, Martin C. Mihm Jr, Donald L. Morton, Merrick I. Ross, Arthur J. Sober, and Vernon K. Sondak

A B S T R A C T

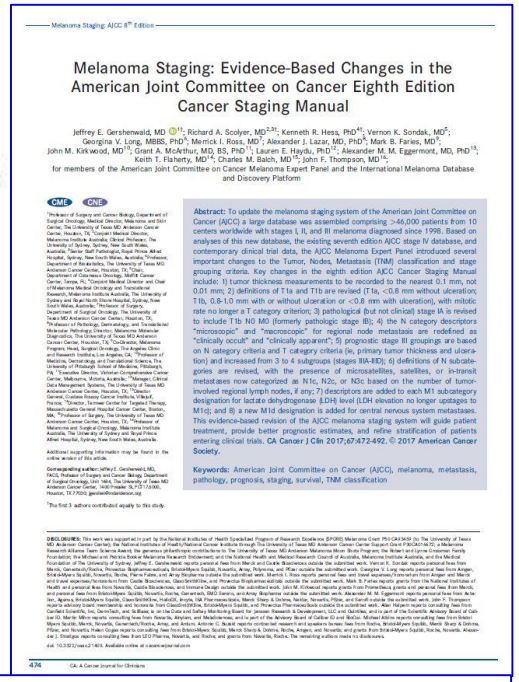
N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis*
		b: Macrometastasis†
N2	2-3	a: Micrometastasis*
		b: Macrometastasis†
		c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	

J Clin Oncol 27:6199-6206. © 2009 by American Society of Clinical Oncology

In the AJCC staging system of 2009, patients with "satellite metastases" were assigned to a worse prognostic category than those with micro- or macrometastases in lymph nodes.

EXTENT OF REGIONAL LYMPH NODE AND/OR LYMPHATIC METASTASIS

N CATEGORY	NO. OF TUMOR-INVOLVED REGIONAL LYMPH NODES	PRESENCE OF IN-TRANSIT, SATELLITE, AND/OR MICROSATELLITE METASTASES
NX	Regional nodes not assessed (eg, sentinel lymph node [SLN] biopsy not performed, regional nodes previously removed for another reason); Exception: pathological N category is not required for T1 melanomas, use clinical N information	No
N0	No regional metastases detected	
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	
N1b	One clinically detected	
N1c	No regional lymph node disease	
N2	Two or 3 tumor-involved nodes or any number of in-transit, satellite, and/or micro-satellite metastases with one tumor-involved node	
N2a	Two or 3 clinically occult (ie, detected by SLN biopsy)	
N2b	Two or 3, at least one of which was clinically detected	
N2c		
N3		
N3a		
N3b		
N3c	of matted nodes	


Melanoma Staging: AJCC 8th Edition

Melanoma Staging: Evidence-Based Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

Jeffrey E. Gershenwald, MD; Richard A. Scolyer, MD; Kenneth R. Hess, PhD; Vernon K. Sondak, MD; Georgina V. Long, MBBS, PhD; Merrick I. Ross, MD; Alexander J. Lazar, MD, PhD; Mark B. Faries, MD; John M. Kirkwood, MD; Grant A. McArthur, MD, BS, PhD; Lauren E. Haydu, PhD; Alexander M. M. Eggermont, MD, PhD; Keith T. Flaherty, MD; Charles M. Balch, MD; John F. Thompson, MD; for members of the American Joint Committee on Cancer Melanoma Expert Panel and the International Melanoma Database and Discovery Platform

CME CNE

Abstract: To update the melanoma staging system of the American Joint Committee on Cancer (AJCC) a large database was assembled comprising >46,000 patients from 10 centers worldwide with stages I, II, and III melanoma diagnosed since 1998. Based on analyses of this new database, the existing seventh edition AJCC stage IV database, and contemporary clinical trial data, the AJCC Melanoma Expert Panel introduced several important changes to the Tumor, Nodes, Metastasis (TNM) classification and stage grouping criteria. Key changes in the eighth edition AJCC Cancer Staging Manual include: 1) tumor thickness measurements to be recorded to the nearest 0.1 mm, not 0.01 mm; 2) definitions of T1a and T1b are revised (T1a, <0.8 mm without ulceration; T1b, 0.8-1.0 mm with or without ulceration or <0.8 mm with ulceration), with mitotic rate no longer a T category criterion; 3) pathological (but not clinical) stage IA is revised to include T1b N0 M0 (formerly pathologic stage IB); 4) the N category descriptors "microscopic" and "macroscopic" for regional node metastasis are redefined as "clinically occult" and "clinically apparent"; 5) prognostic stage III groupings are based on N category criteria and T category criteria (ie, primary tumor thickness and ulceration) and increased from 3 to 4 subgroups (stages IIIA-IIID); 6) definitions of N subcategories are revised, with the presence of microsatellites, satellites, or in-transit metastases now categorized as N1c, N2c, or N3c based on the number of tumor-involved regional lymph nodes, if any; 7) descriptors are added to each M1 subcategory designation for lactate dehydrogenase (LDH) level (LDH elevation no longer upstages to M1c); and 8) a new M1d designation is added for central nervous system metastases. This evidence-based revision of the AJCC melanoma staging system will guide patient treatment, provide better prognostic estimates, and refine stratification of patients entering clinical trials. CA Cancer J Clin 2017;67:472-492. © 2017 American Cancer Society.

Keywords: American Joint Committee on Cancer (AJCC), melanoma, metastasis, pathology, prognosis, staging, survival, TNM classification

474 CA: A Cancer Journal for Clinicians

Microsatellites, satellites, and in-transit metastases have been shown to portend a relatively poor prognosis.

In the most recent version of "AJCC melanoma staging" that has been implemented this year, "satellite", "in-transit" and lymph node metastases have been placed in the same category, but with a note that *"microsatellites, satellites, and in-transit metastases have been shown to portend a relatively poor prognosis."*

Multivariate Analysis of Prognostic Factors in Regional Cutaneous Metastases of Extremity Melanoma

S. EVA SINGLETARY, MD,* SUSAN L. TUCKER, PHD,† AND ARTHUR W. BODDIE JR, MD*

In 135 patients with regional cutaneous recurrence of extremity melanoma, the prognostic significance of 12 clinical and pathologic variables was analyzed in four alternative Cox stepwise regression models and by single variable analysis. A highly significant fit of the regression ($P < 0.01$) identified four factors that particularly influenced survival: the presence of intradermal or mixed (as opposed to purely subcutaneous) metastases ($P < 0.001$), sex ($P = 0.032$), excision of regional cutaneous metastases with or without perfusion ($P = 0.033$), and the presence of subcutaneous metastases ($P = 0.201$). Not predictive of survival were age at diagnosis; site of primary; anatomic location, number, size, or distance from the primary of the regional cutaneous metastases; time since primary treatment; number of positive regional lymph nodes; and single- or triple-drug perfusion.

***Cancer* 61:1437–1440, 1988.**

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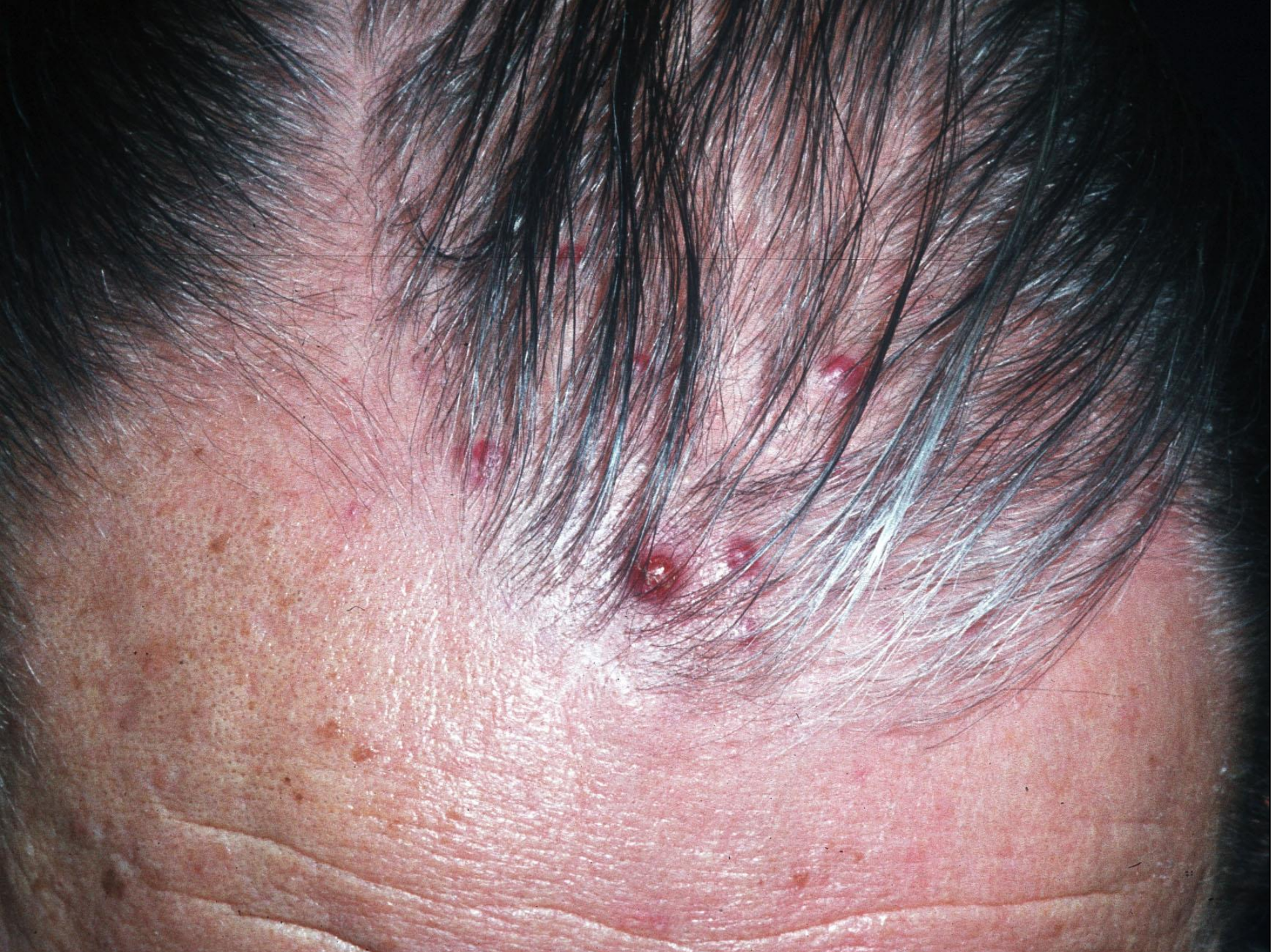
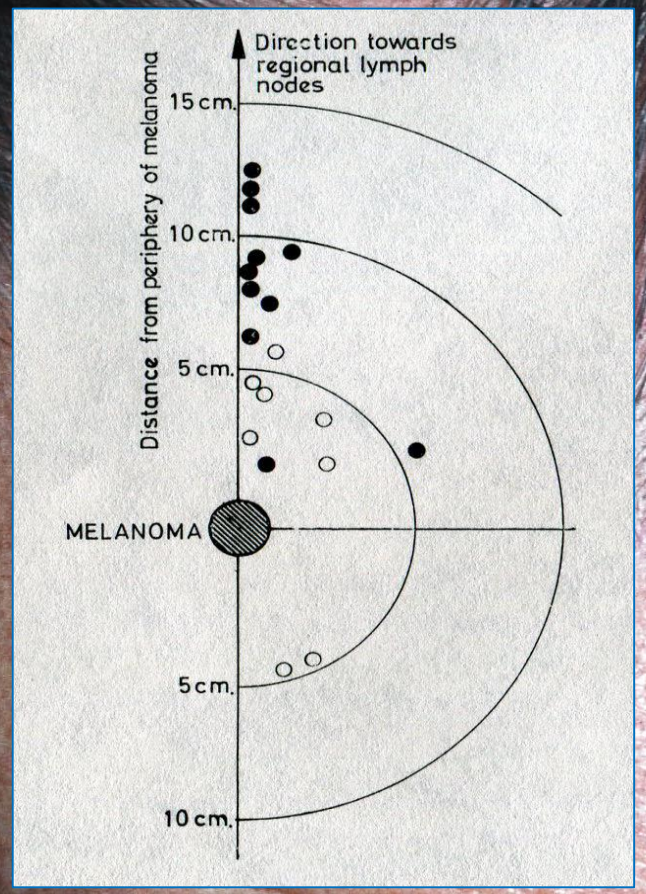
life-table method. Prognostic factors were identified by

The virulent clinical behavior of extremity melanoma complicated by regional cutaneous metastases is reflected in the deaths of 102 of the 135 patients (76%) from disseminated melanoma.

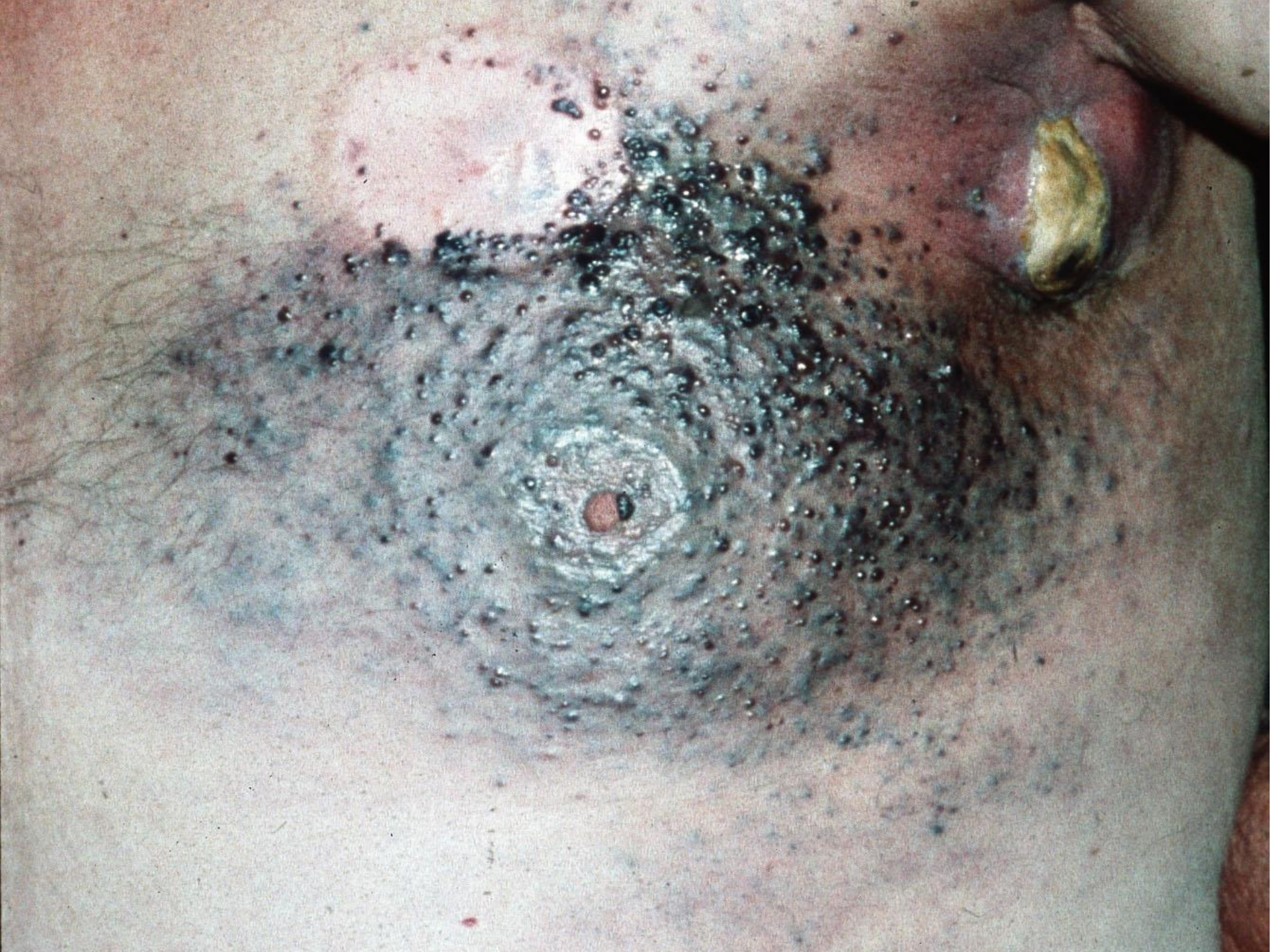
For example, Singletary found in 1988 that *"the virulent clinical behavior of extremity melanoma complicated by regional cutaneous metastases is reflected in the deaths of 102 of the 135 patients (76%) from disseminated* melanoma."



In short, patients with regional cutaneous metastases have little benefit from surgical treatment because they usually have disseminated disease. This is not to say that such metastases should not be treated once they become apparent, but it makes no sense to cut out clinically normal skin under the vague assumption that there might be some occult micrometastasis, especially because one cannot predict their location. Metastases do not obey the 1 to 3 cm-rule of surgeons but may appear at any site.

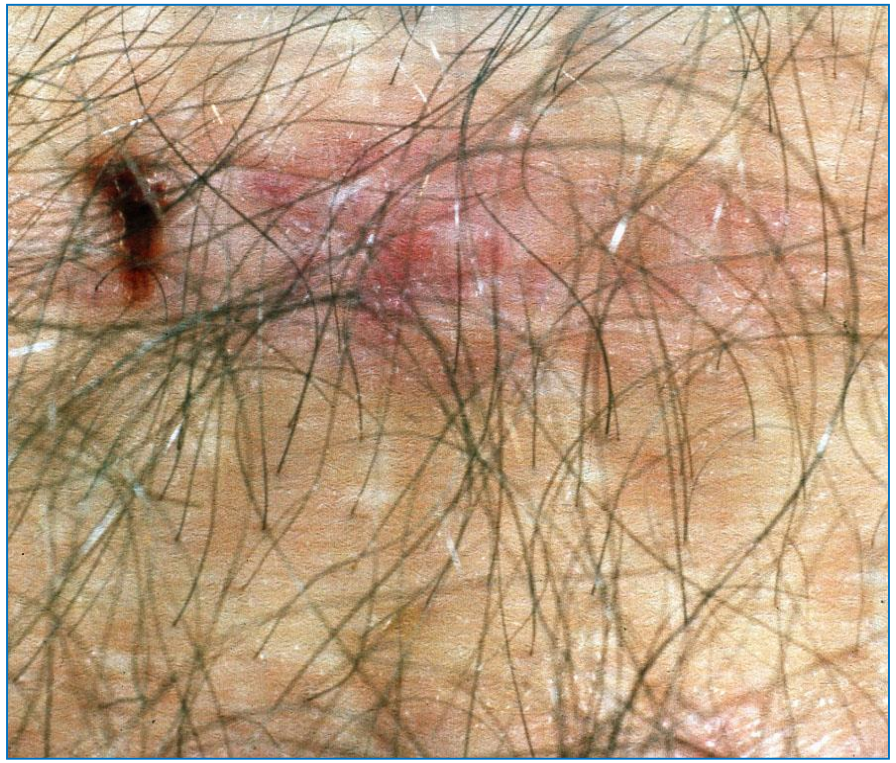


Petersen found them 15 cm away from the primary tumor and suggested to extend margins of excision to cover that distance.

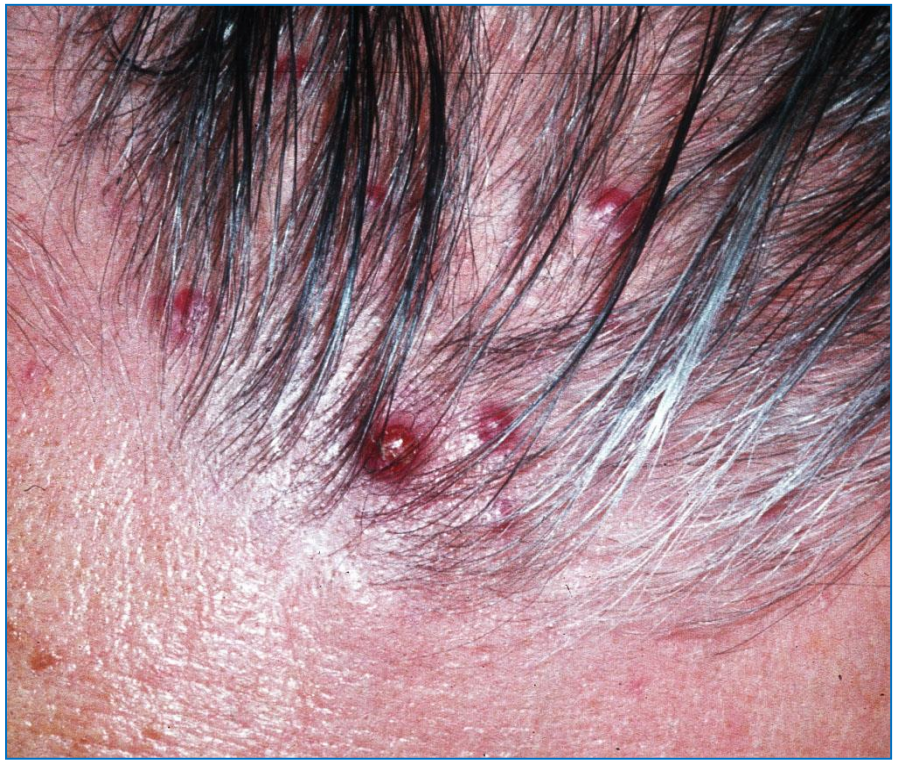


But what would he have recommended in a case such this one? If one takes into account all information available today, only one conclusion is possible: surgical procedures for the purpose of removing clinically inapparent “satellite metastases” are not justifiable.

rationale for deep and wide excisions



prevention of persistence of the primary melanoma



removal of clinically inapparent satellite metastases

The second possible rationale for wide excisions is much more compelling, namely, prevention of persistence of the primary melanoma. The borders of melanoma are often indistinct, and it may be extremely difficult to determine the true extent of the lesion. Therefore, melanomas may occasionally persist at the local site although they seemed to have been removed completely. Today, this is a rare event,

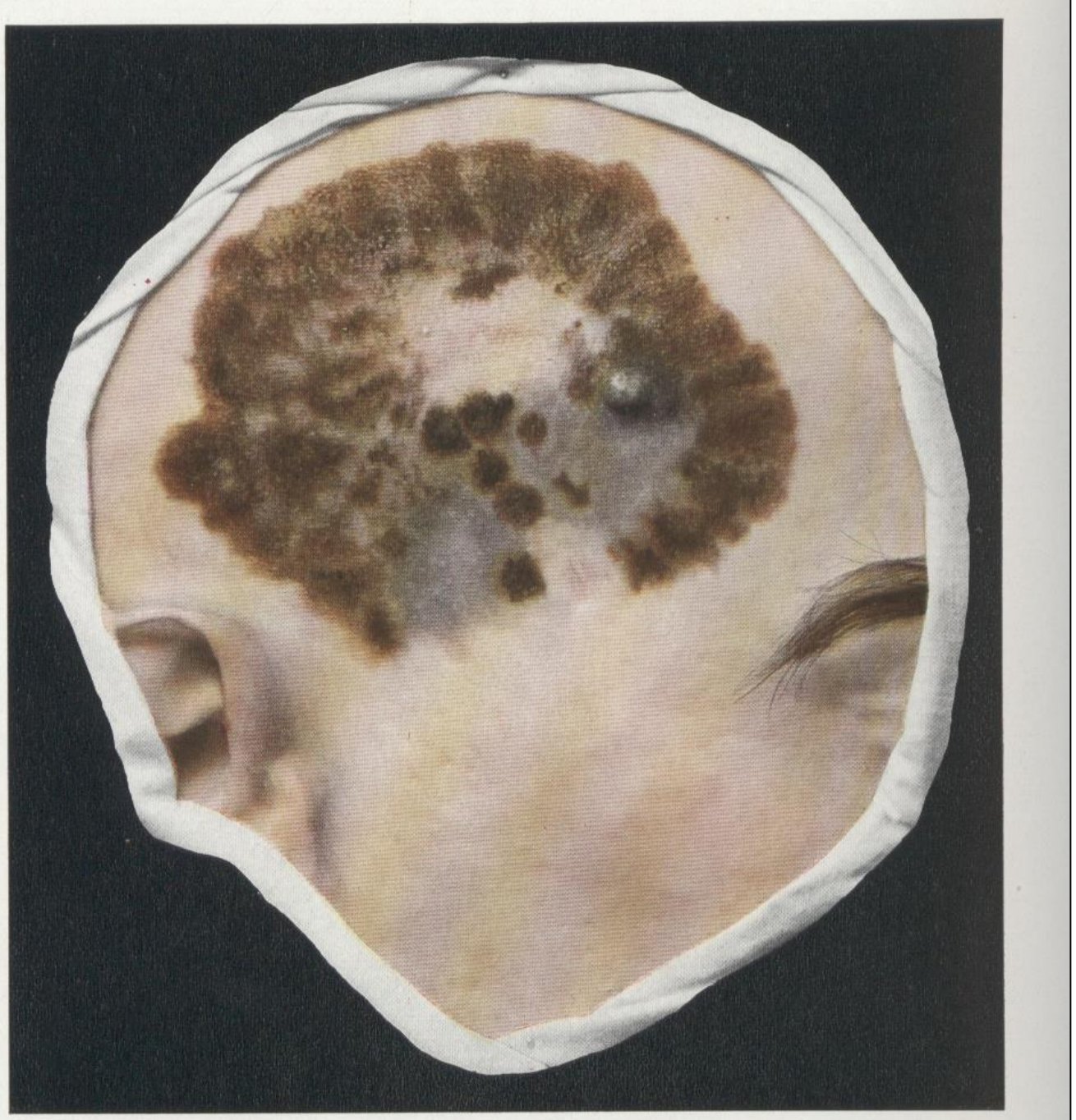


Abb. 47. Ausgedehnte melanotische Präcancerose mit Tumorbildung oder Naevus tardus in maligner Entartung?

but it was common in the past when dermatologists focused on the nodule only. Only the latter was considered to be malignant whereas the macular component was interpreted as a nevus or, at best, as “melanotic precancerosis” that was often left in place.

TRAVAUX ORIGINAUX

DE LA MÉLANOSE CIRCONSCRITE PRÉCANCÉREUSE

Par **M. W. Dubreuilh.**

I

Les tumeurs malignes d'origine épithéliale sont très fréquemment précédées et préparées par des lésions d'apparence bénigne qu'on peut appeler lésions précancéreuses ou plus brièvement précancéroses.

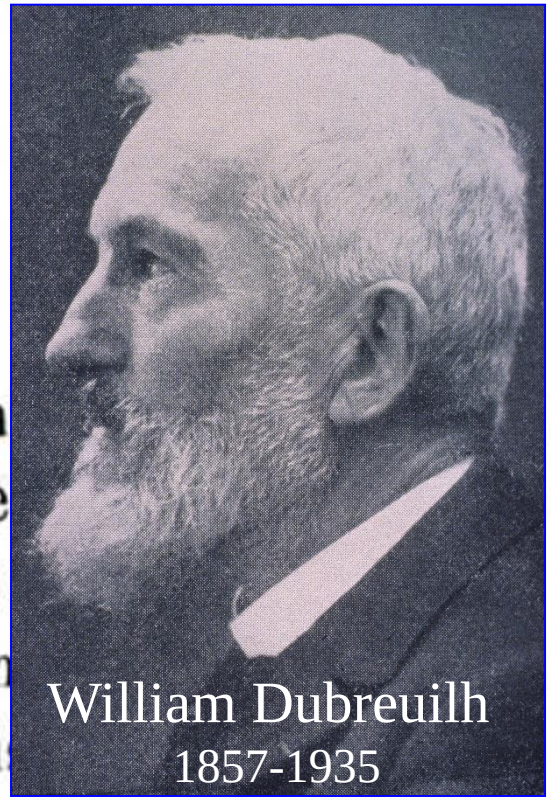
Ces lésions peuvent rester indéfiniment stationnaires, elles peuvent même guérir spontanément mais tant qu'elles existent elles sont susceptibles de donner naissance à une néoplasie maligne. Ce n'est pas

For example, William Dubreuilh who coined the term precancerosis and described melanoma in situ under the name, "melanose circonscrite précancéreuse,"

TRAVAUX ORIGINAUX

DE LA MÉLANOSE CIRCONSCRITE PRÉCANCÉREUSE

Par **M. W. Dubreuilh.**


William Dubreuilh
1857-1935

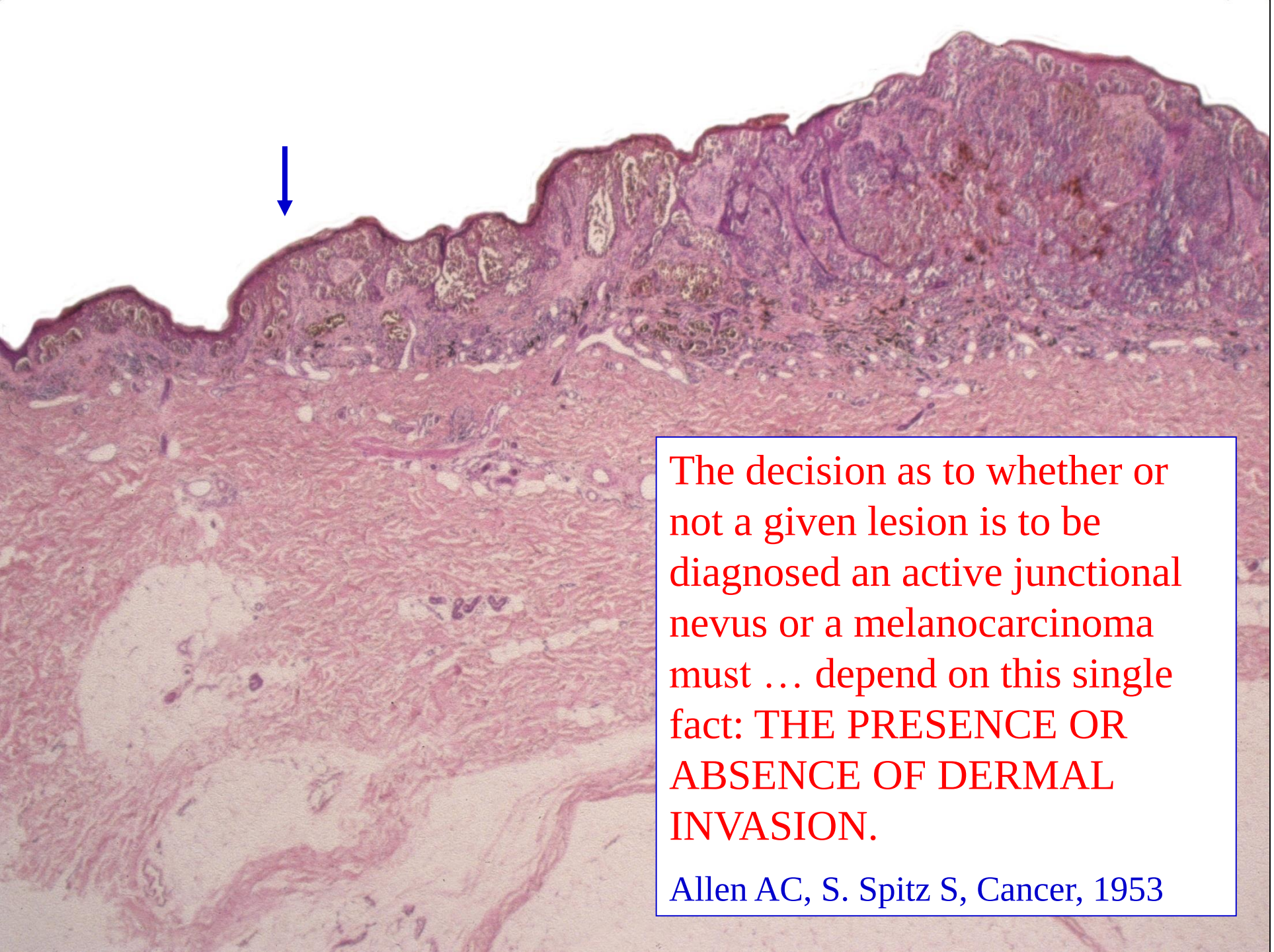
To me, the surgical operation does not seem to be justified in regard to the pure melanosis … One would have to be sure that it is really radical and that one exceeds the limits of the lesion. But we do not know those limits. …. One should remove the tumor completely, but not the entire melanotic plaque, especially when it is extensive and when the operation necessitates considerable disfigurement.

William Dubreuilh, 1912

ceptibles de donner naissance à une néoplasie maligne. Ce n'est pas

stated in 1912 that, *"to me, the surgical operation does not seem to be justified in regard to the pure melanosis … One would have to be sure that it is really radical and that one exceeds the limits of the lesion. But we do not know those limits. …. One should remove the tumor completely, but not the entire melanotic plaque, especially when it is extensive and when the operation necessitates considerable disfigurement."*

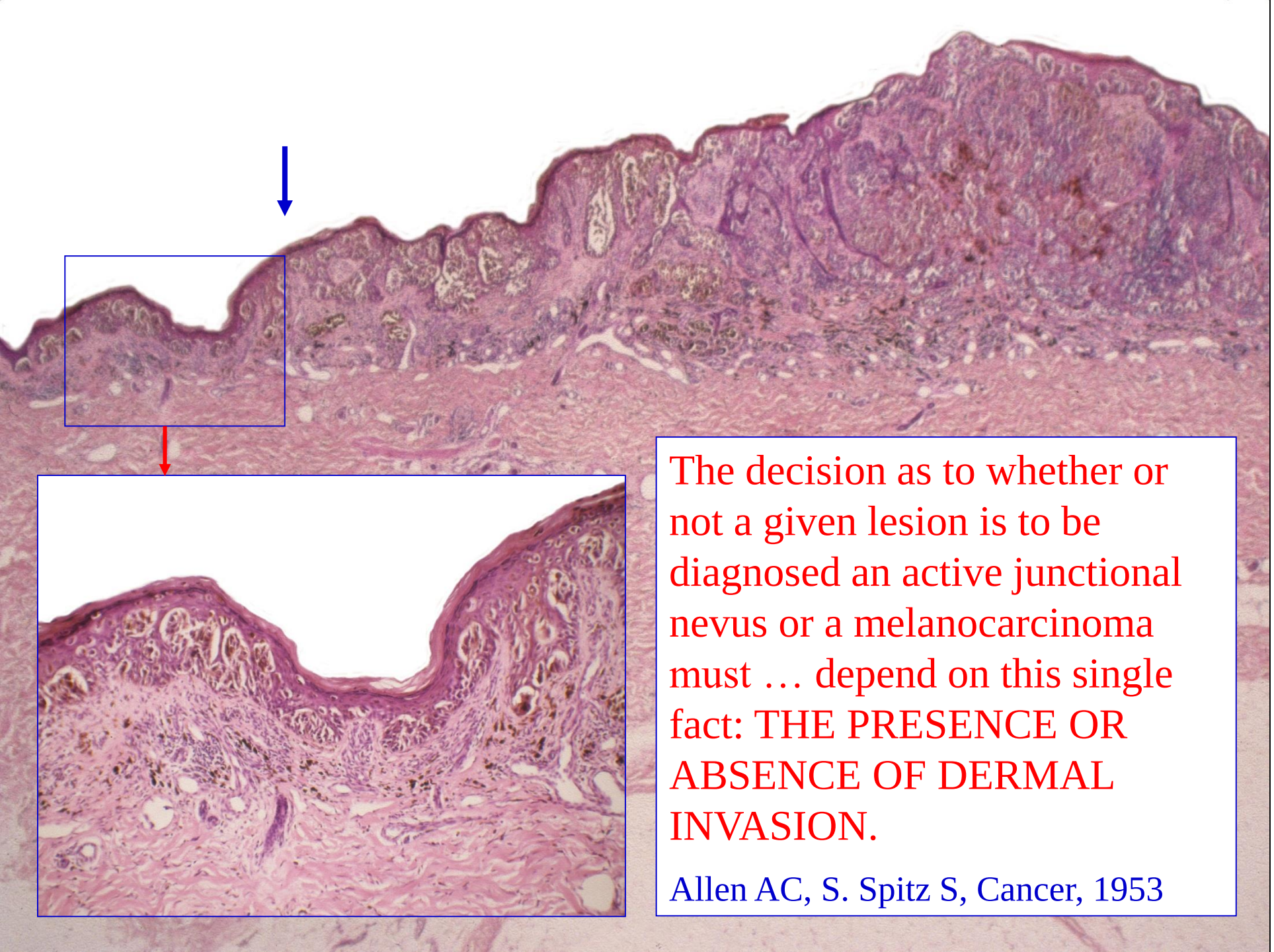
As late as in the mid 20th century, the diagnosis of melanoma was accepted only in the presence of an intradermal component. In 1953, Allen and Spitz stated unambiguously: *"The decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must ... depend on this single fact: THE PRESENCE OR ABSENCE OF DERMAL INVASION."* Accordingly, a lesion such as this one qualified as melanoma,



The decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must … depend on this single fact: THE PRESENCE OR ABSENCE OF DERMAL INVASION.

Allen AC, S. Spitz S, Cancer, 1953

but only to the point where the last melanocytes resided in the dermis. The rest of the lesion was qualified as junctional nevus,

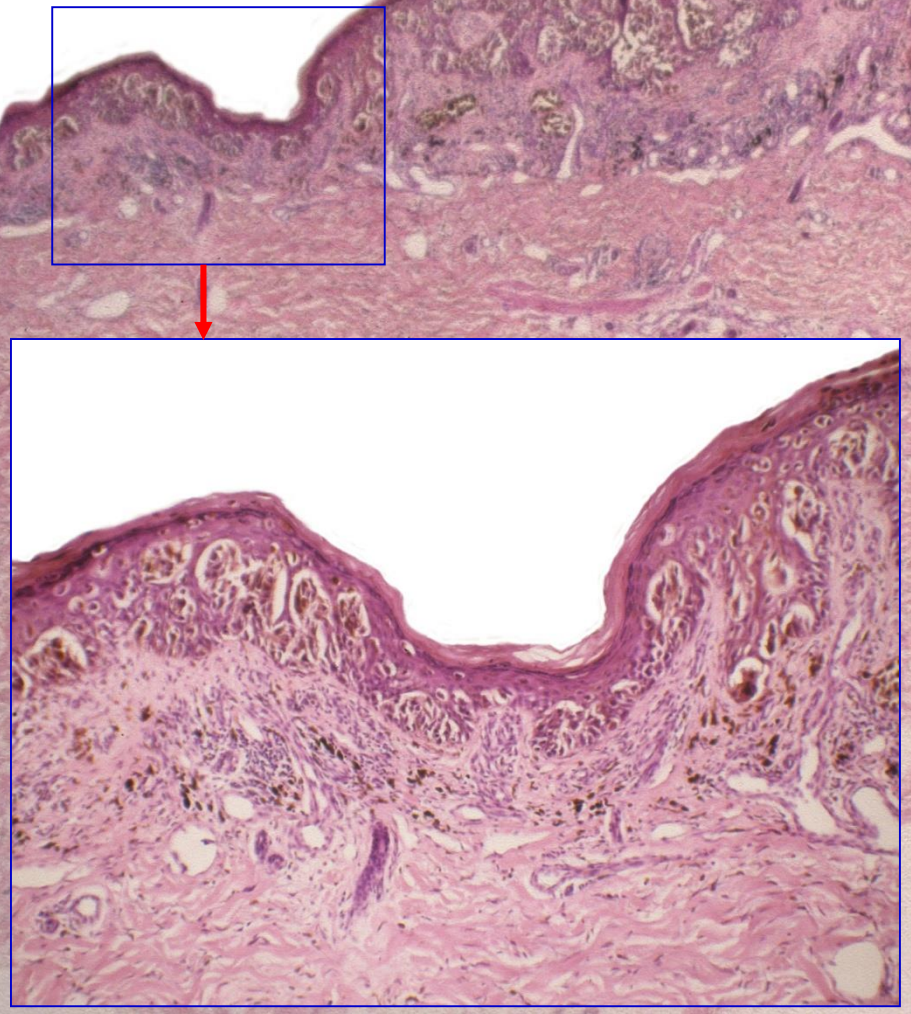


The decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must … depend on this single fact: THE PRESENCE OR ABSENCE OF DERMAL INVASION.

Allen AC, S. Spitz S, Cancer, 1953

despite the presence of markedly atypical melanocytes throughout the epidermis. Of course, Allen and Spitz were experienced pathologists and knew full well that these were not the changes of an ordinary nevus. To explain that discrepancy,

“Activation hypothesis”



It is our impression that in patients with cutaneous melanocarcinomas there is a tendency to activate junctional nevi. Possibly that tendency receives more concentrated expression in the epidermis in the vicinity of the primary tumor.

Allen AC, S. Spitz S, Cancer, 1953

they introduced the “activation hypothesis.“ This is what they wrote: *“... it is our impression that in patients with cutaneous melanocarcinomas there is a tendency to activate junctional nevi. Possibly that tendency receives more concentrated expression in the epidermis in the vicinity of the primary tumor.”*

MALIGNANT MELANOMAS OF THE SKIN

A Study of the Origin, Development, Ætiology, Spread, Treatment, and Prognosis

By N. C. Petersen, D. C. Bodenham, F.R.C.S.E., and O. C. Lloyd, M.D.

From the Department of Plastic Surgery, Frenchay Hospital, and the Department of Pathology, University of Bristol

PART I

This study is based on a consecutive series of 226 tumours in 220 cases, examined and treated by a single team during the period 1947 to 1960. The opportunity has also been taken to include certain facts from an additional consecutive series of 401 cases from the records of the South Western Regional Cancer Bureau during the same period and which have been treated by other surgeons. This total of 621 represents the majority of all cases of melanoma occurring in a well-defined population averaging 2·8 million during the thirteen years under review and representing an incidence of 1·7 per 100,000. However, the number of registered cases is rising and the true incidence may well be in the order of 2·5 per 100,000, as found in a survey of the Danish Cancer Bureau, 1953 to 1957 (Clemmesen and Schultz, 1960) (*see also* Table I).

The study began in 1947 when it became apparent that sufficient material was being referred to us to justify a long-term survey.

From the outset, all excised material has been examined histologically by one of us (O. C. L.). All cases have been operated on by members of a closely integrated team according to agreed standards. All cases have been followed up at intervals of three months for the first one to two years, and thereafter every six months, mostly by the team, but when the patients have left the area, by arrangement with other specialists or practitioners. In only two cases has final information had to be obtained from relatives, both patients being alive and well at the time of this report. This has resulted in an up-to-date follow-up on every one of the 220 cases treated by the team.

Policy during Survey.—The features of malignancy are generally so evident to the experienced observer that we have usually gone ahead with elective surgery. If, however, any doubt should exist we have carried out an excisional biopsy and in some cases had a frozen section.

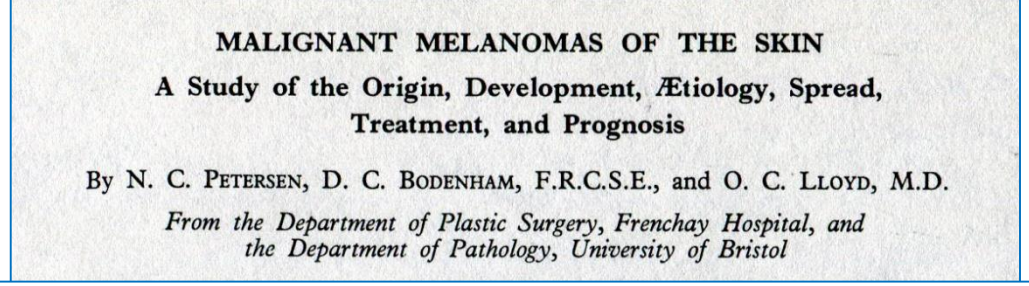
A number of patients have had an incisional biopsy or an incomplete excision before being referred, in which case the original section or block has, in all cases except one, been examined by one of us (O. C. L.) to confirm diagnosis and establish staging.[1]

The extent of the excision has been related to the stage of the lesion, the site of origin, and the age of the patient.

[1] The recognition of three stages in the development of malignant melanomas is described on page 58. The criteria are new, based on the morbid anatomy, and have been found to be useful in prognosis. They do not correspond to the clinical stages described by some other writers, *e.g.*, George *et al.* (1960).

The “activation hypothesis” was subsequently expanded by Petersen who stated in 1962:

Br J Plast Surg, 1962; 15: 49-166



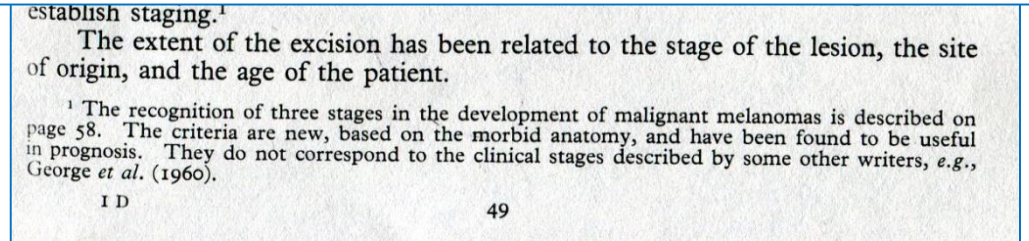
MALIGNANT MELANOMAS OF THE SKIN

A Study of the Origin, Development, Ætiology, Spread, Treatment, and Prognosis

By N. C. Petersen, D. C. Bodenham, F.R.C.S.E., and O. C. Lloyd, M.D.

From the Department of Plastic Surgery, Frenchay Hospital, and the Department of Pathology, University of Bristol

Melanocytes are linked together by ... processes to form a continuous system in the skin ... This is of importance when one comes to consider the margin of excision of a lesion, for the malignant potential ... will often have been communicated outside the zone of visible pigmentation ... The linking together of epidermal melanocytes by their dendritic processes provides the means by which these potentials may be passed from one cell to the next.



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Br J Plast Surg, 1962; 15: 49-166

"Melanocytes are linked together by ... processes to form a continuous system in the skin ... This is of importance when one comes to consider the margin of excision of a lesion, for the malignant potential of a malignant lentigo will often have been communicated outside the zone of of visible pigmentation ... The linking together of epidermal melanocytes by their dendritic processes provides the means by which these potentials may be passed from one cell to the next."

ACTA CHIRURGICA SCANDINAVICA
SUPPLEMENTUM 365

THE MALIGNANT MELANOMA OF THE SKIN

NEW THEORIES BASED ON A STUDY OF 500 CASES

BY

GRETE OLSEN

THE FINSEN INSTITUTE
AND RADIUM CENTRE

Although there was no evidence for that mysterious “malignant potential,” Petersen’s concept was spread under the designations “field change” or “contamination hypothesis.” The latter term was coined in 1966 by Grete Olsen of Sweden

ACTA CHIRURGICA SCANDINAVICA
SUPPLEMENTUM 365

THE MALIGNANT MELANOMA OF THE SKIN

METASTASIZATION BY "CONTAMINATION"

It has been mentioned already (p. 17) that *Masson* described the mutual connection between the melanocytes through the dendrites and their "cytocrine function", i. e. their production of pigment and its transport *via* the dendrites to the surrounding cells. Furthermore, *Lloyd* (1962) is of the opinion that other substances too are transported by this route, substances which may activate, and possibly, malignize other melanocytes.

Since the present author has found, in several histological preparations, a certain activation of melanocytes, and in one case actual malignization of cells at a certain distance from the tumour, this form of spread is considered, if not proved, then at least possible and likely (Fig. 19). It is, therefore, included in the survey of metastasization in spite of the fact it does not quite fulfill the classic definition of a metastasis:

who explained that she had *"found, in several histologic preparations, a certain activation of melanocytes, and in one case actual malignization of cells, at a certain distance from the tumour."*

Dermatologica *141*: 215–225 (1970)

A Study of Melanocytes in the Normal Skin Surrounding Malignant Melanomata[1]

C. K. Wong[2]

Department of Dermatology, The Radcliffe Infirmary, University of Oxford

Abstract. The melanocytes situated in the skin at a distance of 5 cm from the edge of the tumour in 12 cases of malignant melanoma were studied both quantitatively and morphologically.

Dopa reaction showed in 7 out of the 12 cases an increase in the number of melanocytes compared with normal figures. In certain cases some of the melanocytes showed bizarre morphological appearances and the interpretation of this is discussed.

The same observation was made by Wong who in 1970 studied *"melanocytes situated in the skin at a distance of 5 cm from the edge of the tumour"* and noted some "*bizarre morphological appearances.*"

HISTOLOGY AND PROGNOSIS IN MALIGNANT MELANOMA

J Pathol 1969; 97: 459-468

A. J. COCHRAN

Department of Pathology, University of Glasgow

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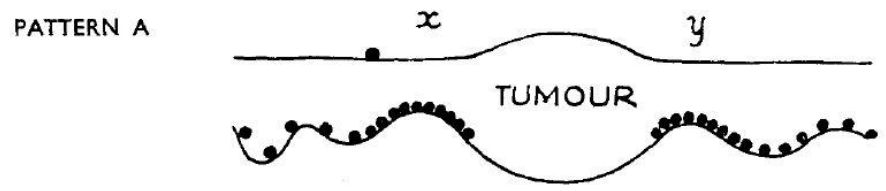
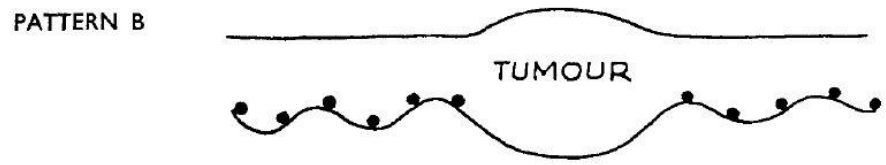
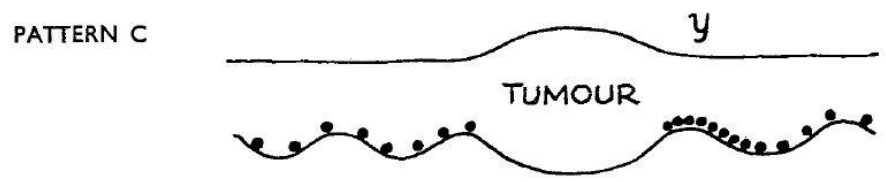
8. *Field change*. In an attempt to delineate more accurately the patterns of field change that undoubtedly exist around primary malignant melanomas, the incidence of melanocytes was assessed in the *stratum basale* of the epidermis adjacent to the tumour. These cells were counted in vertical skin sections. At least 500 cells in the *stratum basale* were identified and counted and the incidence



The incidence of basal melanocytes increases as the tumour is approached. Junctional activity may be present at or between *x* and *y*.



Incidence of melanocytes is similar to that normal for the site of the tumour. Junctional activity present over tumour only.



A combination of A and B. Junctional activity may be present at y as well as over tumour.

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Alistair Cochran observed three different patterns of melanocytes in the vicinity of melanomas. "Pattern A" consisted of an increased number of solitary melanocytes at both sides of the nodule, a constellation referred to as "field change." In "pattern B", solitary melanocytes were not increased in number, and then there were cases with an increase only at one side.

HISTOLOGY AND PROGNOSIS IN MALIGNANT MELANOMA

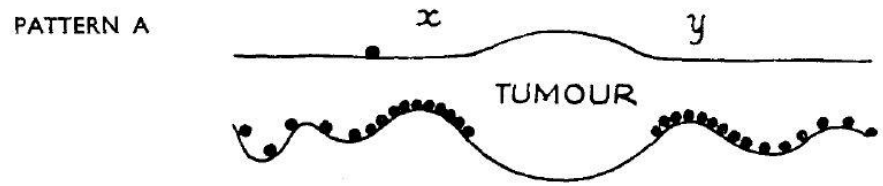
J Pathol 1969; 97: 459-468

A. J. COCHRAN

Department of Pathology, University of Glasgow

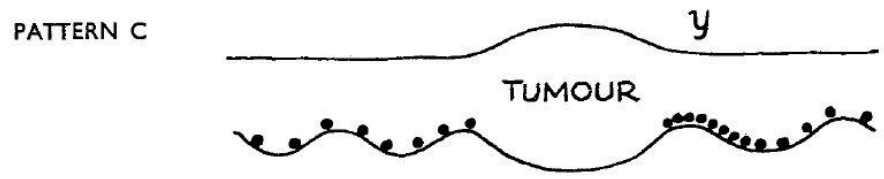
ONE of the ch… vide range of its histologica… rance can be regarded as a… earances that seem related … uthors have reported on th… ften " malig- nant melanon… pathologists. The acceptan… d be assessed and included i… presentation of series of m… athology and its relevance t… vas prepared. The clinical f… be published elsewhere (Co…

8. *Field change*. In an attempt to delineate more accurately the patterns of field change that undoubtedly exist around primary malignant melanomas, the incidence of melanocytes was assessed in the *stratum basale* of the epidermis adjacent to the tumour. These cells were counted in vertical skin sections. At least 500 cells in the *stratum basale* were identified and counted and the incidence



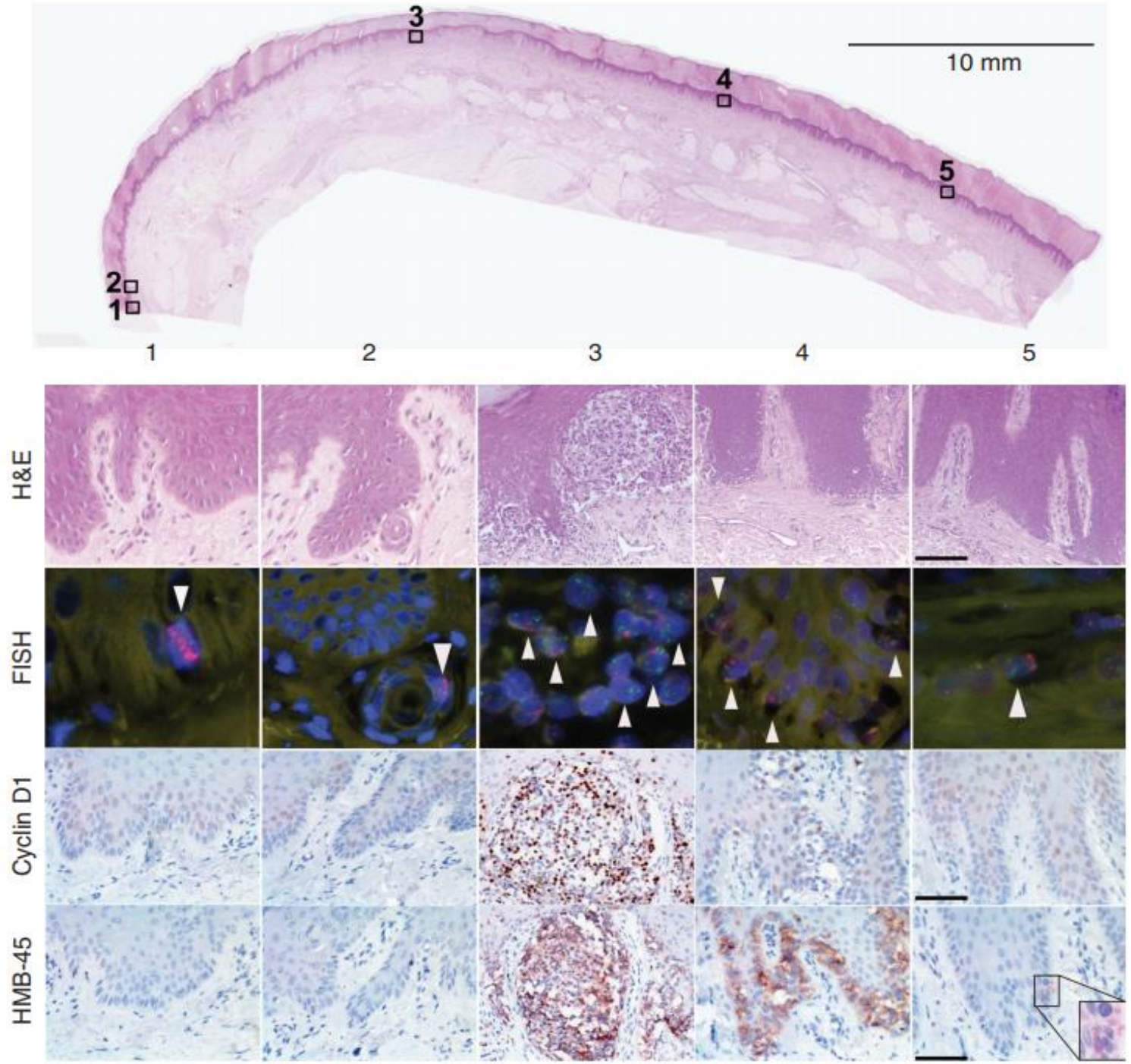
The incidence of basal melanocytes increases as the tumour is approached. Junctional activity may be present at or between *x* and *y*.

It is difficult to explain the occurrence of pattern C if … melanocyte increase is the result of locally active substances produced by the tumour.



A combination of A and B. Junctional activity may be present at y as well as over tumour.

Cochran acknowledged that *"it is difficult to explain the occurrence of pattern C if … melanocyte increase is the result of locally active substances produced by the tumour,"* but he did not arrive at the obvious conclusion suggested by the asymmetrical pattern, namely, that those cells were part of the melanoma.



In the meantime, there is further evidence for that conclusion. Molecular studies in acral melanomas have shown that specific genetic alterations of tumor cells are present in individual melanocytes in seemingly normal skin at a distance from the obvious melanoma.

ORIGINAL ARTICLE

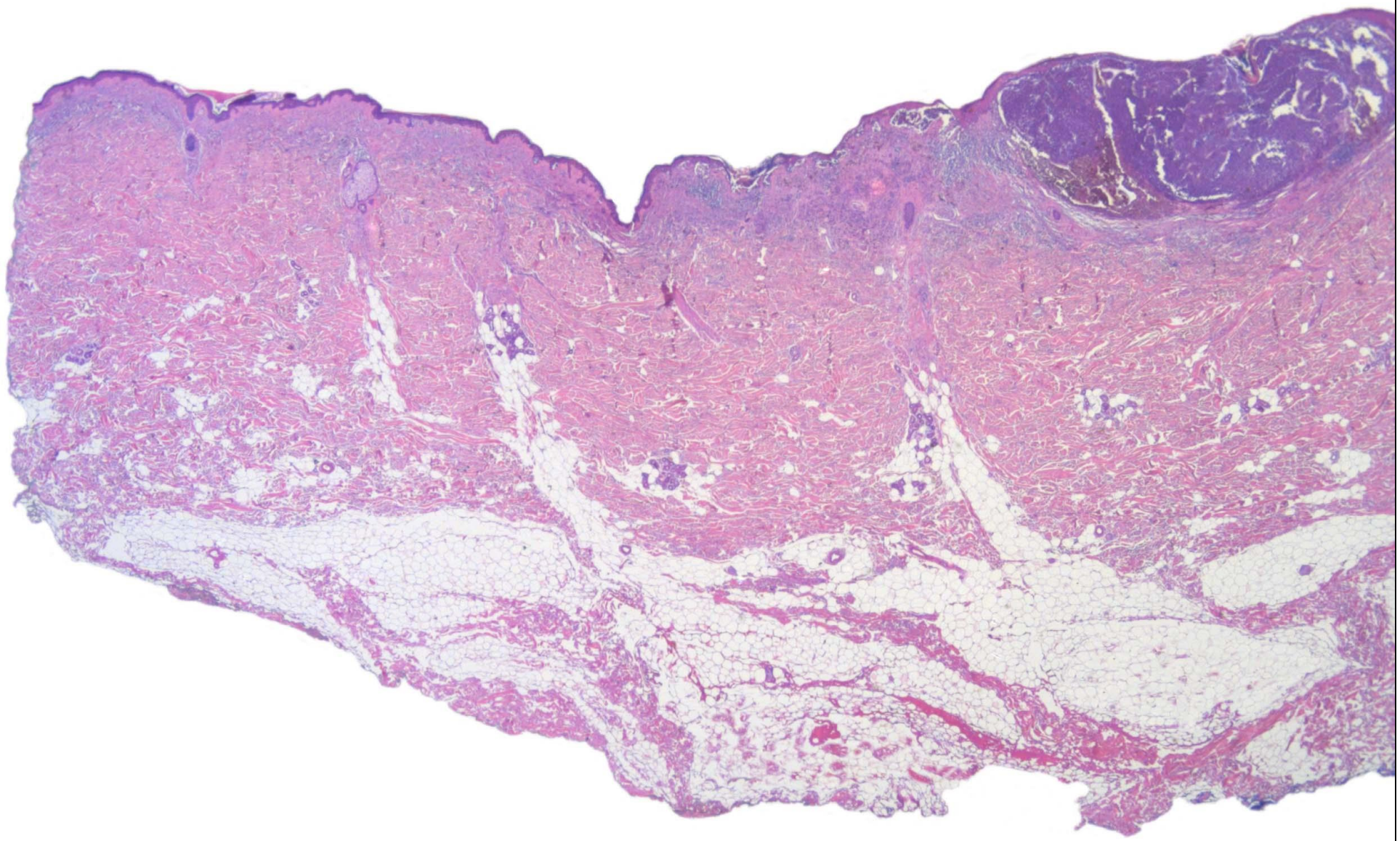
Distribution and Significance of Occult Intraepidermal Tumor Cells Surrounding Primary Melanoma

Jeffrey P. North[1,2], Toshiro Kageshita[3], Daniel Pinkel[4,5], Philip E. LeBoit[4,6] and Boris C. Bastian[4,6]

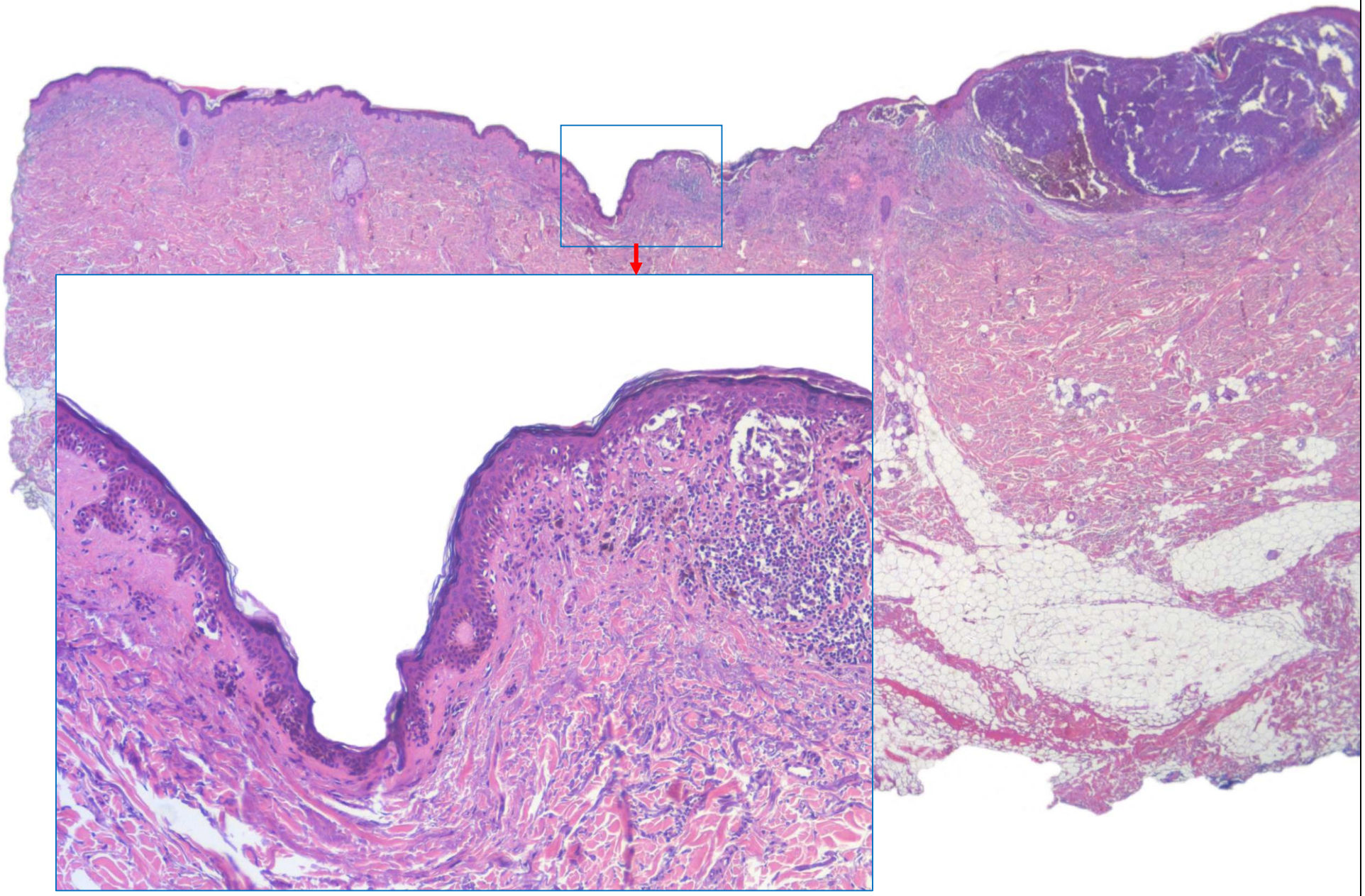
Primary melanoma can recur at the excision site if not excised with a safety margin of surrounding uninvolved skin. To characterize the nature of residual melanoma in the skin surrounding primary tumors targeted by safety margins, we used array comparative genomic hybridization and fluorescent *in situ* hybridization to detect and spatially map aberrations in the skin adjacent to acral melanomas. Melanocytic cells with genetic amplifications in histopathologically normal skin (field cells) were detected exclusively in the epidermis in 84% of 19 cases, with a mean extension of 6.1 mm (*in situ* melanomas) and 4.5 mm (invasive melanomas) beyond the histopathological margin. Genetic profiling of these field cells indicated that they represent an early phase of disease preceding melanoma *in situ*. The extent of field cells did not correlate with tumor depth or diameter, indicating that tumor depth is not suited to predict the extent of field cells. These results demonstrate that, on acral sites, melanoma field cells extend significantly into seemingly normal skin. These field cells provide a plausible explanation for the tendency of certain melanoma types to recur locally despite apparently having undergone complete excision.

Journal of Investigative Dermatology (2008) **128,** 2024–2030; doi:10.1038/jid.2008.41; published online 6 March 2008

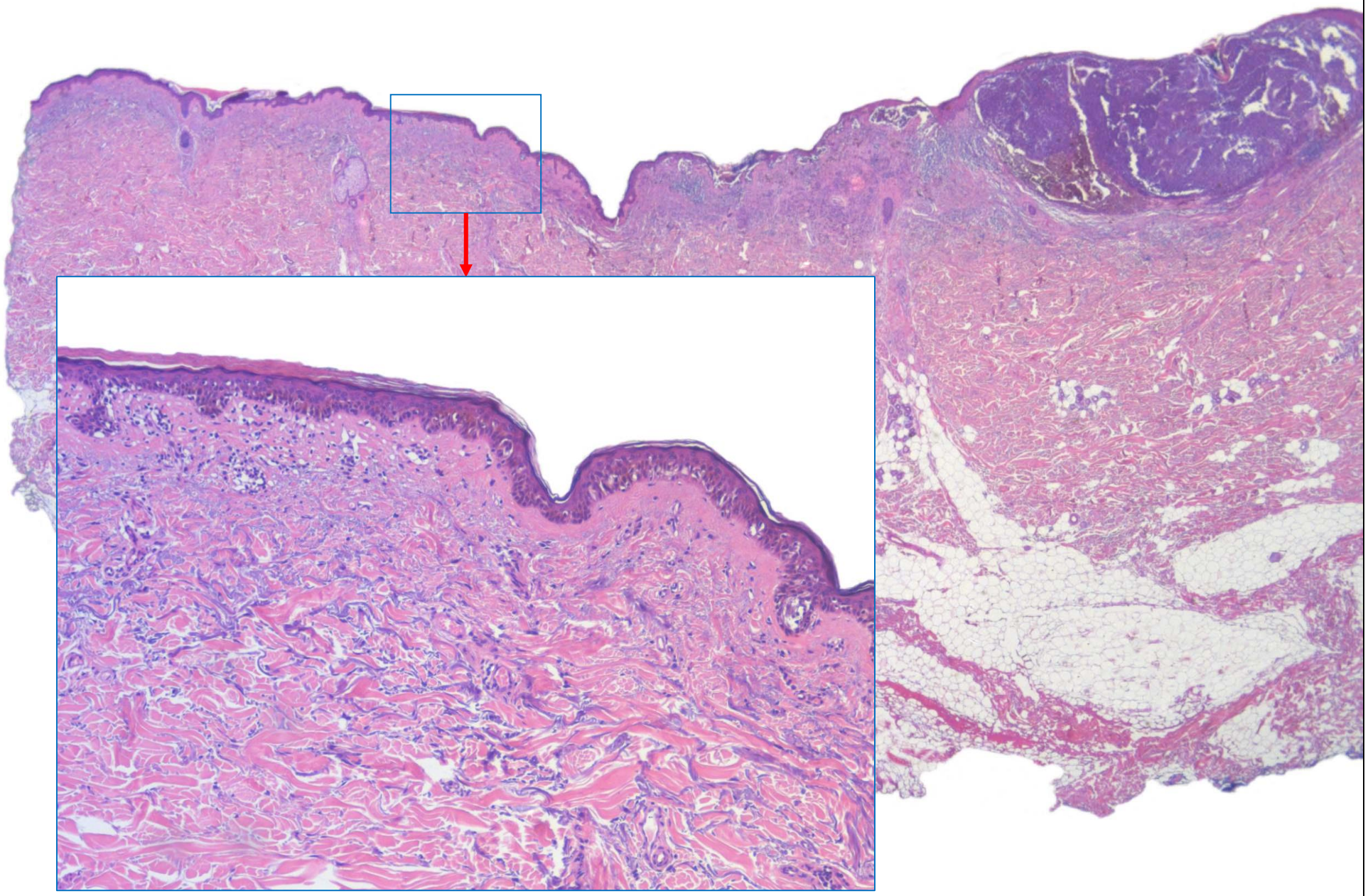
The authors still referred to those *"melanocytic cells with genetic amplifications in histopathologically normal skin"* as *"field cells,"* but they concluded that *"they represent an early phase of disease preceding melanoma in situ."* In my view, this is not precise; they are better referred to as an "early phase of melanoma in situ preceding visible manifestations of it." In truth, however, those cells are not entirely invisible. One of the authors of that study, Phil LeBoit, told me that they were enlarged and had hyperchromatic nuclei,



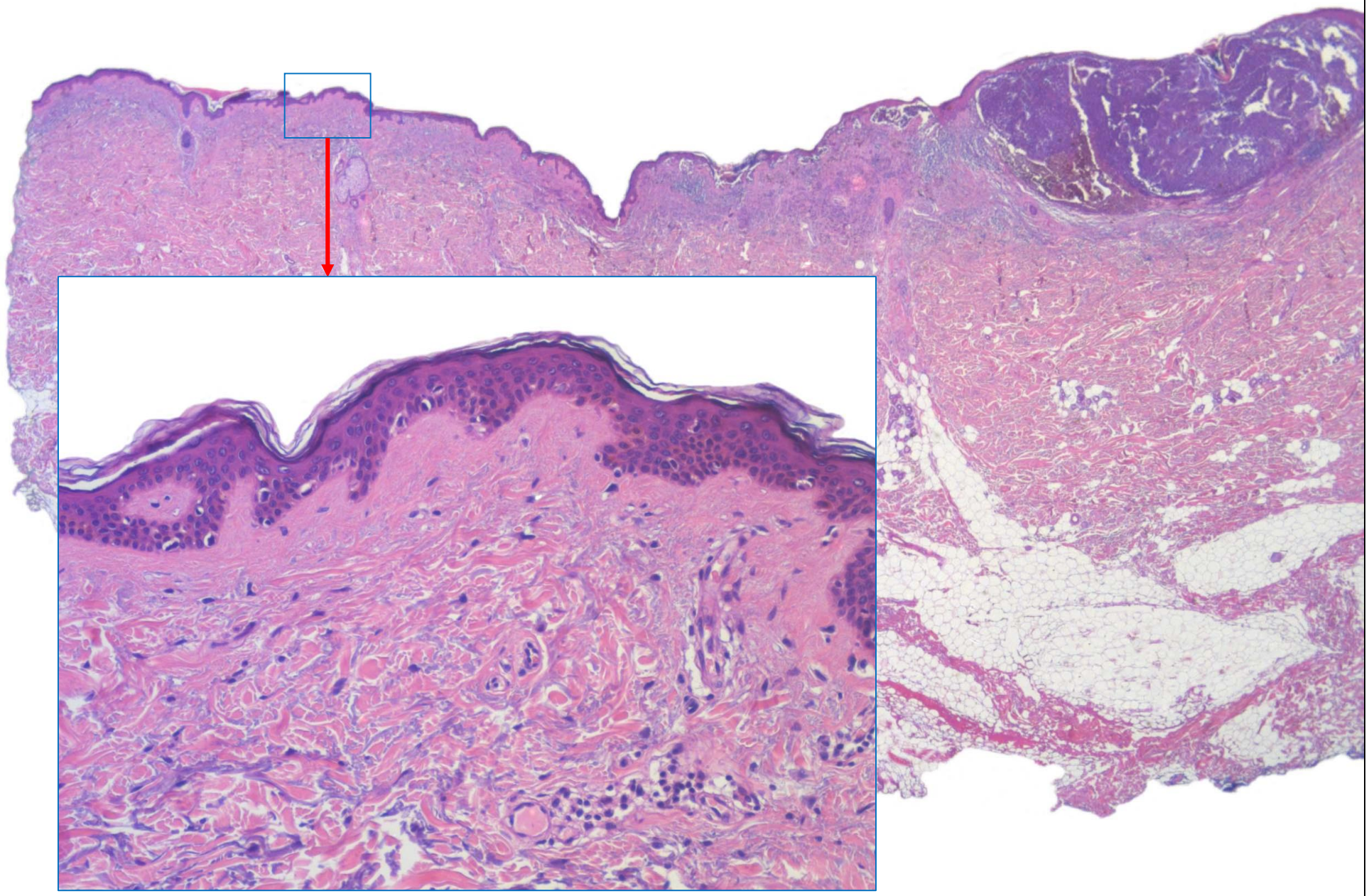
Just as described by Olsen and Wong a few decades before. Those cells can be picked up by histopathologic examination. For example, this advanced melanoma is poorly circumscribed.



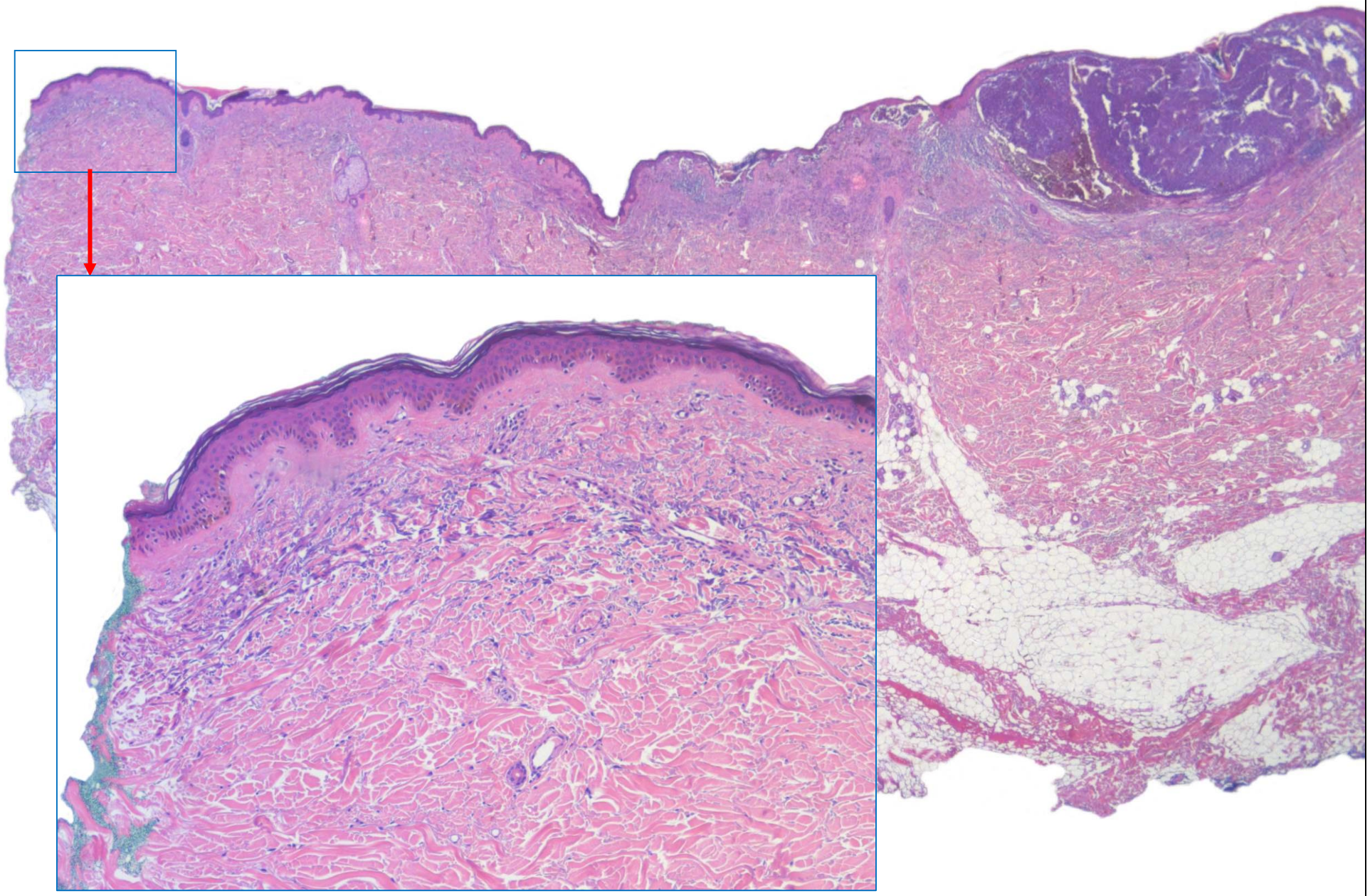
In the vicinity of the nodule, there are still some nests,



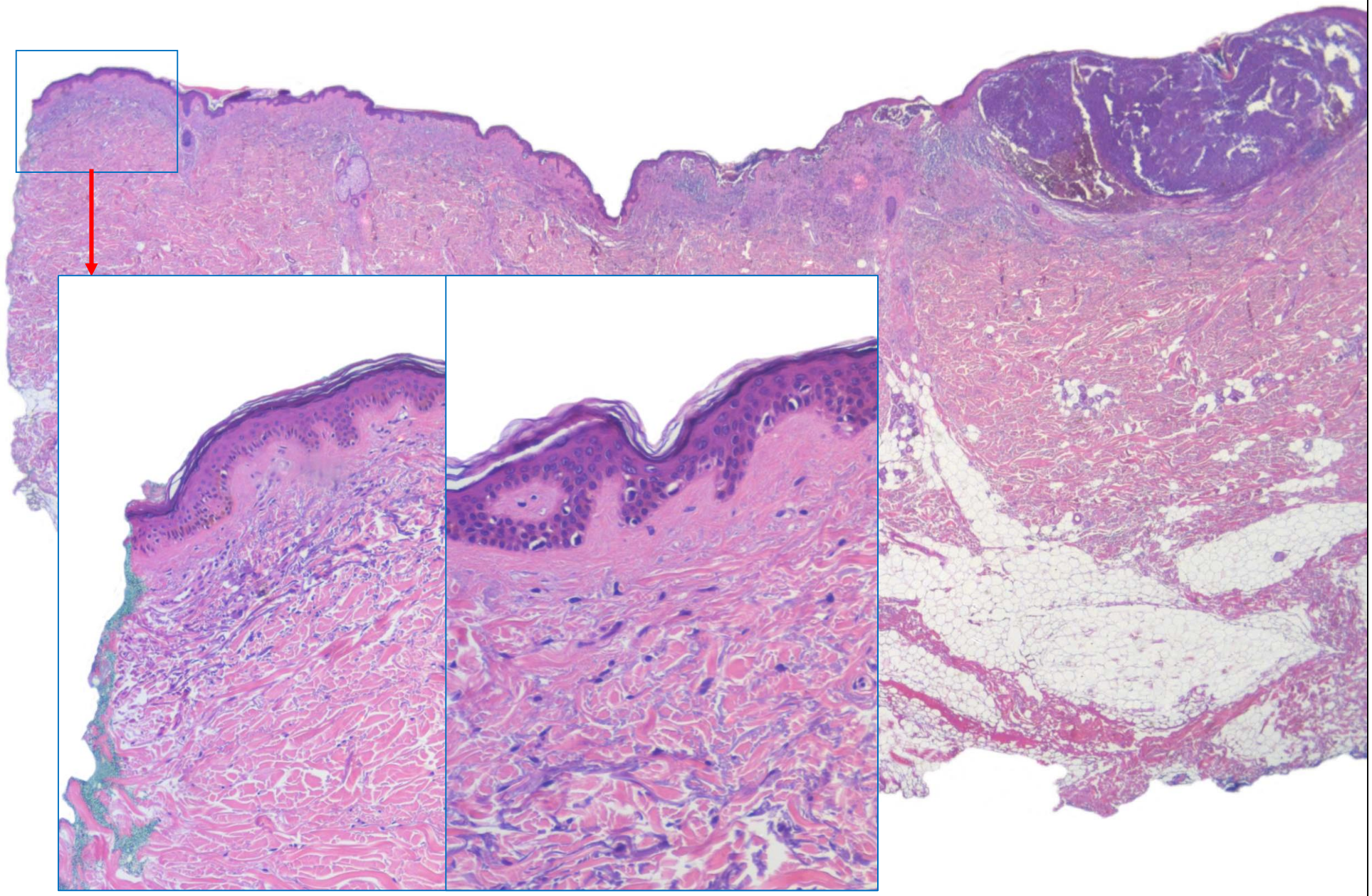
but then there are solitary melanocytes only. Because the latter are markedly increased in number, occasionally present above the basal layer, and distributed in irregular fashion, they are clearly part of the melanoma.



A little bit further out, solitary melanocytes are present only at the junction, but they are still increased in number and have large, hyperchromatic nuclei,



especially if compared to normal melanocytes in the periphery.



Those large melanocytes must be considered part of the melanoma, and if this is done, histopathologic assessment of margins becomes far more dependable.

Failure to pay heed to the true histopathologic margins of melanoma diminuishes greatly the validity of all studies concerning margins of excision.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 19, 2004 VOL. 350 NO. 8

Excision Margins in High-Risk Malignant Melanoma

J. Meirion Thomas, F.R.C.S., Julia Newton-Bishop, F.R.C.P., Roger A'Hern, M.Sc., Gill Coombes, R.G.N., Michael Timmons, F.R.C.S., Judy Evans, F.R.C.S., Martin Cook, F.R.C.Path., Jeffery Theaker, F.R.C.Path., Mary Fallowfield, F.R.C.Path., Trevor O'Neill, F.R.C.S., Wlodek Ruka, M.D., and Judith M. Bliss, M.Sc., for the United Kingdom Melanoma Study Group, the British Association of Plastic Surgeons, and the Scottish Cancer Therapy Network

ABSTRACT

BACKGROUND

Controversy exists concerning the necessary margin of excision for cutaneous melanoma 2 mm or greater in thickness.

METHODS

We conducted a randomized clinical trial comparing 1-cm and 3-cm margins.

RESULTS

Of the 900 patients who were enrolled, 453 were randomly assigned to undergo surgery with a 1-cm margin of excision and 447 with a 3-cm margin of excision; the median follow-up was 60 months. A 1-cm margin of excision was associated with a significantly increased risk of locoregional recurrence. There were 168 locoregional recurrences (as first events) in the group with 1-cm margins of excision, as compared with 142 in the group with 3-cm margins (hazard ratio, 1.26; 95 percent confidence interval, 1.00 to 1.59; P=0.05). There were 128 deaths attributable to melanoma in the group with 1-cm margins, as compared with 105 in the group with 3-cm margins (hazard ratio, 1.24; 95 percent confidence interval, 0.96 to 1.61; P=0.1); overall survival was similar in the two groups (hazard ratio for death, 1.07; 95 percent confidence interval, 0.85 to 1.36; P=0.6).

CONCLUSIONS

A 1-cm margin of excision for melanoma with a poor prognosis (as defined by a tumor thickness of at least 2 mm) is associated with a significantly greater risk of regional recurrence than is a 3-cm margin, but with a similar overall survival rate.

From the Royal Marsden Hospital National Health Service Trust, London (J.M.T., R.A.); the Division of Genetic Epidemiology, Cancer Research UK, Clinical Center, Leeds, Yorkshire (J.N.-B.); the Institute of Cancer Research, Sutton, Surrey (G.C., J.M.B.); Bradford Royal Infirmary, Bradford, Yorkshire (M.T.); Nuffield Hospital, Plymouth, Devon (J.E.); Royal Surrey Hospital, Guildford, Surrey (M.C.); Southampton General Hospital, Southampton, Hampshire (J.T.); Broomfield Hospital, Colchester, Essex (M.F.); and Norfolk and Norwich Hospital, Norwich, Norfolk (T.O.) — all in the United Kingdom; and the Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland (W.R.). Address reprint requests to Mr. Thomas at the Royal Marsden NHS Trust, Fulham Rd., London SW3 7JJ, United Kingdom.

N Engl J Med 2004;350:757-66.

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The vast majority of those studies considered clinical margins only. Among them was a British *"trial comparing 1-cm and 3-cm margins"* in melanoma *"2 mm or greater in thickness."* The authors found that *"a 1-cm margin of excision … is associated with a significantly greater risk of of regional recurrence than is a 3-cm margin, but with a similar overall survival rate,"* a result probably caused by incomplete excision of some of those lesions.

Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: long-term follow-up of survival in a randomised trial

Andrew J Hayes, Lauren Maynard, Gillian Coombes, Julia Newton-Bishop, Michael Timmons, Martin Cook, Jeffrey Theaker, Judith M Bliss, J Meirion Thomas*, for the UK Melanoma Study Group, the British Association of Plastic, Reconstructive, and Aesthetic Surgeons, and the Scottish Cancer Therapy Network*

Lancet Oncol 2016; 17: 184–92

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See Comment page 127

*Joint senior authors and contributed equally

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Correspondence to: Dr Andrew J Hayes, The Royal Marsden Hospital National Health Foundation Trust, London SW3 6JJ, UK andrew.hayes@rmh.nhs.uk

Summary

Background The necessary margin of excision for cutaneous melanomas greater than 2 mm in thickness is controversial. At a median follow-up of 5 years, findings from our previously published randomised trial of narrow (1 cm) versus wide (3 cm) excision margins in patients with thick cutaneous melanomas showed that narrow margins were associated with an increased frequency of locoregional relapse, but no significant difference in overall survival was apparent. We now report a long-term survival analysis of that trial.

Methods We did a randomised, open-label multicentre trial in 59 hospitals—57 in the UK, one in Poland, and one in South Africa. Patients with one primary localised cutaneous melanoma greater than 2 mm in Breslow thickness on the trunk or limbs (excluding palms or soles) were randomly assigned (1:1) centrally to receive surgery with either a 1 cm or 3 cm excision margin following an initial surgery. The randomisation lists were generated with random permuted blocks and stratified by centre and extent of initial surgery. The endpoints of this analysis were overall survival and melanoma-specific survival. Analyses were done in the intention-to-treat population. This trial was not registered because it predated mandatory trial registration.

Findings Between Dec 16, 1992, and May 22, 2001, we randomly assigned 900 patients to surgery with either a 1 cm excision margin (n=453) or a 3 cm excision margin (n=447). At a median follow-up of 8·8 years (106 months [IQR 76–135], 494 patients had died, with 359 of these deaths attributed to melanoma. 194 deaths were attributed to melanoma in the 1 cm group compared with 165 in the 3 cm group (unadjusted hazard ratio [HR] 1·24 [95% CI 1·01–1·53]; p=0·041). Although a higher number of deaths overall occurred in the 1 cm group compared with the 3 cm group (253 *vs* 241), the difference was not significant (unadjusted HR 1·14 [95% CI 0·96–1·36]; p=0·14). Surgical complications were reported in 35 (8%) patients in the 1 cm excision margin group and 65 (15%) patients in the 3 cm group.

Interpretation Our findings suggest that a 1 cm excision margin is inadequate for cutaneous melanoma with Breslow thickness greater than 2 mm on the trunk and limbs. Current guidelines advise a 2 cm margin for melanomas greater than 2 mm in thickness but only a 1 cm margin for thinner melanomas. The adequacy of a 1 cm margin for thinner melanomas with poor prognostic features should be addressed in future randomised studies.

Funding Cancer Research UK, North Thames National Health Service Executive, Northern and Yorkshire National Health Service Executive, British United Provident Association Foundation, British Association of Plastic Surgeons, the Meirion Thomas Cancer Research Fund, and the National Institute for Health and Research Biomedical Research Centre at The Royal Marsden NHS Foundation Trust.

Twelve years later, the same material was re-evaluated in regard to survival, and the authors found that, *"although a higher number of deaths overall occurred in the 1 cm group compared with the 3 cm group …, the difference was not significant."* Nevertheless, they concluded that *"a 1 cm excision margin is inadequate for cutaneous melanomas with Breslow thickness greater than 2 mm."*

Cochrane Library

Cochrane Database of Systematic Reviews

Surgical excision margins for primary cutaneous melanoma (Review)

Sladden MJ, Balch C, Barzilai DA, Berg D, Freiman A, Handiside T, Hollis S, Lens MB, Thompson JF

Summary of main results

This systematic review summarises the evidence regarding the width of surgical excision margins for primary cutaneous melanoma. None of the five published trials has shown a statistically significant difference in overall survival when comparing narrow with wide excision. Furthermore, our meta-analysis has not shown a statistically significant difference in overall survival

Cochrane Datebase Syst Rev 2009; 4: CD004835

The vast majority of studies, as dubious as their material may be, came to a different conclusion. In a Cochrane meta-analysis in 2009, the authors pointed out that *"none of the five published trials has shown a statistically significant difference in overall survival when comparing narrow with wide excision. Furthermore, our meta-analysis has not shown a statistically significant difference in overall survival."*

The lack of benefit of wide margins had been demonstrated long before.

ACTA CHIRURGICA SCANDINAVICA
SUPPLEMENTUM 365

THE MALIGNANT MELANOMA OF THE SKIN

TABLE 64.

Frequency of recurrence in relation to margin of excision of primary tumour

Margin	All patients No. pts.	All patients Recurrence	Patients with no previous treatment No. pts.	Patients with no previous treatment Recurrence	Series A on 5-year date No. pts.	Series A on 5-year date Recurrence
0– 9 mm	69	12 = 17%	19	1 = 5%	60	11 = 18%
10–14 mm	51	6 = 12%	35	3 = 9%	45	6 = 13%
15–19 mm	46	6 = 13%	35	2 = 6%	45	6 = 13%
20–29 mm	139	13 = 9%	109	4 = 4%	117	12 = 10%
30–49 mm	67	11 = 16%	53	9 = 17%	51	10 = 20%
≥ 50 mm	79	10 = 13%	51	3 = 6%	30	9 = 30%
? mm	5	1	0		4	1
	456	58 = 13%	302	22 = 7%	352	55 = 16%

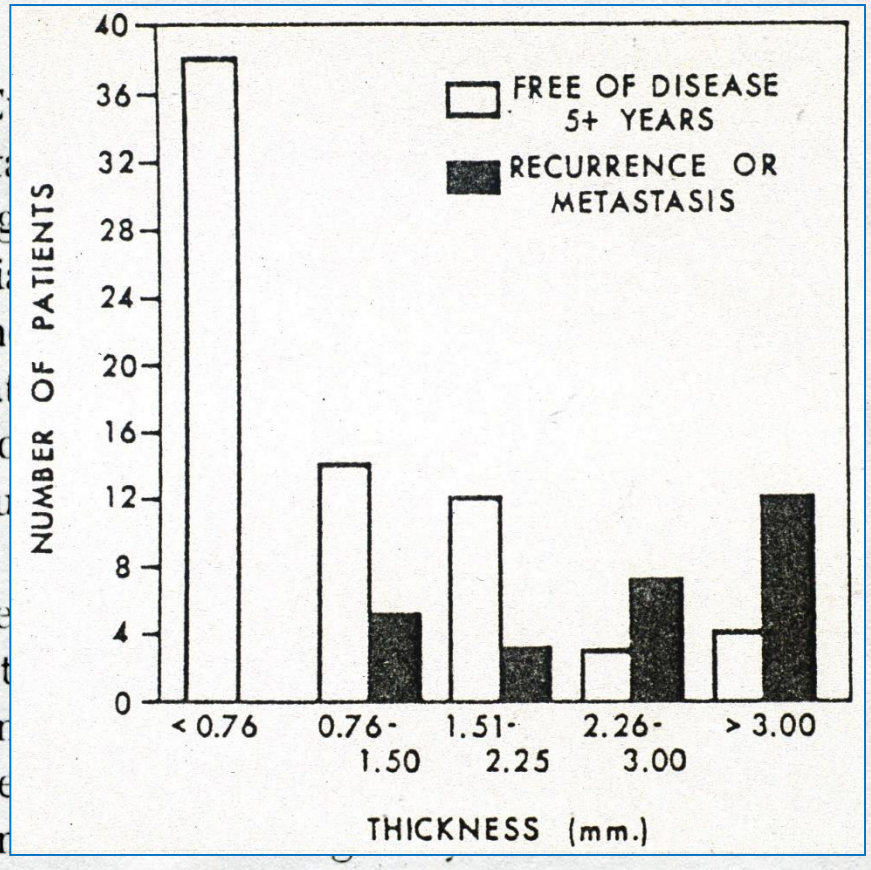
The first major study calling in question established habits of melanoma surgery was the one by Grete Olsen in 1966. Olsen noted no significant difference in the rate of recurrences between melanomas excised with clinical margins of only 1 or more than 5 cm.

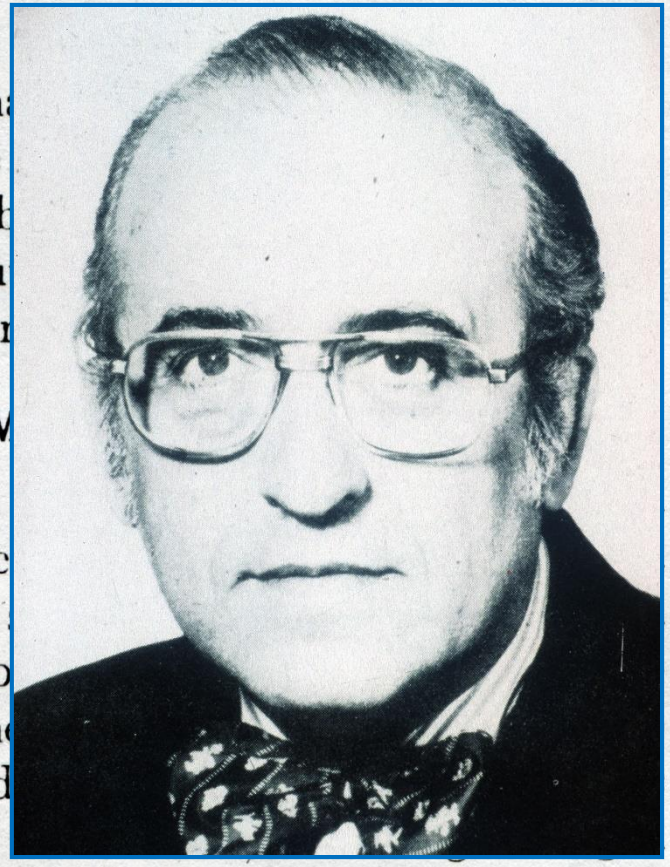
Thickness, Cross-Sectional Areas and Depth of Invasion in the Prognosis of Cutaneous Melanoma

Ann Surg 1970; 172: 902-908

ALEXANDER BRESLOW,* M.D.

From The George Washington University School of Medicine, Washington, D. C.





Nonetheless, it took many more years until margins of excision were reduced. This was accomplished chiefly by Alexander Breslow who in 1970 described the thickness of melanoma as the most important prognostic parameter. In melanomas measuring less than 0.76 mm in thickness, not a single recurrence or metastasis was observed. Because of the excellent prognosis, Breslow considered standard margins of excision to be excessive for those lesions,

OPTIMAL SIZE OF RESECTION MARGIN FOR THIN CUTANEOUS MELANOMA

Surg Gynecol Obstet
1977; 145:691-692

Alexander Breslow, M.D., *and* Steven D. Macht, M.D., *Washington, District of Columbia*

THE QUESTION of how much normal appearing skin to remove when resecting a cutaneous melanoma has troubled surgeons for years. Suggestions range from 2 to 15 centimeters without convincing evi
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One such facto
sults of earlier
have shown
recurrences d
tumors were
while for thicker lesions, the rate of metastasis was directly proportional to tumor thickness. Similar results were obtained by Hansen and McCarten (6), Wanebo and colleagues (7) and Clark (3). During the course of these studies, we

melanoma site, the patient was excluded, unless the surgeon's records confirmed that a re-excision had not been performed. Also excluded were patients in whom the description was incomplete,
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ght had le-
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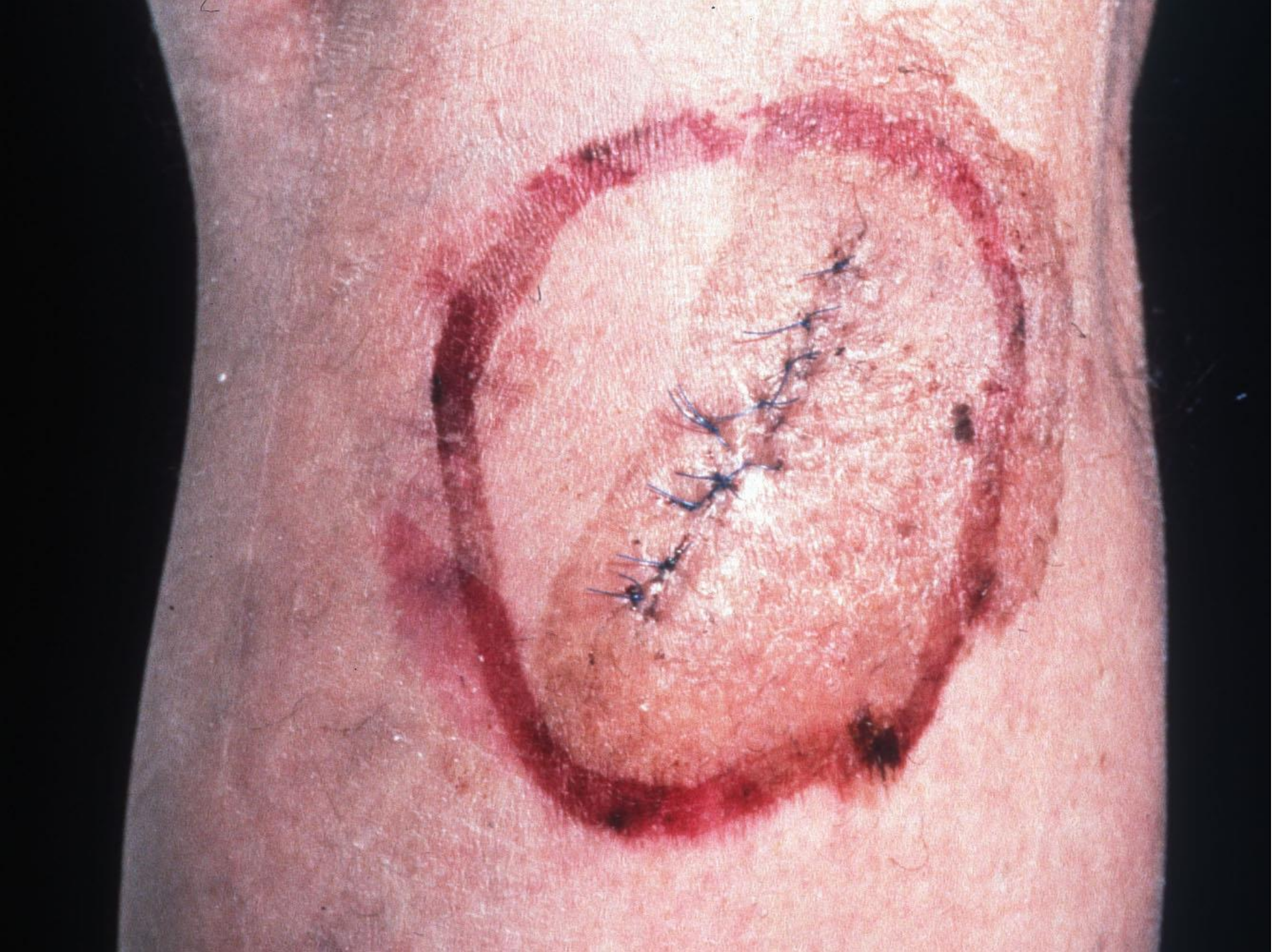
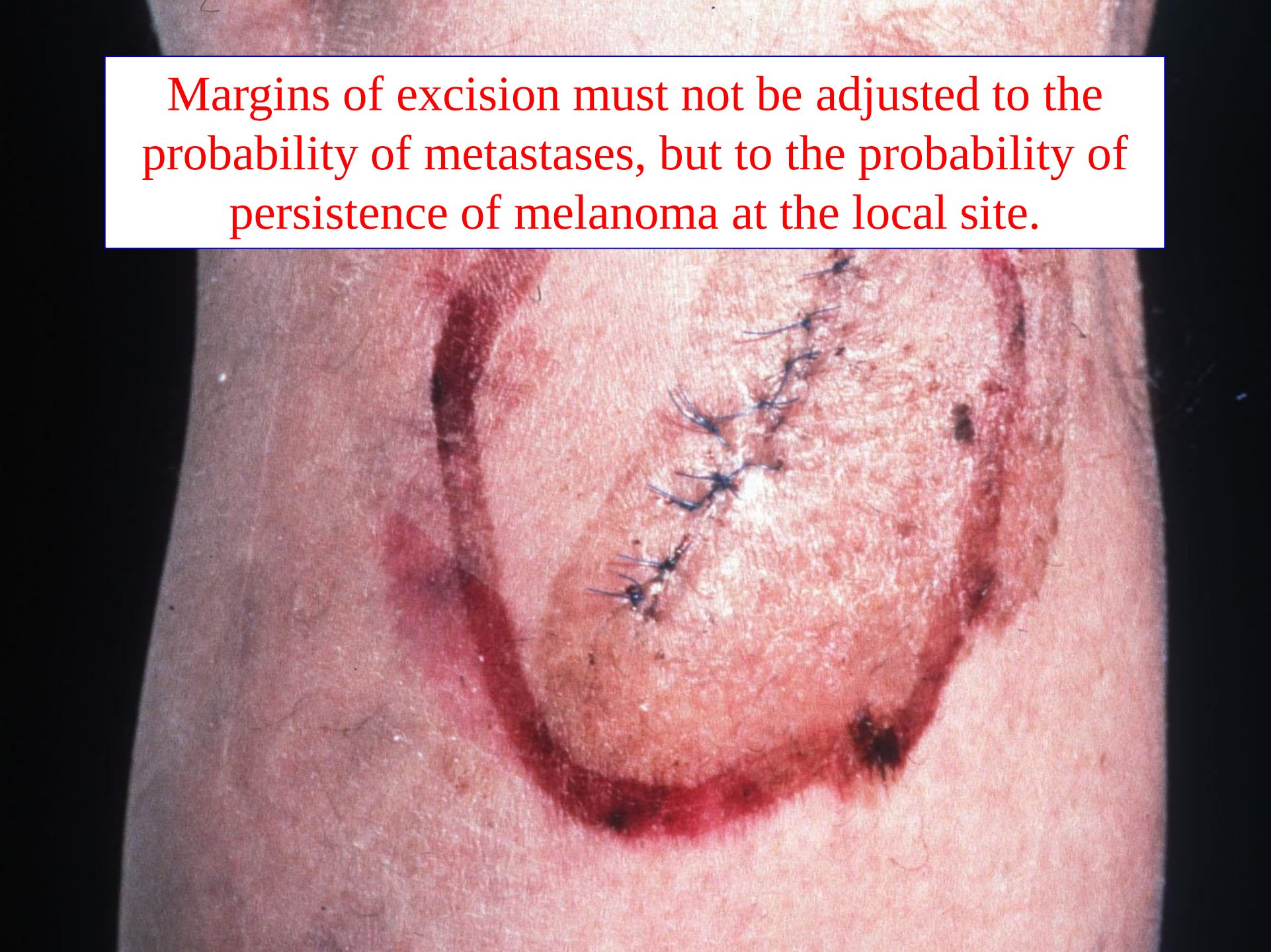
ge from 18
rs. Follow-
was small,
and several sections were taken through the center of the lesion if it was large. Sections were fixed in Bouins solution during the first half of the study and in neutral formaldehyde solution during the second half; slides were prepared and

It appears that these thin tumors should be treated conservatively. ... In most instances, skin grafting should not be necessary.

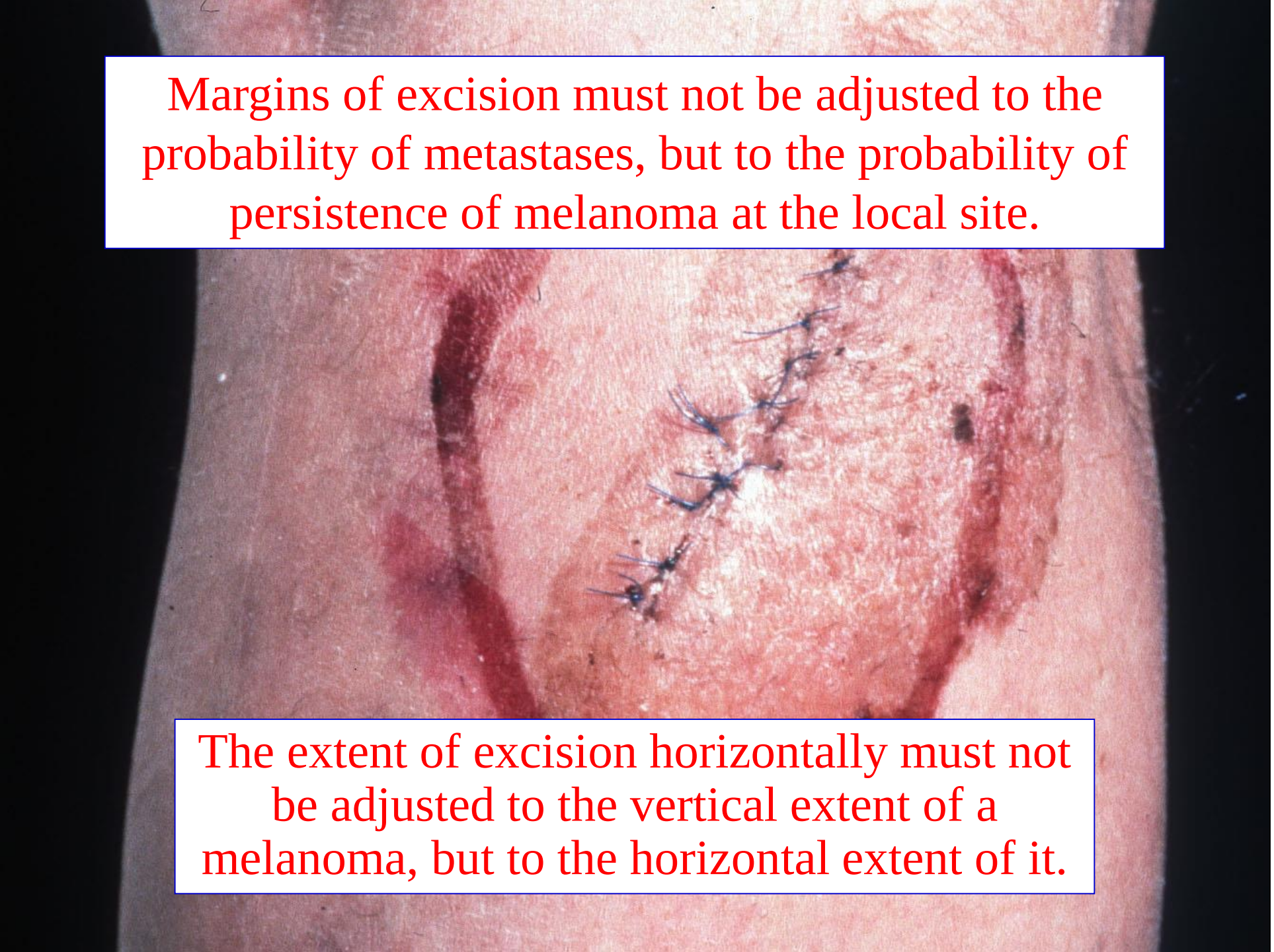
and he noted in 1977: *"It appears that these thin tumors should be treated conservatively. ... In most instances, skin grafting should not be necessary."*



This statement helped to rescue tons of healthy skin for melanoma patients around the world, but is was associated with two striking lapses in logic.



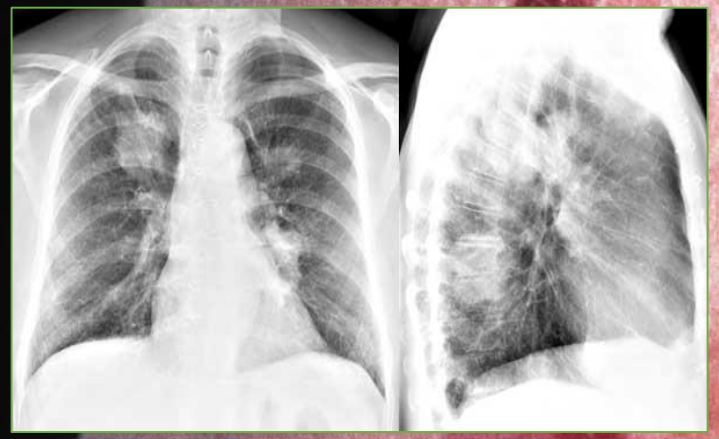
First, margins of excision must not be adjusted to the prognosis of melanoma, i.e., probability of metastases based on thickness, but to the probability of persistence of melanoma at the local site.



Second, the extent of excision horizontally must not be adjusted to the vertical extent of a melanoma, but to the horizontal extent of it.

Both of those demands are self-evident: how should an excision of healthy skin at the arm or leg

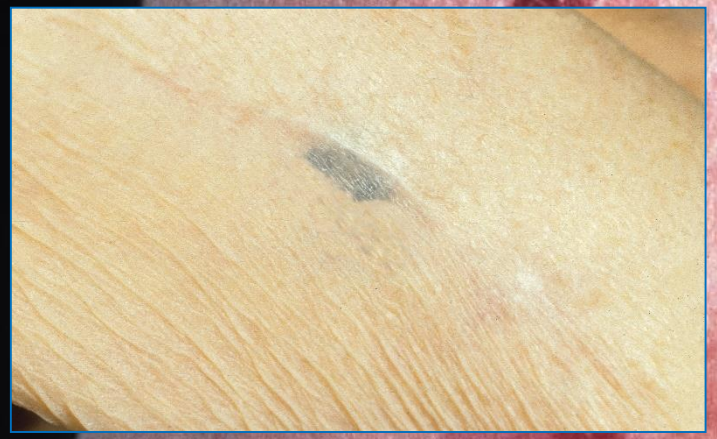
Margins of excision must not be adjusted to the probability of metastases, but to the probability of persistence of melanoma at the local site.



The extent of excision horizontally must not be adjusted to the vertical extent of a melanoma, but to the horizontal extent of it.

influence metastases in the liver or lung that are responsible for death? Surgery cannot reverse distant metastases

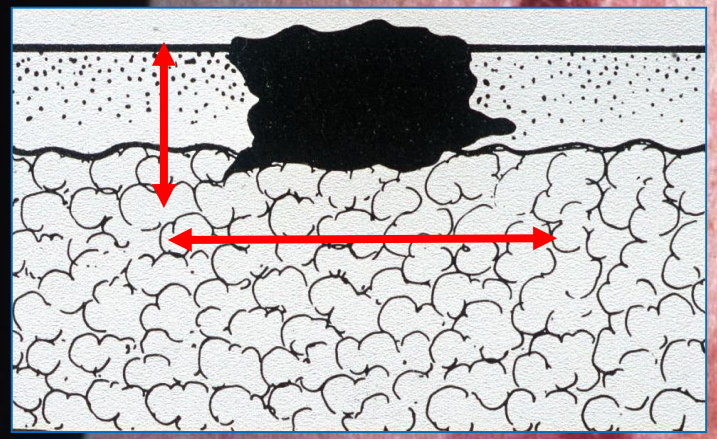
Margins of excision must not be adjusted to the probability of metastases, but to the probability of persistence of melanoma at the local site.



The extent of excision horizontally must not be adjusted to the vertical extent of a melanoma, but to the horizontal extent of it.

but can only prevent recurrences at the site of excision, and the test for the quality of a surgical procedure is not the overall survival rate but the question how effective it is in preventing persistence of the primary tumor.

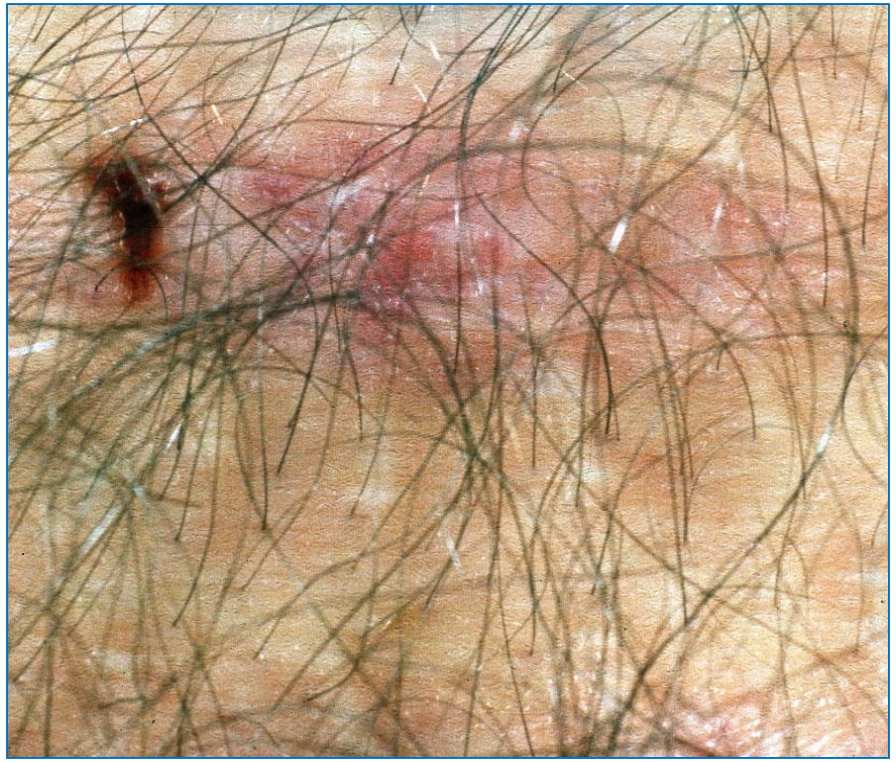
Margins of excision must not be adjusted to the probability of metastases, but to the probability of persistence of melanoma at the local site.



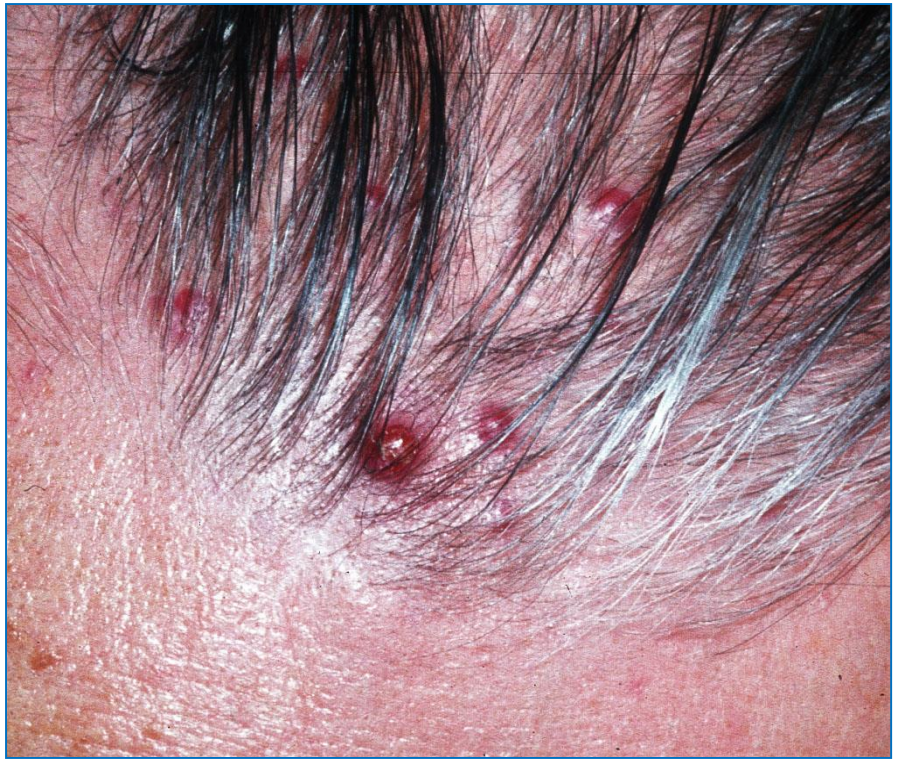
The extent of excision horizontally must not be adjusted to the vertical extent of a melanoma, but to the horizontal extent of it.

Hence, the dimensions of the tumor must be heeded, and the excision must be wide enough for its width and deep enough for its depth, but not the wider, the deeper. Despite those flagrant lapses in logic, however, the link between vertical tumor thickness and horizontal extent of the excision has become accepted worldwide and determines treatment of melanoma to this date.

“local recurrence”



persistent primary melanoma



satellite metastases

The most important reason for failure to recognize and amend that mistake was the leveling of local metastases and persistence of the primary melanoma. Both phenomena continued to be lumped together as “local recurrence.” That such recurrences were slightly more common in thick melanomas was probably chiefly caused by an increased rate of regional metastases, rather than persistence of the primary tumor. Nevertheless, confusion of both phenomena gave credence to the link between tumor thickness and margins of excision.

ORIGINAL ARTICLES

The Prognosis and Treatment of True Local Cutaneous Recurrent Malignant Melanoma

CHRISTINE D. BROWN, MD
JOHN A. ZITELLI, MD

ELSEVIER

BACKGROUND. *The prognosis and treatment of true local cutaneous recurrent malignant melanoma is presently unknown. We define this entity as melanoma bearing an in situ component that recurs contiguous with the scar of the primary excision. Although previously uncommon, the incidence of true local recurrent melanoma may rise due to the recent use of more narrow margins for excision of thin primary melanoma.*

OBJECTIVE. *We hypothesized that there is a difference in prognosis between true local cutaneous recurrent melanoma versus local recurrence from satellite or in-transit metastases. Also, we defined guidelines for the surgical management of true local cutaneous recurrent melanoma.*

METHODS. *We calculated the surgical margin necessary to reach a tumor-free plane using Mohs surgery in 50 patients with true local recurrent melanoma. Patient survival was determined by the Kaplan-Meier method.*

RESULTS. *Seventy-six percent of the tumors were completely excised using a margin of less than 1 cm. However, a margin of up to 2 cm was required to successfully treat all 50 patients. Thicker tumors did require significantly larger margins. The Kaplan-Meier 5-year overall and melanoma survival rates were 89% and 98%, respectively. The 5-year disease-free survival rate was 66%.*

CONCLUSION. *The prognosis of true local recurrent melanoma is related to tumor thickness. We recommend full-thickness excision of the entire old scar including a 2-cm margin or Mohs surgery if a narrower margin of resection is desired.* Dermatol Surg 1995;21:285–290.

In the 1990s, both phenomena started to be considered seperately. For example, Brown and Zitelli studied patients with persistent primary tumors *"bearing an in situ component that recurs contiguous with the scar of the primary excision."* When trating those recurrences by Mohs surgery, they noted that the subclinical in-situ component increased with tumor thickness and concluded: *"Thicker tumors did require significantly larger margins."*

Clinical and pathologic factors associated with subclinical spread of invasive melanoma

Thuzar M. Shin, MD, PhD, Waqas R. Shaikh, MD, MPH, Jeremy R. Etzkorn, MD, Joseph F. Sobanko, MD, David J. Margolis, MD, PhD, Joel M. Gelfand, MD, MSCE, Emily Y. Chu, MD, PhD, Rosalie Elenitsas, MD, and Christopher J. Miller, MD
Philadelphia, Pennsylvania

Background: Indications to treat invasive melanoma with Mohs micrographic surgery (MMS) or analogous techniques with exhaustive microscopic margin assessment have not been defined.

Objective: Identify clinical and histologic factors associated with subclinical spread of invasive melanoma.

Methods: This retrospective, cross-sectional study evaluated 216 invasive melanomas treated with MMS and melanoma antigen recognized by T cells 1 immunostaining. Logistic regression models were used to correlate clinicopathologic risk factors with subclinical spread and construct a count prediction model.

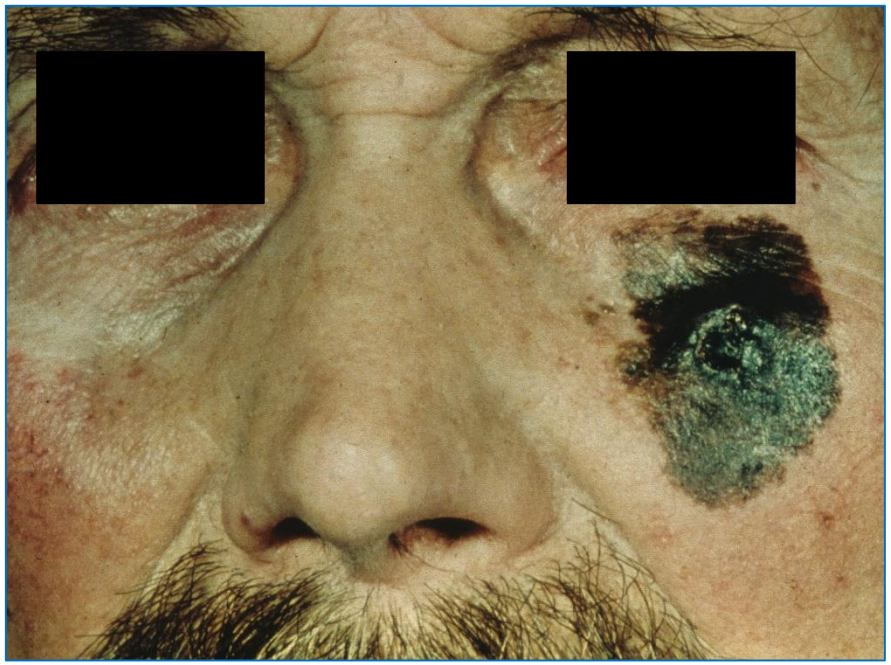
Results: Risk factors associated with subclinical spread by multivariate analysis included tumor localization on the head and neck (OR 3.28, 95% confidence interval [CI] 1.16-9.32), history of previous treatment (OR 4.18, 95% CI 1.42-12.32), age ≥65 (OR 4.45, 95% CI 1.29-15.39), and ≥1 mitoses/mm^2 (OR 2.63, 95% CI 1.01-6.83). Tumor thickness and histologic subtype were not associated with subclinical spread. The probability of subclinical spread increased per number of risk factors, ranging from 9.22% (95% CI 2.57%-15.86%) with 1 factor to 80.32% (95% CI 68.13%-92.51%) with 5 factors.

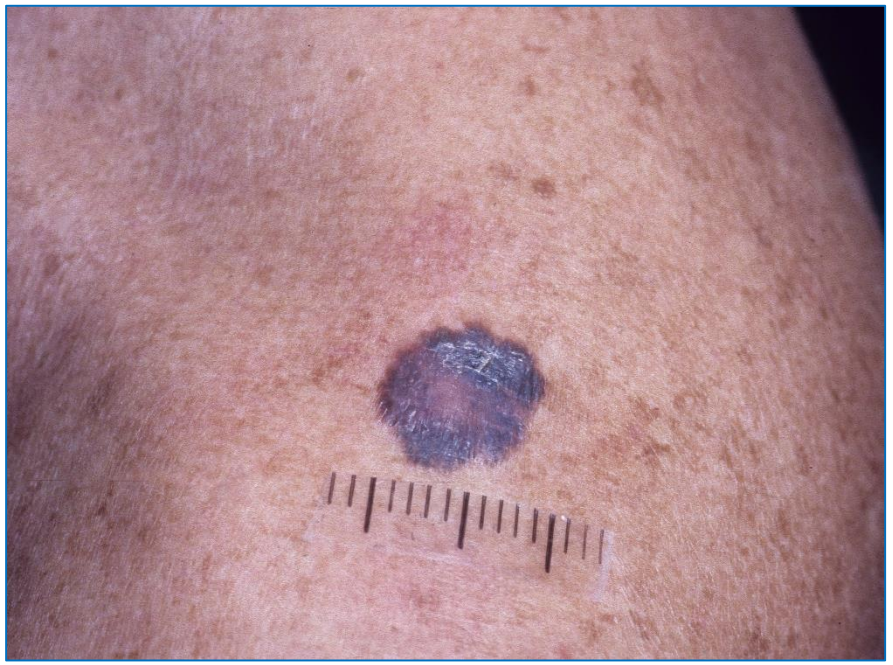
Limitations: This study was conducted at a single academic institution with a small study population using a retrospective study design that was subject to potential referral bias.

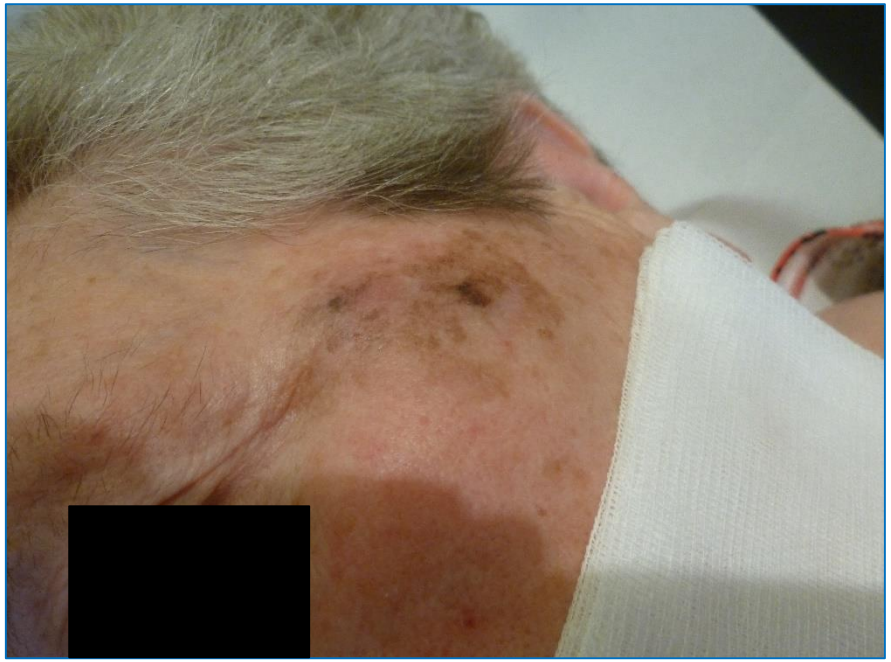
Conclusion: Clinical and histologic factors identify invasive melanomas that are at increased risk for subclinical spread and might benefit from MMS or analogous techniques prior to reconstruction. (J Am Acad Dermatol 2017;76:714-21.)

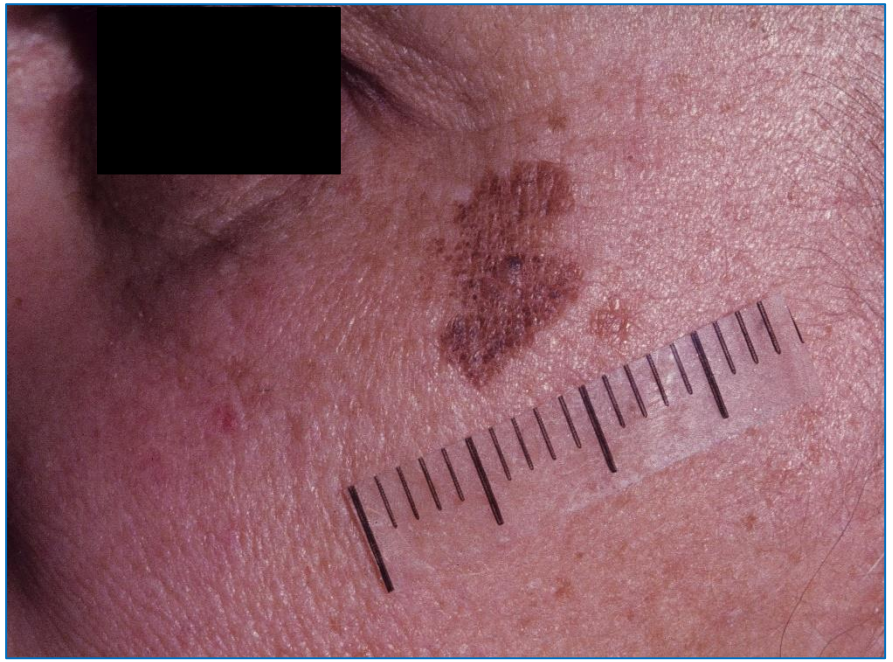
Later studies, however, could not confirm that finding. The most recent study about *"clinical and pathologic factors associated with subclinical spread"* of melanomas revealed a higher risk of subclinical spread in melanomas localized on the head and neck and with a history of previous treatment. By contrast, it was pointed out explicitly: *"Tumor thickness and histologic subtype were not associated with subclinical spread."*

This corresponds to clinical and histopathologic experience.

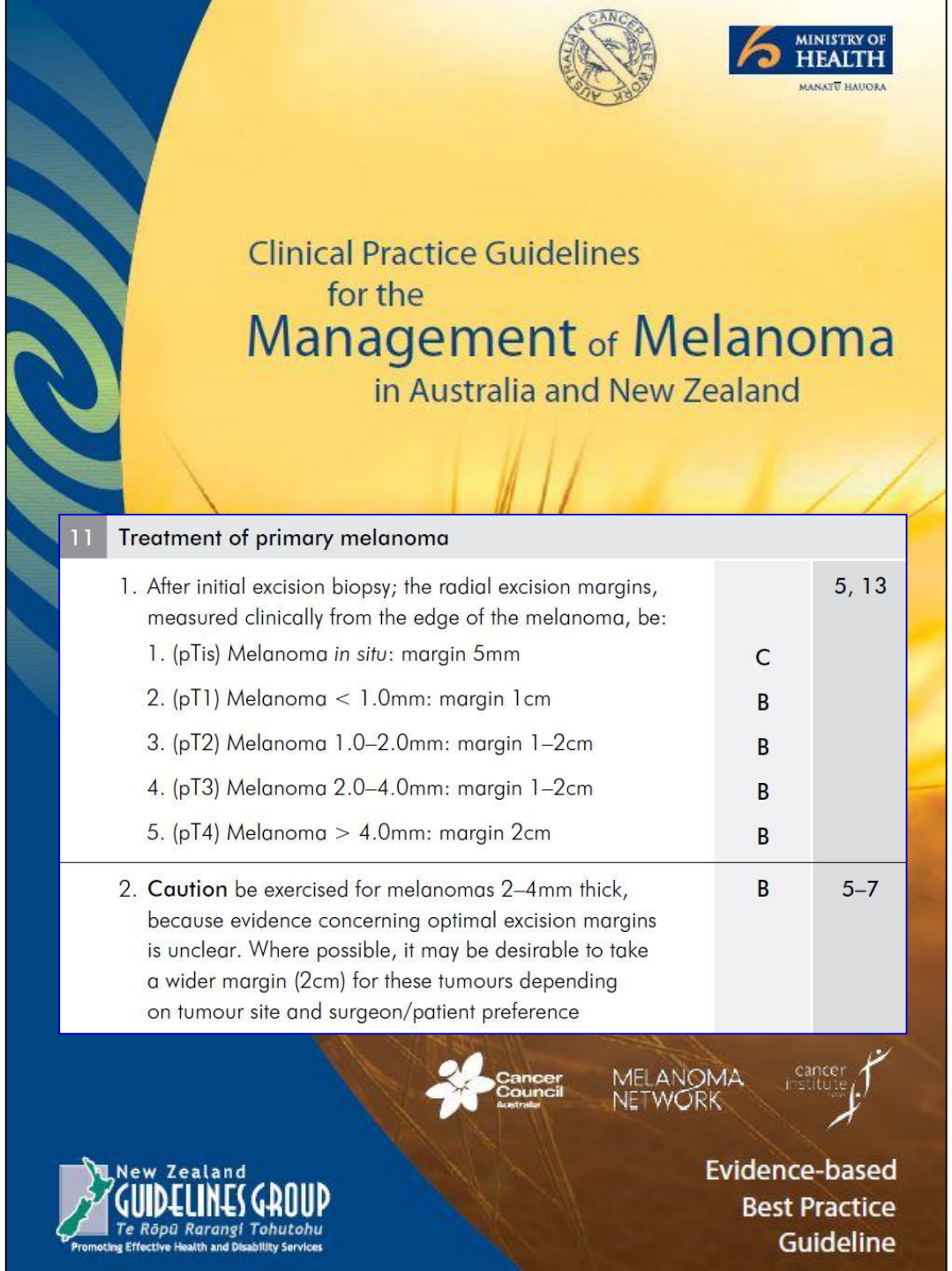








Some thick melanomas are poorly, and others relatively sharply circumscribed. The same applies to thin melanomas. The sharpness of demarcation can already be appraised clinically. In poorly demarcated melanomas, a wider margin should be used from the outset. The thickness of the lesion is irrelevant for that decision. Considering the variety among melanomas, recommendations concerning clinical margins of excision can only be vague rules of thumb; the decision must depend on the individual lesion.



Nonetheless, the illogical link between tumor thickness and fixed margins of excision prevails to this date. Throughout the world, guidelines require inflexible margins of excision of 1 to 3 cm depending on tumor thickness, be it Australia and New Zealand,

BJD
British Journal of Dermatology

Revised U.K. guidelines for the management of cutaneous melanoma 2010

J.R. Marsden, J.A. Newton-Bishop,* L. Burrows,† M. Cook,‡ P.G. Corrie,§ N.H. Cox,¶ M.E. Gore,** P. Lorigan,†† R. MacKie,‡‡ P. Nathan,§§ H. Peach,¶¶ B. Powell*** and C. Walker

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Correspondence

Disclaimer

Table 7 Recommended surgical excision margins

Breslow thickness	Excision margins	Level of evidence	Grading of evidence
In situ	5-mm margins to achieve complete histological excision	III	B
< 1 mm	1 cm	Ib	A
1·01–2 mm	1–2 cm	Ib	A
2·1–4 mm	2–3 cm	Ib	A
> 4 mm	3 cm	Ib	B

Palliative care: J. Speakman, F. Calman
National Institute for Health and Clinical Excellence: N. Summerton
Scottish Intercollegiate Guidelines Network: S. Qureshi
Primary care: P. Murchie

DOI 10.1111/j.1365-2133.2010.09883.x

NHS Evidence

NHS Evidence has accredited the process used by the British Association of Dermatologists to produce guidelines. Accreditation is valid for three years from May 2010 and is applicable to guidance produced using the processes described in the British Association of Dermatologists' guideline development manual (Bell & Ormerod, 2009). More information on accreditation can be viewed at www.evidence.nhs.uk.

clans, the Royal College of Radiologists, London, the Royal College of Surgeons of England, the Royal College of Pathologists (pathology section only), the Royal College of General Practitioners, London, and the Department of Health.

These consensus guidelines have been drawn up by a multidisciplinary working party with membership drawn from a variety of groups and coordinated by the U.K. Melanoma Study Group and the British Association of Dermatologists.

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the United Kingdom,

Guidelines of the Brazilian Dermatology Society for diagnosis, treatment and follow up of primary cutaneous melanoma - Part I*

Luiz Guilherme Martins Castro[1,2,3]
Walter Loureiro[5]
João Pedreira Duprat Neto[7]
Flávia Vasques Bittencourt[8]
Sérgio Schrader Serpa[10]
Gabriel Gontijo[8]
Maria Cristina Messina[1,2,3,4]
Ricardo Silvestre Macarenco[1,6]
Thais Helena Bello Di Giacomo[1,2,3]
Renato Marchiori Bakos[9]
Hamilton Ometto Stolf[11]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20154707

Abstract: The last Brazilian guidelines on melanoma were published in 2002. Development in diagnosis and treatment made updating necessary. The coordinators elaborated ten clinical questions, based on PICO system. A Medline search, according to specific MeSH terms for each of the 10 questions was performed and articles se-

It is important to remember that for both *in situ* and invasive melanomas, histological examination with paraffin embedded sections is the gold standard for evaluation of surgical margins and that margins expansion surgery should be performed preferably

The usefulness of the various methods of micrographic control of margins is very discussed. [45,101,103] The most disseminated is Mohs' method, but several other methods of margins micrographic control appear in the literature, with different nomenclatures

TABLE 1: Surgical Margins for the treatment of primary cutaneous melanoma

Breslow thickness (mm)	Surgical margin (cm)	Level of evidence
In situ	0.5 #	A
Up to 1.00	1.0	A
From 1.01 to 2. 00	1.0 to 2.0 *	B
More than 2.00	2.0	A

t-test

* The surgical margins can be modified to contemplate anatomical, functional or aesthetic needs. Experts agree that margins between 1cm and 2 cm are acceptable in areas where margins of 2 cm would cause significant aesthetic, functional or anatomical losses. The patient should be informed and agree with the doctor about the best option.

Conflict of interest: None.

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10 Universidade Estácio de Sá (UNESA) – Rio de Janeiro (RJ) Brazil.
11 Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP) – Botucatu (SP), Brazil.

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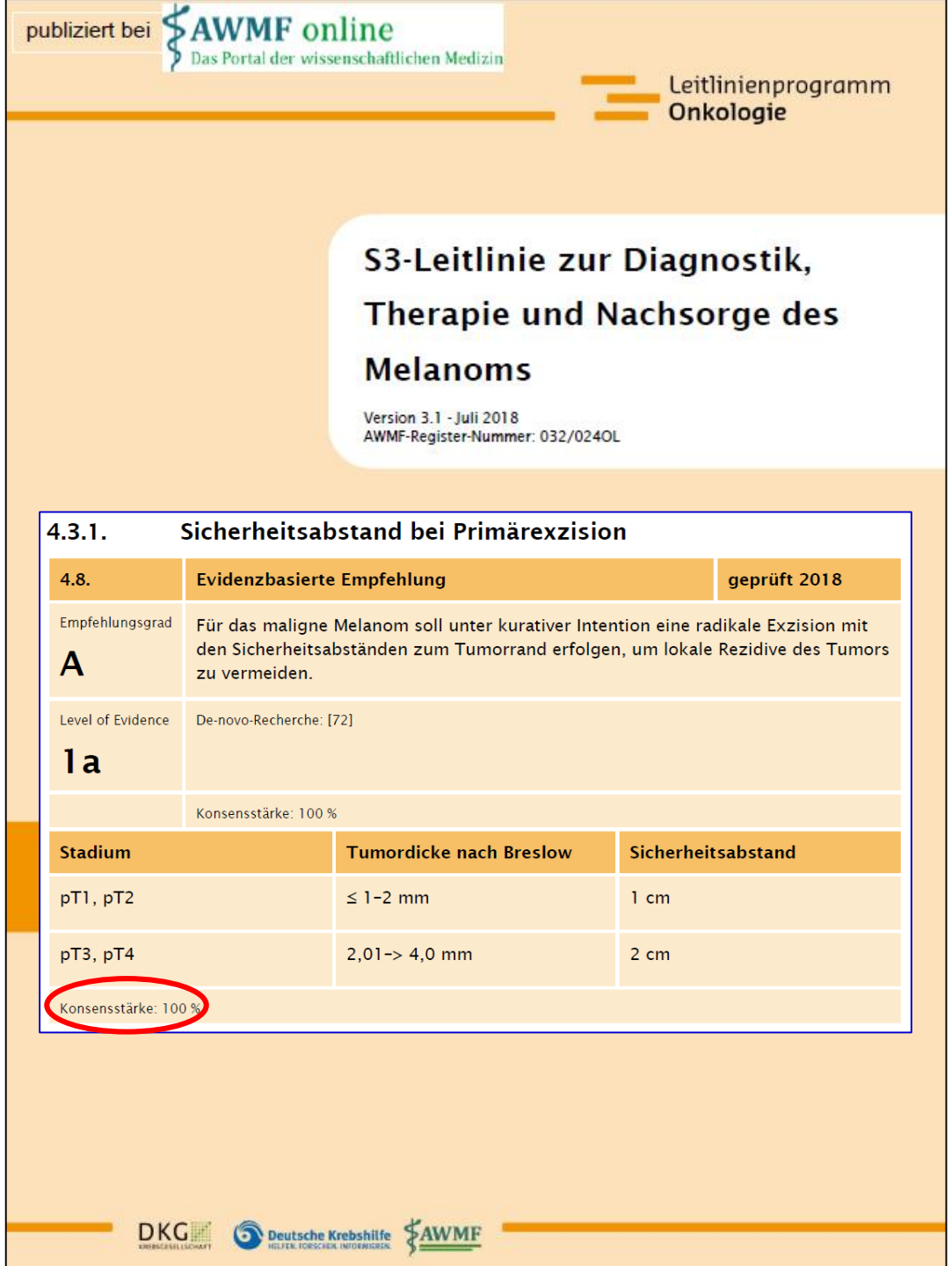
Brazil,



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Version 3.1 - Juli 2018
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4.3.1. Sicherheitsabstand bei Primärexzision

4.8.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Für das maligne Melanom soll unter kurativer Intention eine radikale Exzision mit den Sicherheitsabständen zum Tumorrand erfolgen, um lokale Rezidive des Tumors zu vermeiden.	
Level of Evidence 1a	De-novo-Recherche: [72]	
	Konsensstärke: 100 %	

Stadium	Tumordicke nach Breslow	Sicherheitsabstand
pT1, pT2	≤ 1–2 mm	1 cm
pT3, pT4	2,01–> 4,0 mm	2 cm
Konsensstärke: 100 %		

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or Germany. In the German guidelines of this year, the consensus was said to be 100% – this acquires the character of religious belief. Moreover, guidelines never specify what is meant by “margin of excision,” the clinical or the histopathologic one. Nearly all studies refer to the clinical margin,

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and one year ago, at the 9th World Congress of Melanoma in Brisbaine, it was emphasized once again that guidelines apply only to clinical margins. The prevailing uncertainty in that regard is a consequence of the illogical link of tumor thickness and clinical margins. Thickness is measured histopathologically and is only known after the excision, the clinical margins are selected previously.

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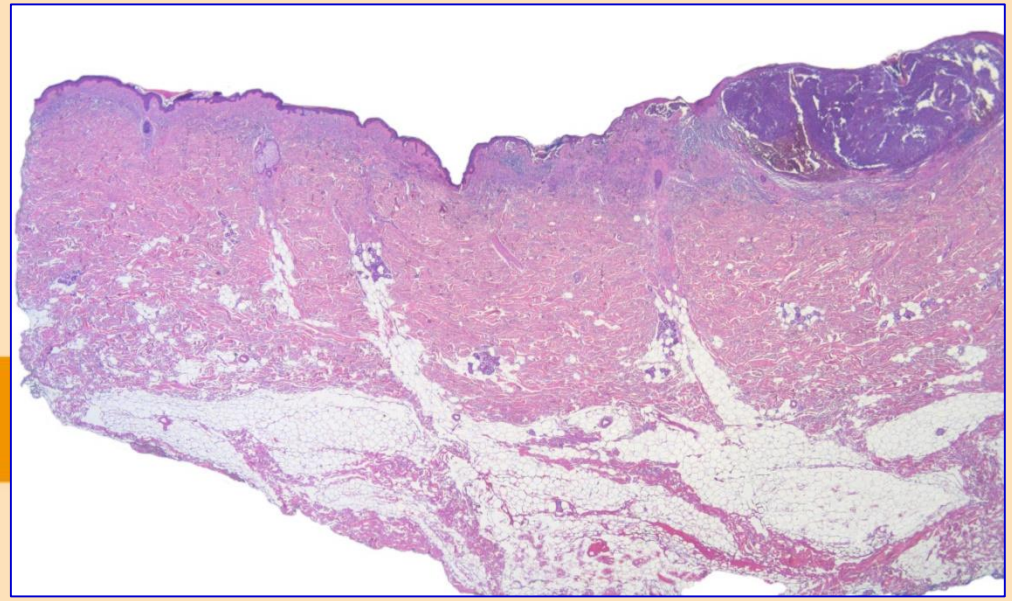

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Once a melanoma has been excised, and thickness is known, clinical margins play no role because the extent of melanoma can be determined histopathologically which is far more precise than clinical judgment.

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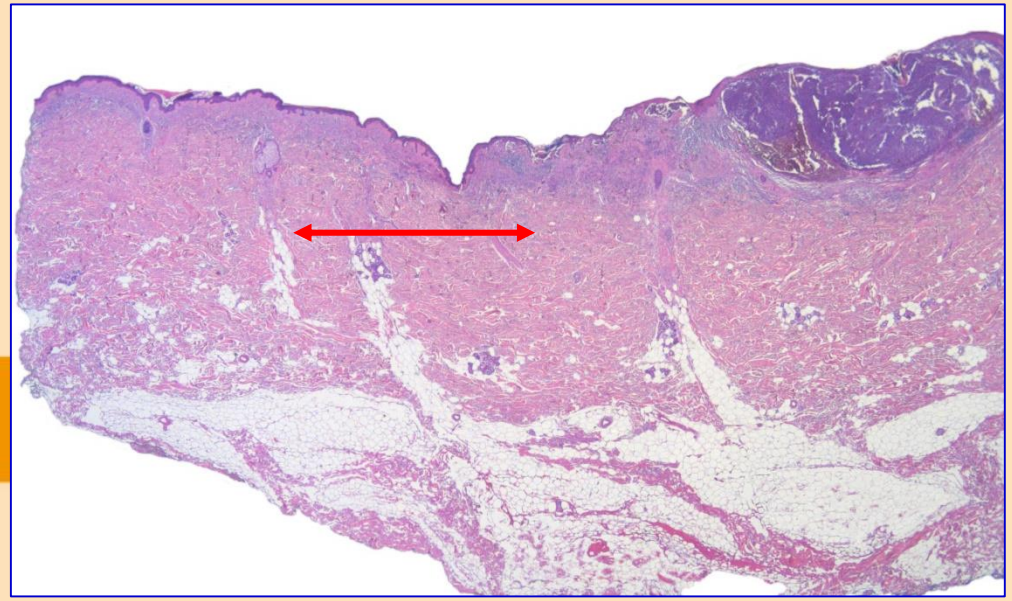

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Because of substantial subclinical spread of many melanomas,

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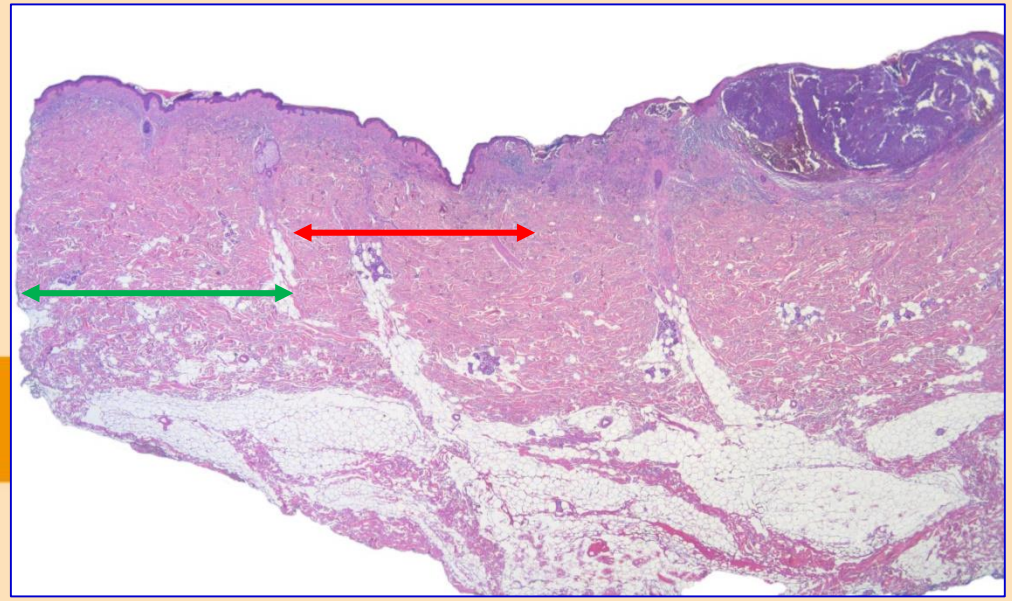

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the distance to the margin of excision measured histopathologically is often much smaller

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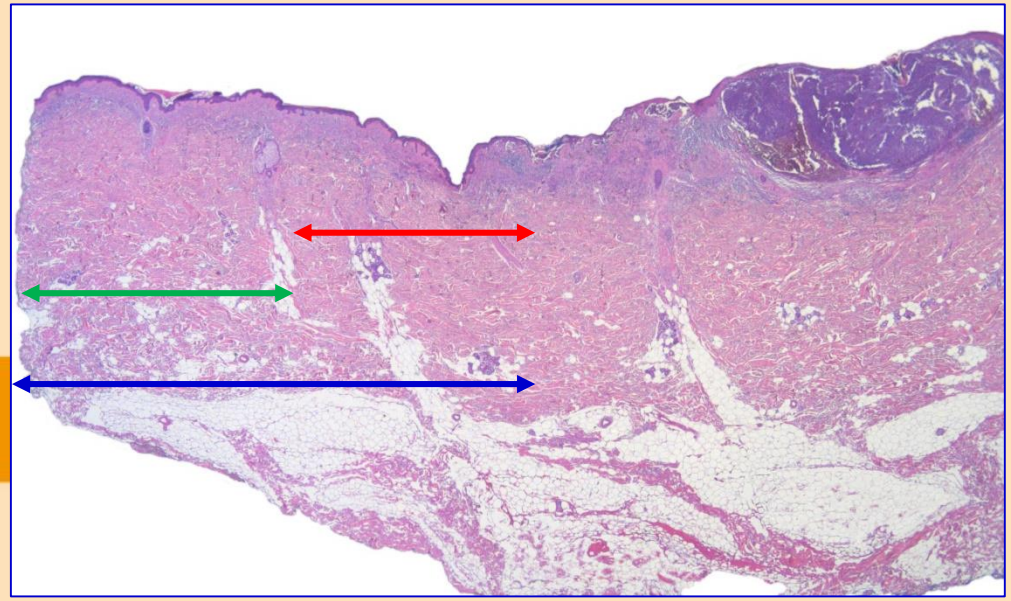

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than previously gauged clinically, but that is of no consequence if one knows of the limits of the lesion. Because of the shattering lack of logic, however, it is not uncommon that the margin measured histopathologically is used as the starting point to fulfill guidelines for clinical margins.

As a consequence, patients that have already been treated in accordance with standard guidelines

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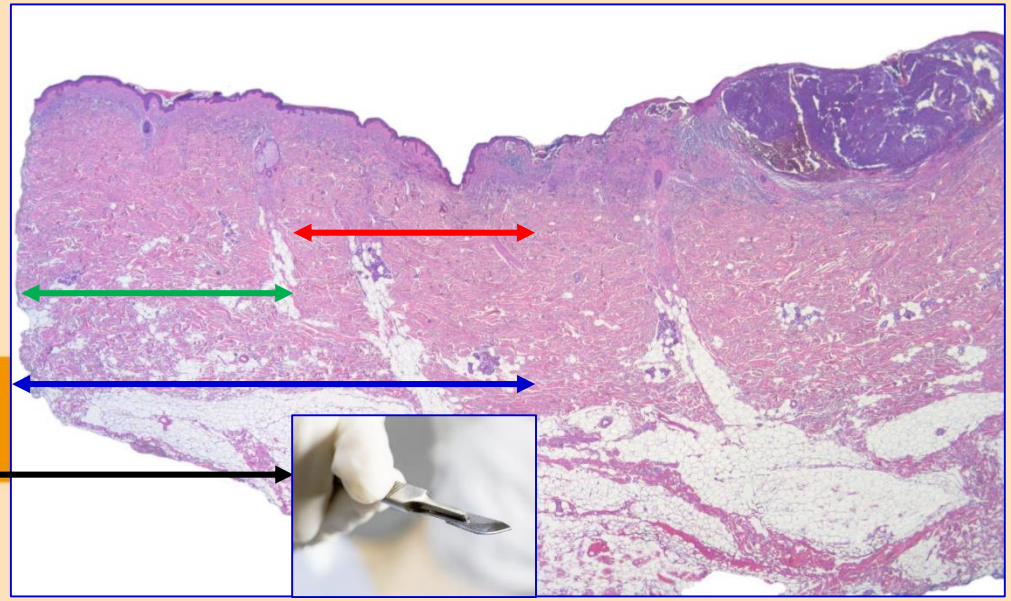

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As a consequence, patients that have already been treated in accordance with standard guidelines are subjected to yet another excision, removing nothing but healthy skin. Although their melanomas are out, without a trace of doubt and with a broad margin, they are attacked by surgeons again.

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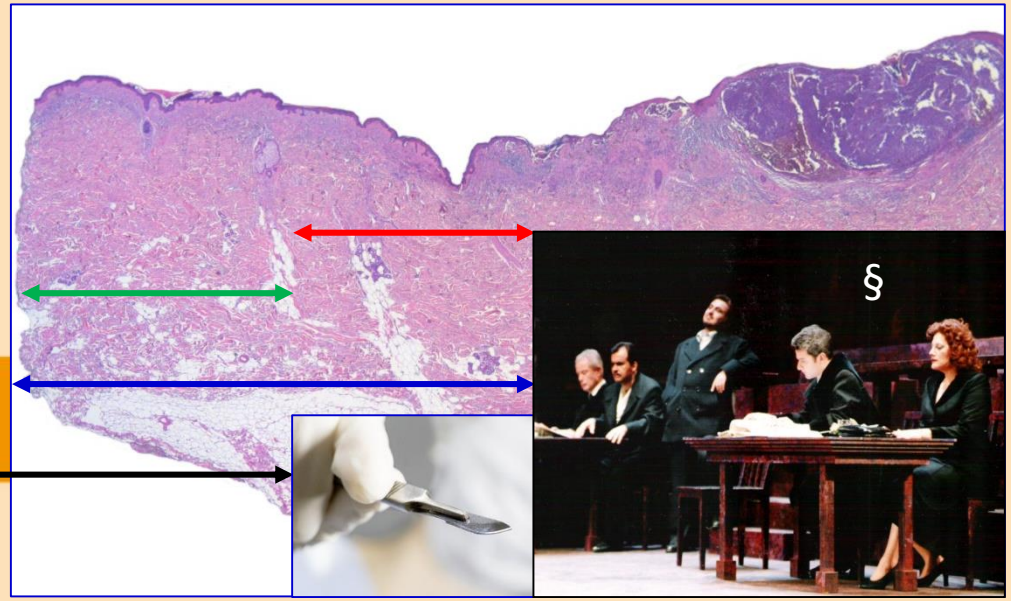

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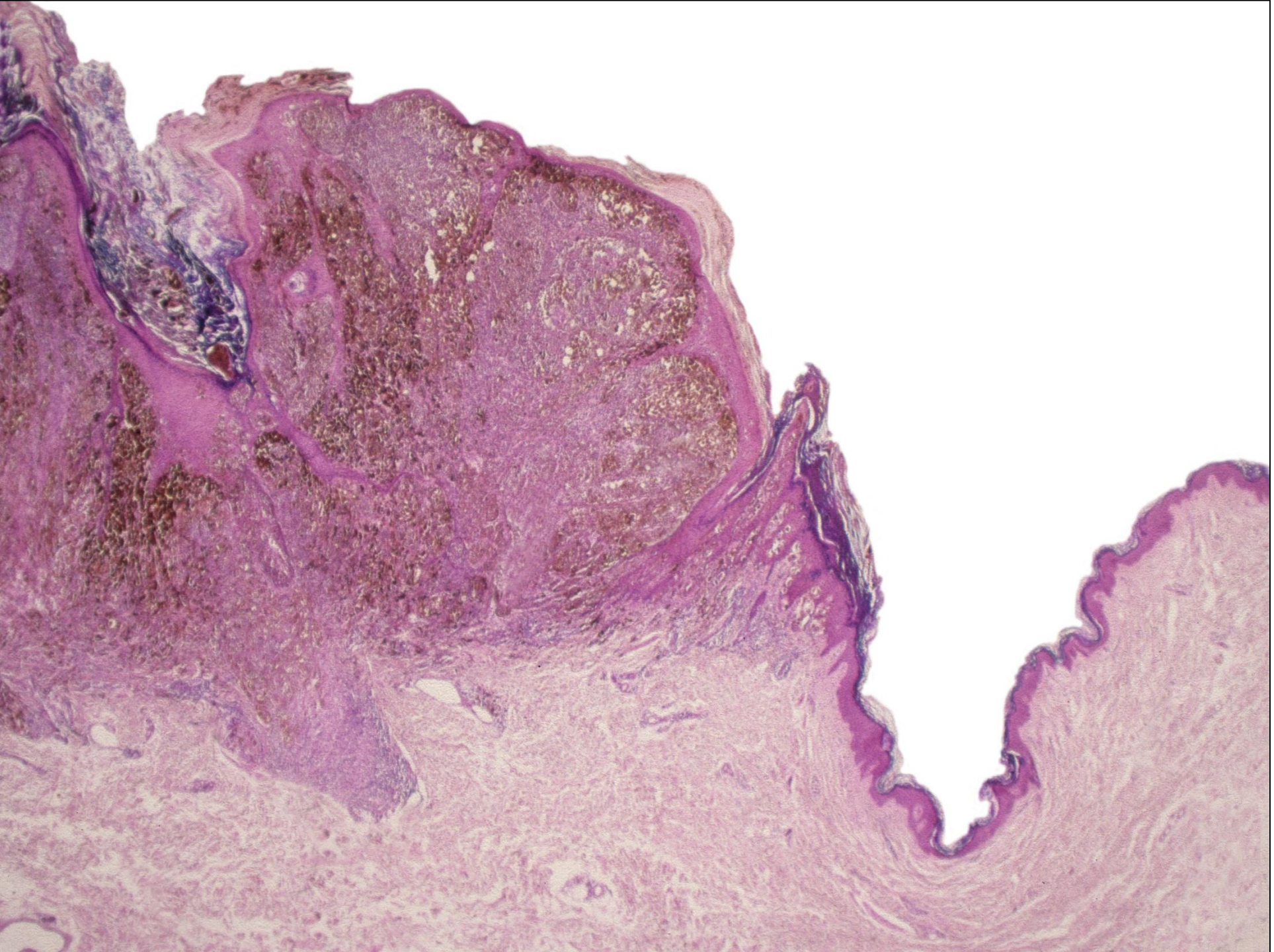
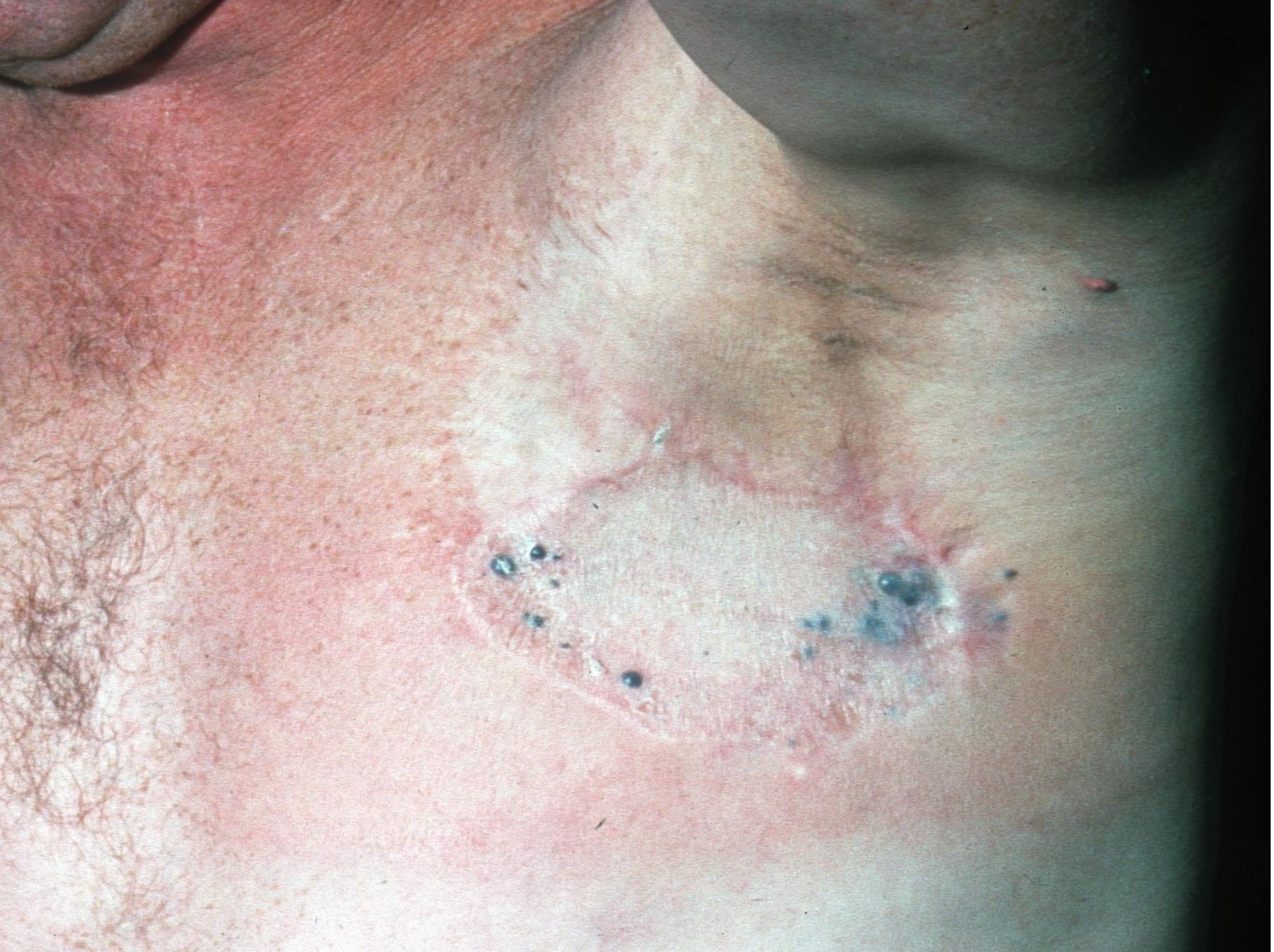
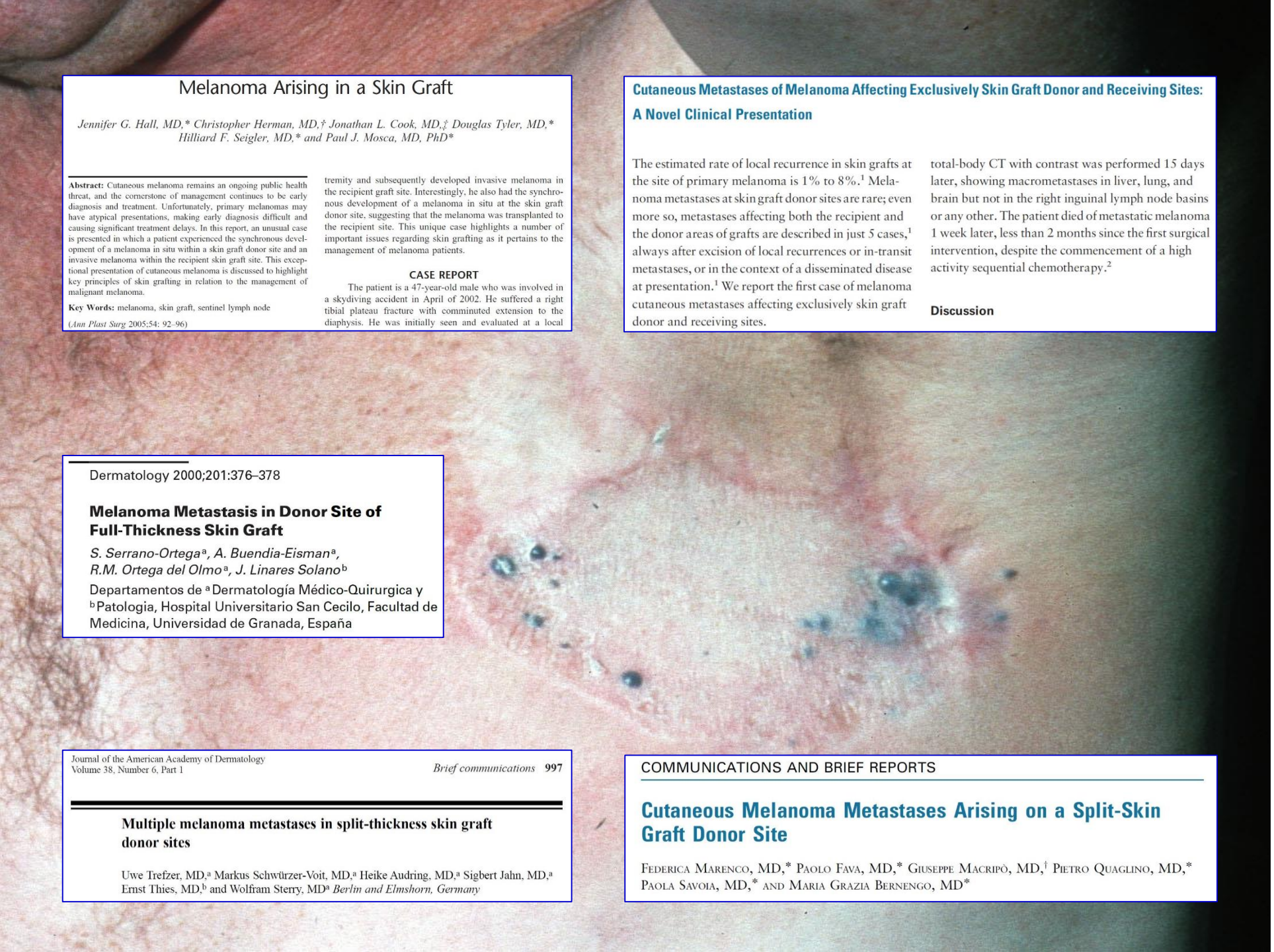
In principle, this fulfills the legal element of aggravated battery.
That legal element is also fulfilled if the last neoplastic cells detectable histopathologically are neglected and only clinical margins are considered, as demanded by current guidelines.



It is fulfilled especially in the case of thick melanomas that are sharply circumscribed. Even if these melanomas have been excised completely, without doubt and with an already generous margin, guidelines call for additional surgery. Patients with melanomas such as this one are at risk, but that risk resides in the lung, liver, or brain and not in normal skin around the primary tumor. In fact, they may be jeopardized by re-excisions



because the latter may lead to lymphedema and fibrosis, offering neoplastic cells that might otherwise be destroyed by the immune system a niche to settle down and grow.



Melanoma Arising in a Skin Graft

Jennifer G. Hall, MD, Christopher Herman, MD,† Jonathan L. Cook, MD,‡ Douglas Tyler, MD,* Hilliard F. Seigler, MD,* and Paul J. Mosca, MD, PhD**

Abstract: Cutaneous melanoma remains an ongoing public health threat, and the cornerstone of management continues to be early diagnosis and treatment. Unfortunately, primary melanomas may have atypical presentations, making early diagnosis difficult and causing significant treatment delays. In this report, an unusual case is presented in which a patient experienced the synchronous development of a melanoma in situ within a skin graft donor site and an invasive melanoma within the recipient skin graft site. This exceptional presentation of cutaneous melanoma is discussed to highlight key principles of skin grafting in relation to the management of malignant melanoma.

Key Words: melanoma, skin graft, sentinel lymph node

(*Ann Plast Surg* 2005;54: 92–96)

tremity and subsequently developed invasive melanoma in the recipient graft site. Interestingly, he also had the synchronous development of a melanoma in situ at the skin graft donor site, suggesting that the melanoma was transplanted to the recipient site. This unique case highlights a number of important issues regarding skin grafting as it pertains to the management of melanoma patients.

CASE REPORT

The patient is a 47-year-old male who was involved in a skydiving accident in April of 2002. He suffered a right tibial plateau fracture with comminuted extension to the diaphysis. He was initially seen and evaluated at a local

Cutaneous Metastases of Melanoma Affecting Exclusively Skin Graft Donor and Receiving Sites: A Novel Clinical Presentation

The estimated rate of local recurrence in skin grafts at the site of primary melanoma is 1% to 8%.[1] Melanoma metastases at skin graft donor sites are rare; even more so, metastases affecting both the recipient and the donor areas of grafts are described in just 5 cases,[1] always after excision of local recurrences or in-transit metastases, or in the context of a disseminated disease at presentation.[1] We report the first case of melanoma cutaneous metastases affecting exclusively skin graft donor and receiving sites.

total-body CT with contrast was performed 15 days later, showing macrometastases in liver, lung, and brain but not in the right inguinal lymph node basins or any other. The patient died of metastatic melanoma 1 week later, less than 2 months since the first surgical intervention, despite the commencement of a high activity sequential chemotherapy.[2]

Discussion

Dermatology 2000;201:376–378

Melanoma Metastasis in Donor Site of Full-Thickness Skin Graft

S. Serrano-Ortega[a], *A. Buendia-Eisman*[a], *R.M. Ortega del Olmo*[a], *J. Linares Solano*[b]

Departamentos de [a] Dermatología Médico-Quirurgica y [b] Patologia, Hospital Universitario San Cecilo, Facultad de Medicina, Universidad de Granada, España

Journal of the American Academy of Dermatology
Volume 38, Number 6, Part 1

Multiple melanoma metastases in split-thickness skin graft donor sites

Uwe Trefzer, MD,[a] Markus Schwürzer-Voit, MD,[a] Heike Audring, MD,[a] Sigbert Jahn, MD,[a] Ernst Thies, MD,[b] and Wolfram Sterry, MD[a] *Berlin and Elmshorn, Germany*

COMMUNICATIONS AND BRIEF REPORTS

Cutaneous Melanoma Metastases Arising on a Split-Skin Graft Donor Site

Federica Marenco, MD,* Paolo Fava, MD,* Giuseppe Macripò, MD,† Pietro Quaglino, MD,* Paola Savoia, MD,* and Maria Grazia Bernengo, MD*

The literature is replete with reports of metastases not only in skin grafts, as in this case, but also in split-skin graft donor sites.

Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: long-term follow-up of survival in a randomised trial

Andrew J Hayes, Lauren Maynard, Gillian Coombes, Julia Newton-Bishop, Michael Timmons, Martin Cook, Jeffrey Theaker, Judith M Bliss, J Meirion Thomas*, for the UK Melanoma Study Group, the British Association of Plastic, Reconstructive, and Aesthetic Surgeons, and the Scottish Cancer Therapy Network*

Lancet Oncol 2016; 17: 184–92

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See Comment page 127

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The Royal Marsden Hospital National Health Foundation Trust, London, UK (A J Hayes FRCS, J M Thomas FRCS); **Clinical Trials and Statistics Unit at The Institute of Cancer Research, London, UK** (L Maynard MSc, G Coombes RN, Prof J M Bliss MSc); **Leeds Institute of Cancer and Pathology, Leeds, UK** (Prof J Newton-Bishop FMedSci); **Bradford Royal Infirmary, Bradford, UK** (M Timmons FRCS); **Royal Surrey County Hospital, Guildford, UK** (Prof M Cook FRCPath); **and University Hospitals Southampton, Southampton, UK** (J Theaker FRCPath)

Correspondence to: Dr Andrew J Hayes, The Royal Marsden Hospital National Health Foundation Trust, London SW3 6JJ, UK **andrew.hayes@rmh.nhs.uk**

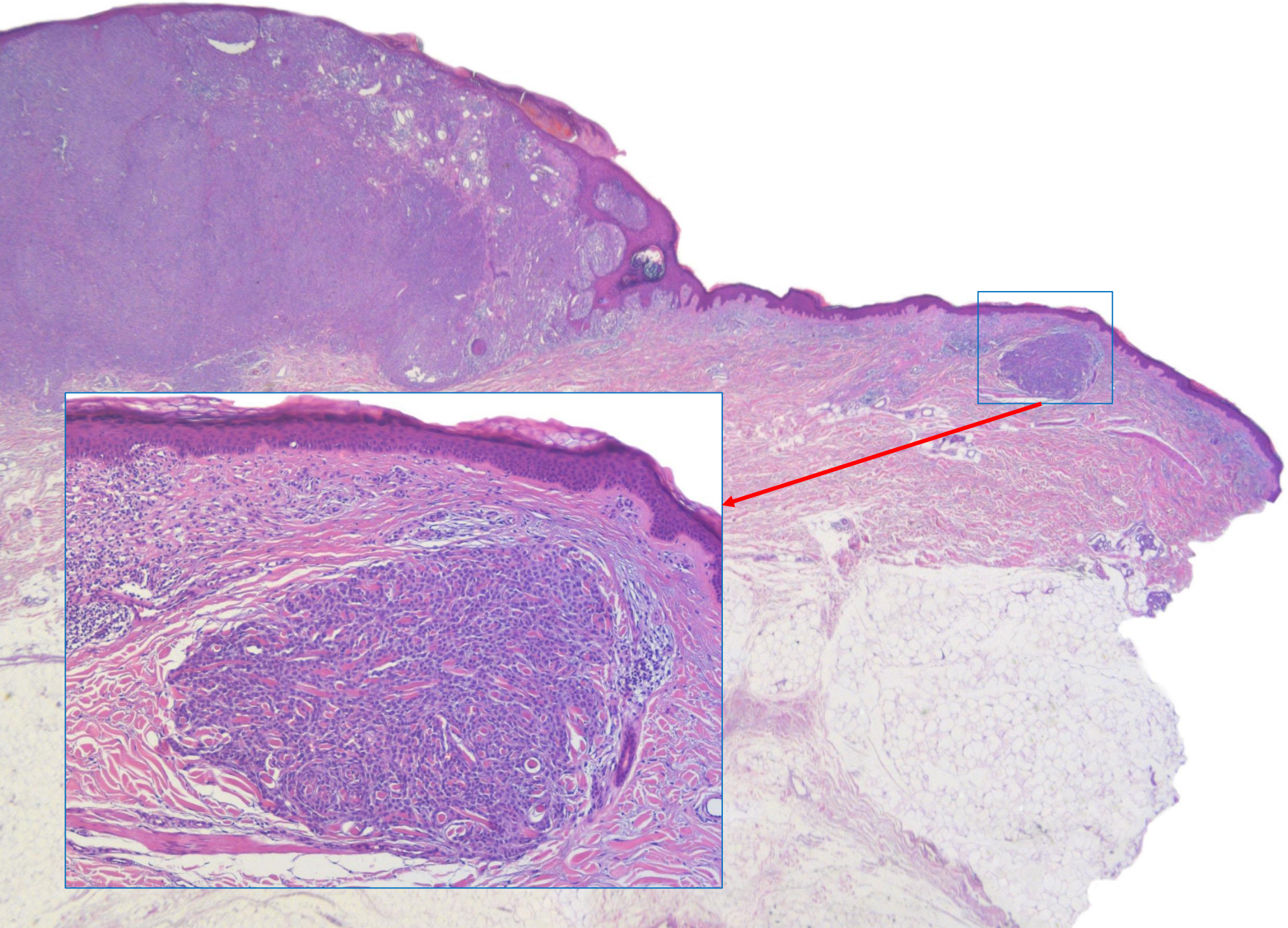
Summary

Background The necessary margin of excision for cutaneous melanomas greater than 2 mm in thickness is controversial. At a median follow-up of 5 years, findings from our previously published randomised trial of narrow (1 cm) versus wide (3 cm) excision margins in patients with thick cutaneous melanomas showed that narrow margins were associated with an increased frequency of locoregional relapse, but no significant difference in overall survival was apparent. We now report a long-term survival analysis of that trial.

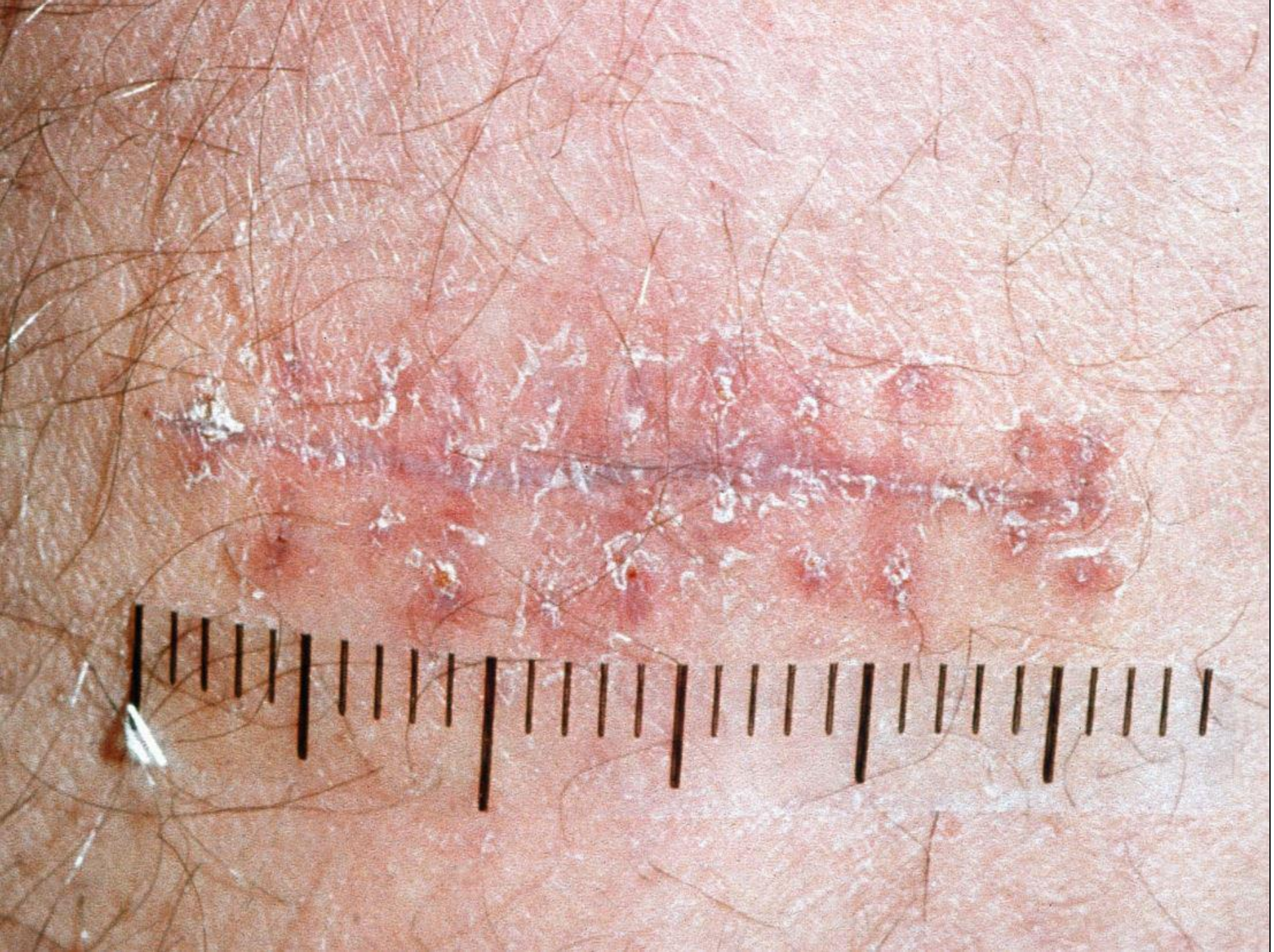
Previous randomised studies of elective[17–21] or selective[22] lymph node dissection have not shown a significant difference in melanoma-specific survival. The absence of a proven survival benefit in these nodal studies is at odds with the probable biological hypothesis for an effect on survival shown in this study—ie, that removal of microsatellites around the primary tumour affects the development of metastatic disease. However, because subgroup analyses in these studies raised the possibility of survival benefit for prophylactic lymph node clearance that was not detected at the point of randomisation,[22]

Health Service Executive, British United Provident Association Foundation, British Association of Plastic Surgeons, the Meirion Thomas Cancer Research Fund, and the National Institute for Health and Research Biomedical Research Centre at The Royal Marsden NHS Foundation Trust.

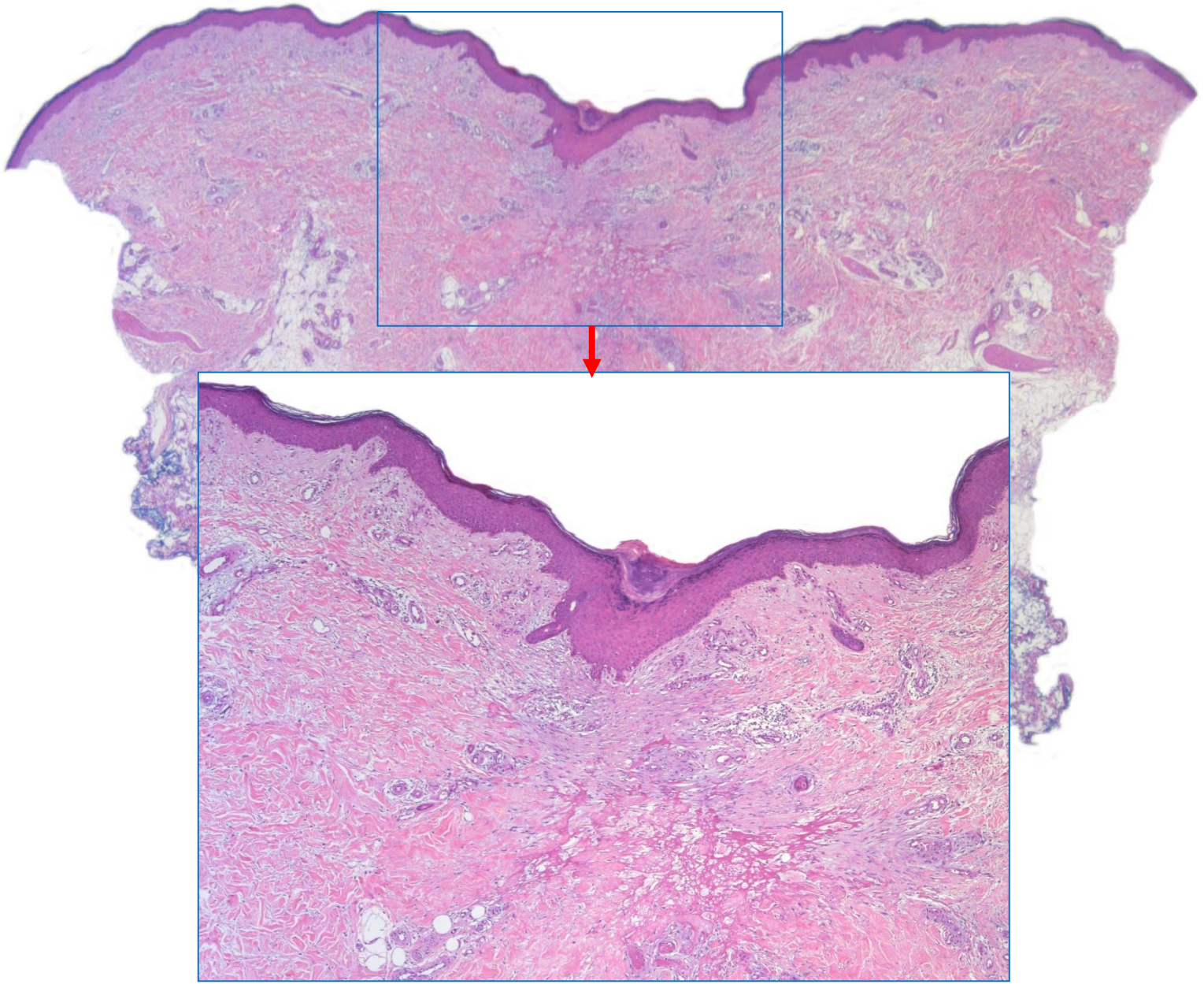
The call for additional surgery in melanomas that have already been excised completely has been justified nearly invariably by the *"probable biological hypothesis for an effect"* of *"removal of microsatellites around the primary tumour."*



Those microsatellites occur but, as we have already seen, removal of them prior to clinical manifestation has no substantial benefit. Moreover, they are extremely rare. Re-excision specimens are examined histopathologically and immunohistochemically day after day, year after year, and microsatellites are practically never seen. In brief, for practical purposes, they are a fiction,



and all that one finds
when excising a scar



is – a scar. Because of guidelines for melanoma surgery, dermatopathologists have become the greatest experts in scars among all pathologists.

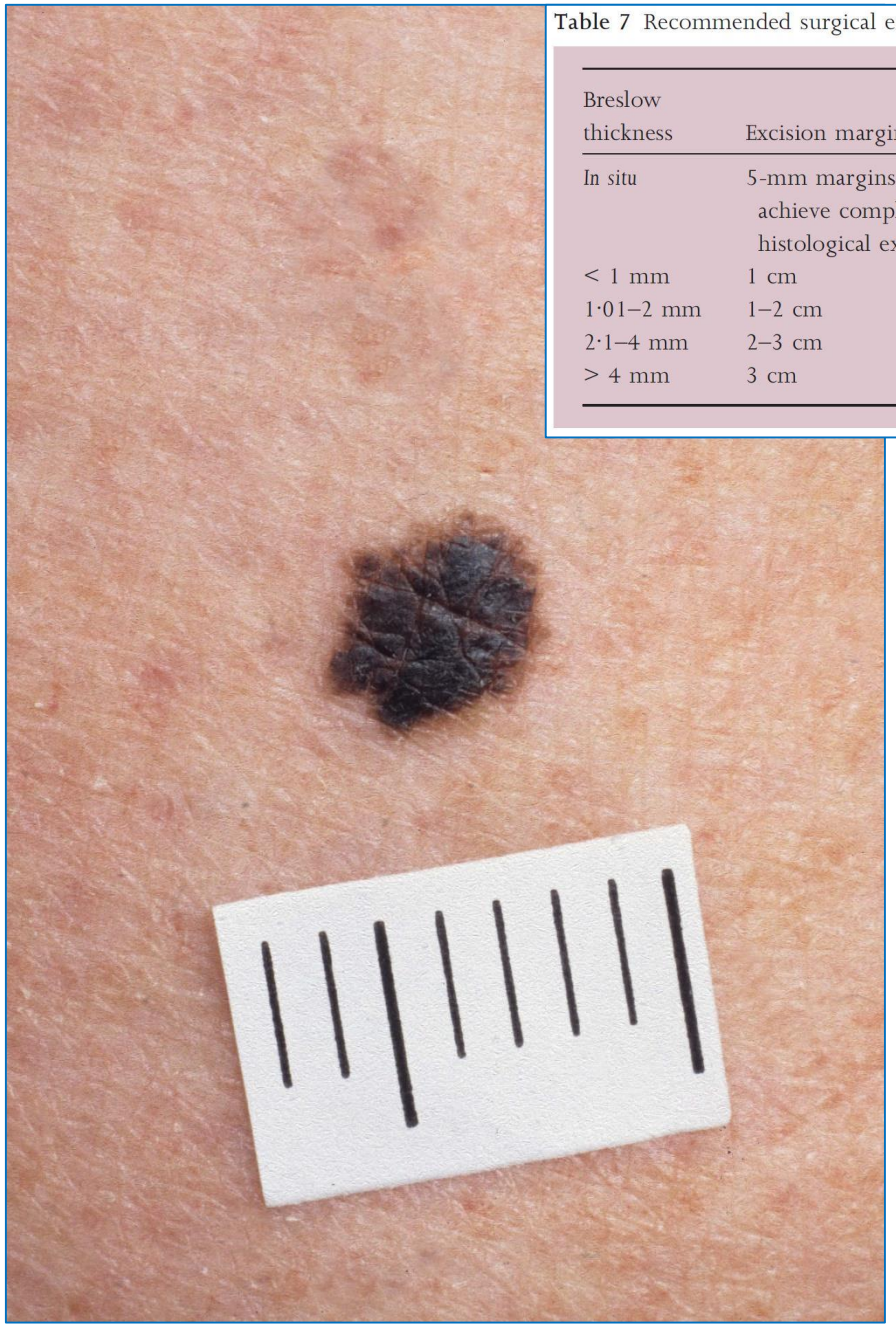
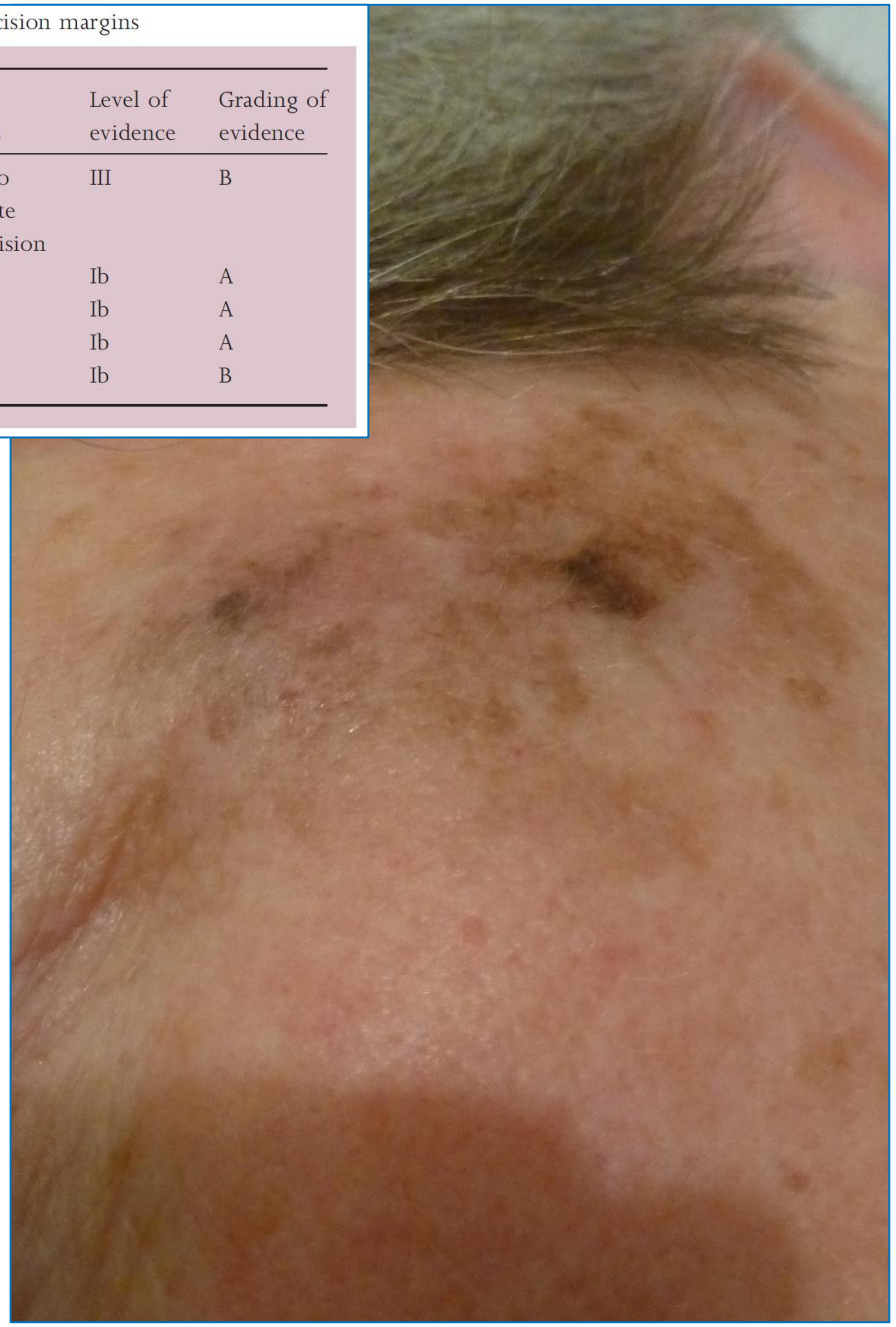


Table 7 Recommended surgical excision margins

Breslow thickness	Excision margins	Level of evidence	Grading of evidence
In situ	5-mm margins to achieve complete histological excision	III	B
< 1 mm	1 cm	Ib	A
1·01–2 mm	1–2 cm	Ib	A
2·1–4 mm	2–3 cm	Ib	A
> 4 mm	3 cm	Ib	B



Another factor at odds with current guidelines for melanoma surgery is the fact that thicker melanomas tend to be more sharply confined than thinner ones, hence requiring not wider, but narrower margins.

Table 7 Recommended surgical excision margins

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In situ	5-mm margins to achieve complete histological excision	III	B
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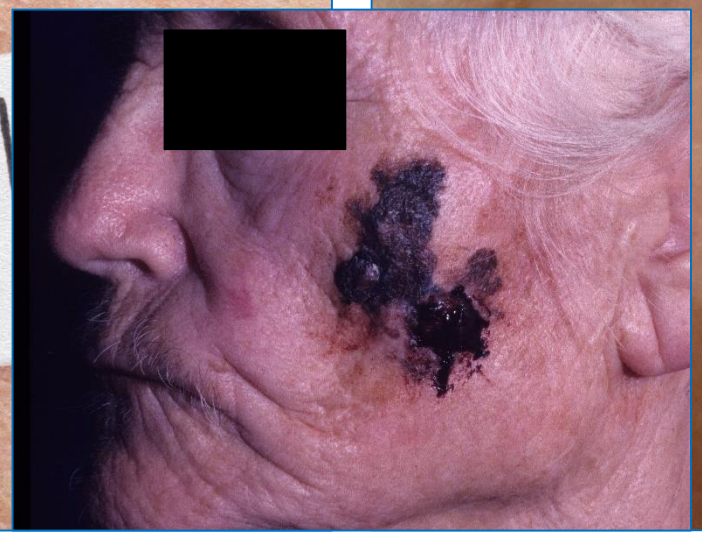

There are exceptions to that rule, as thick nodules may develop on top of a larger thin component, but, in general, thicker tumors have a higher rate of proliferation and show more expansile growth, whereas thin melanomas tend to grow slowly and spread.

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Experimental Dermatopathology

Gérald E. Piérard, Editor

Relationship of Tumor Cell Motility and Morphologic Patterns

Part 1. Melanocytic Skin Tumors

Josef Smolle, M.D., Freyja-Maria Smolle-Juettner, M.D., Haro Stettner, M.D., and Helmut Kerl, M.D.

In the diagnosis of melanocytic skin tumors, the assessment of the overall architectural pattern (silhouette) is often essential. We have previously shown by a computer simulation model that tumor patterns are likely to depend on the relative degrees of proliferation and motility of the tumor cells. In this study, we examined the morphological pattern of 12 cases each of nevocellular nevi, primary melanoma, and metastatic melanoma by image analysis. The patterns of the individual melanocytic skin tumors were compared statistically with patterns generated by computer simulation, which facilitates estimates of biological properties of the tumor cells. Additionally, mitotic counts were made to measure tumor cell proliferation. A comparison of the [illegible] the cells of nevocellular [illegible] tility, which, however, [illegible] of proliferation. The [illegible] ous small nests and [illegible] common. In primary [illegible] tility and tumor cell [illegible] creased in various [illegible] morphological patterns [illegible] ingly elevated degree [illegible] slightly elevated degree [illegible] demarcated, "expansive" lesions. To check the validity of the technical procedure, estimates of proliferation based on pattern analysis alone were compared with the results obtained by mitotic counts. There was a significant correlation, indicating that the assumptions of the computer model and the image analysis procedure are in fact applicable to real-life melanocytic skin tumors. The study shows that architectural features routinely observed in melanocytic skin tumors are related at least in part to certain biological properties of the tumor cells.

Key Words: Tumor cell motility—Tumor cell invasion—Melanoma—Melanocytic nevus—Image analysis—Computer simulation.

From the Department of Dermatology, University of Graz (J.M., F.-M.S.-J., H.K.), and the Institute of Mathematics, University of Klagenfurt (H.S.), Austria.

A summary of this paper was presented at the American Society of Dermatopathology, Atlanta, Georgia, 1990.

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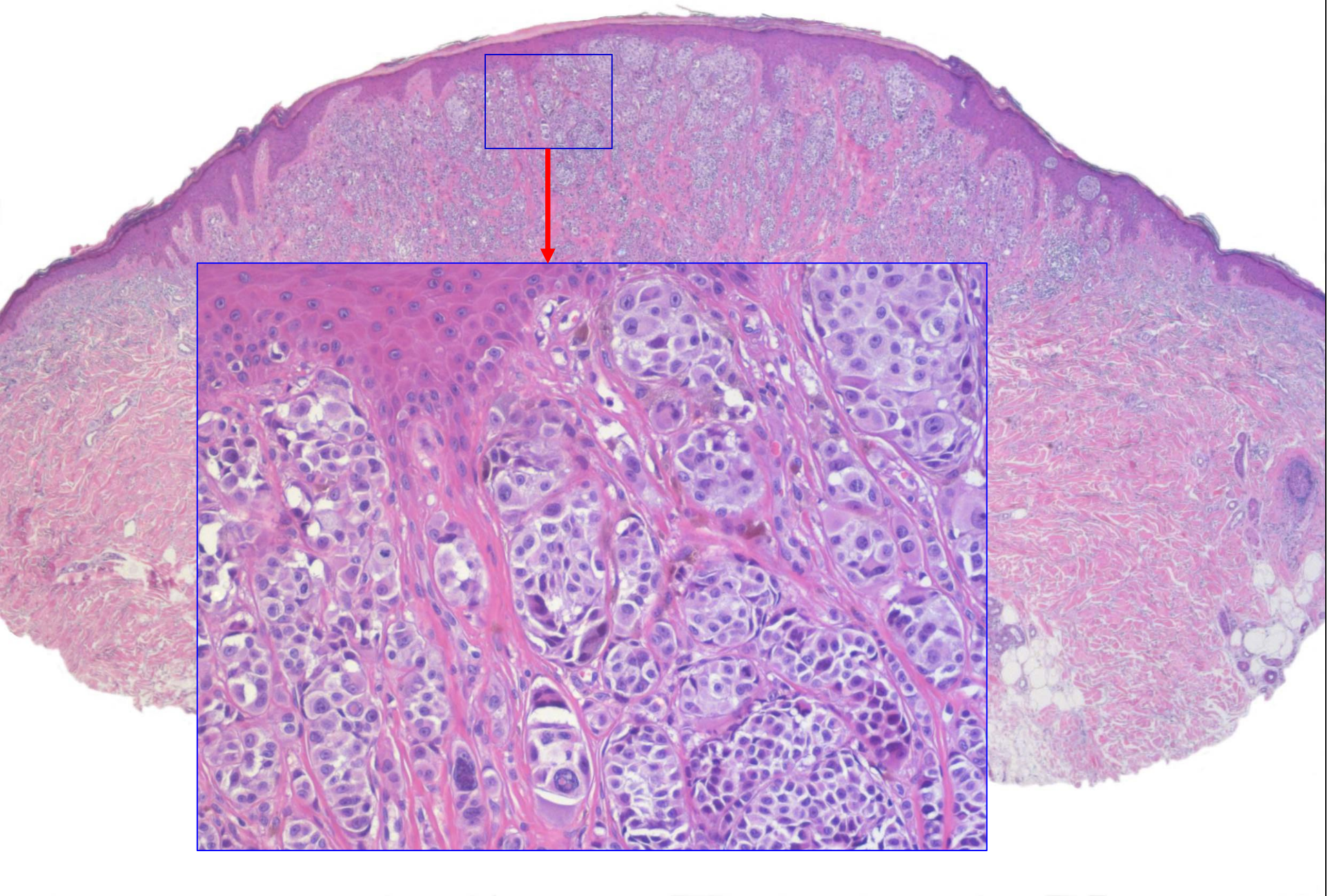
Tumor diagnosis was formerly based on the assessment of cytological criteria such as nuclear atypia, hyperchromatism, and nucleus-cytoplasmic ratio, but in recent years, the study of tumor patterns at scanning magnification ("tumor silhouette") has gained increasing attention (1–4). The outline and demarcation of a lesion; the arrangement of tumor cells in densely packed areas, sheets, and nests of various size and shape; and the occurrence of single cells in the center or at the periphery are all of diagnostic value, particularly in melano[illegible] evolve and the way in which they are determined by biological properties of the tumor cells are still not understood.

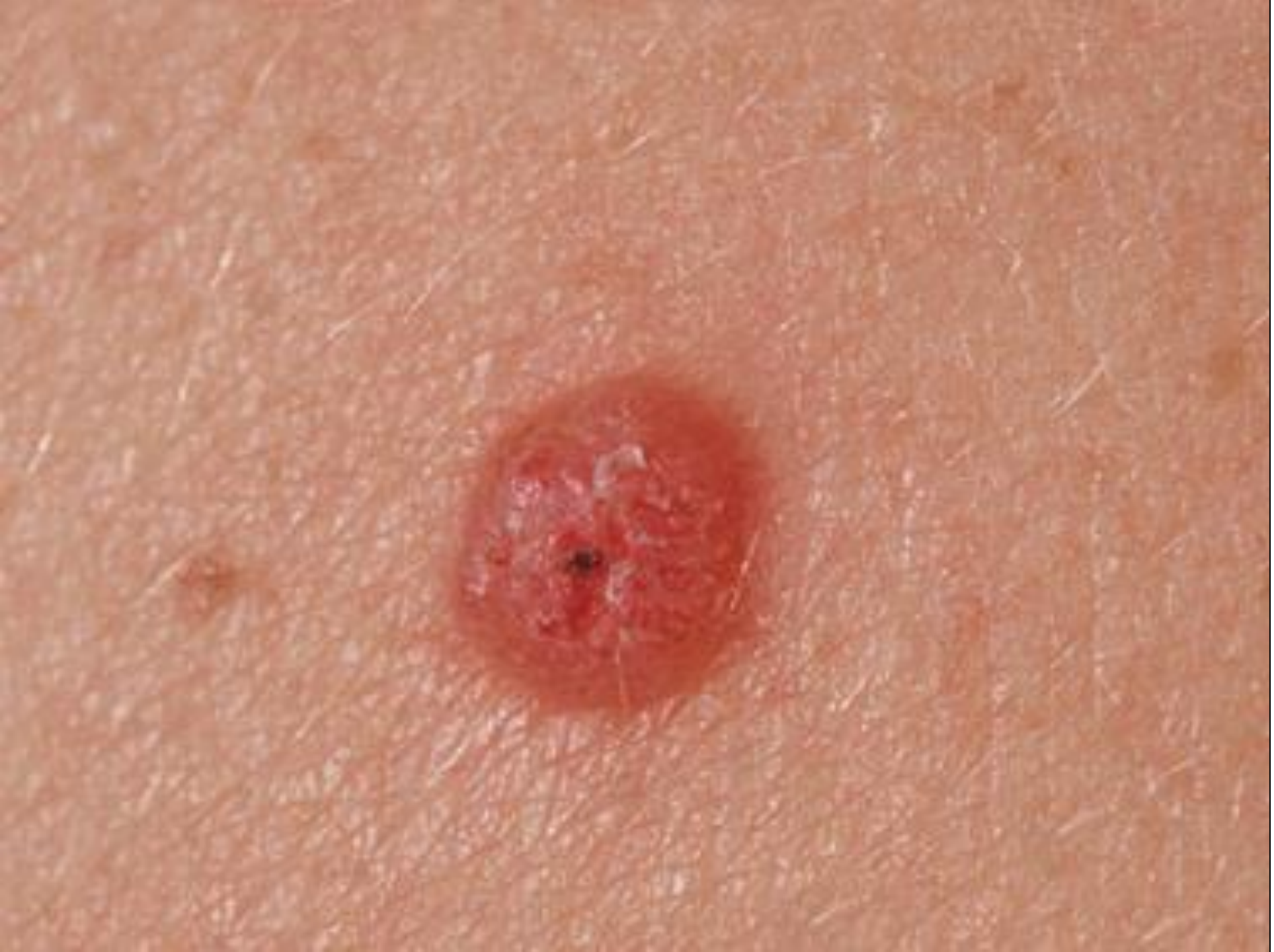
In a previous study, we used computer simulation to study this problem (6). A program was developed that simulates tumor growth, starting with a single cell. For this tumor cell—and all daughter cells derived from it—biological properties can be determined arbitrarily. Therefore, it was possible to establish, which pattern would develop for a given set of cellular properties. Since invasion is believed to depend largely on tumor cell proliferation on one hand (7) and tumor cell motility on the other (8), both properties were included in the computer model. A computerized pattern analysis procedure, which can be applied to simulated patterns as well as to the pattern of real histological specimens, was subsequently developed (9). Thus, it was possible to compare real tumors (for which the cellular prop-

often essential. We have previously shown by a computer simulation model that tumor patterns are likely to depend on the relative degrees of proliferation and motility of the tumor cells. In this study, we examined the morphologi-

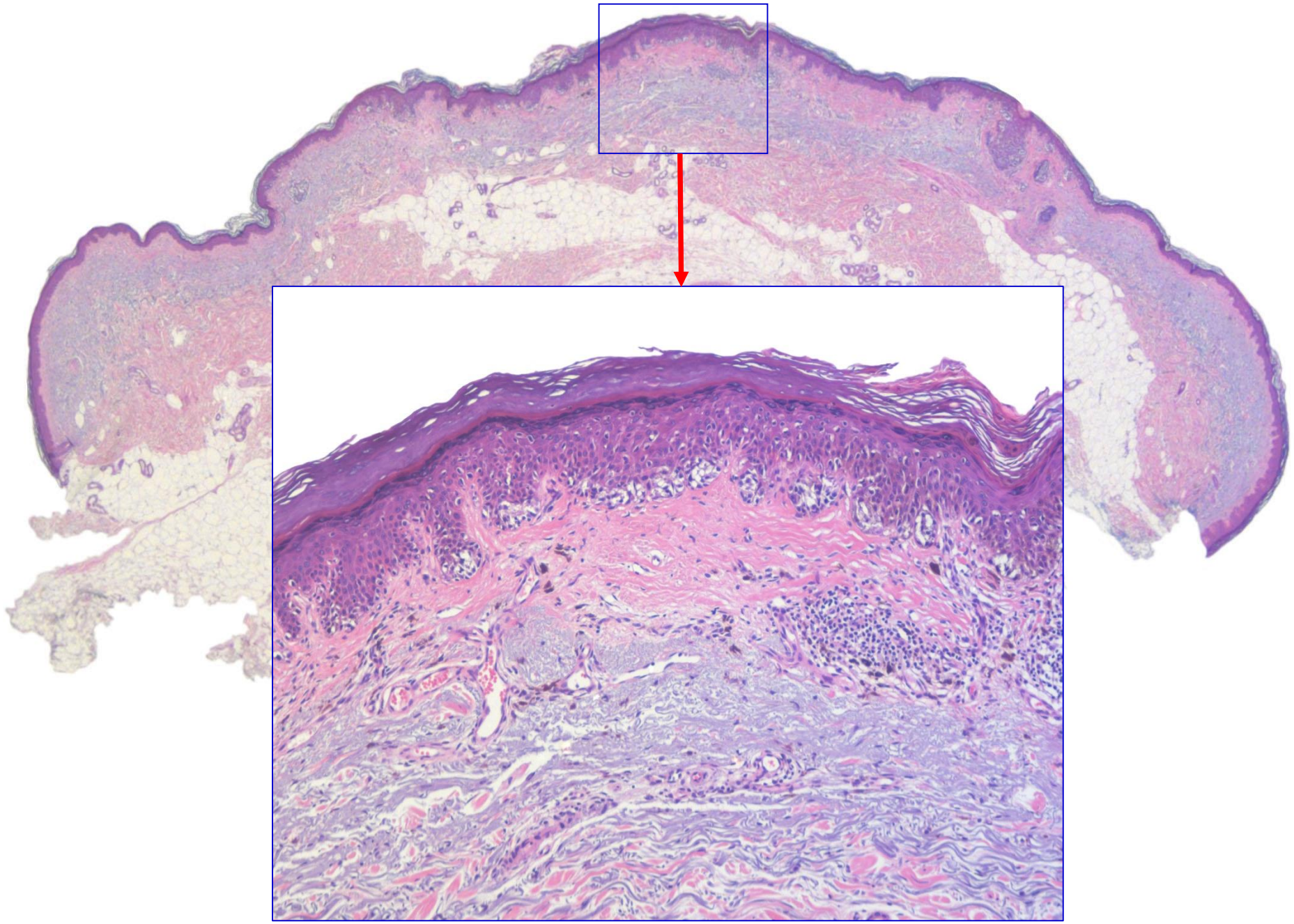
This has been studied in a computer simulation model by Smolle and co-workers who pointed out that *"tumor patterns are likely to depend on the relative degrees of proliferation and motility of the tumor cells."*



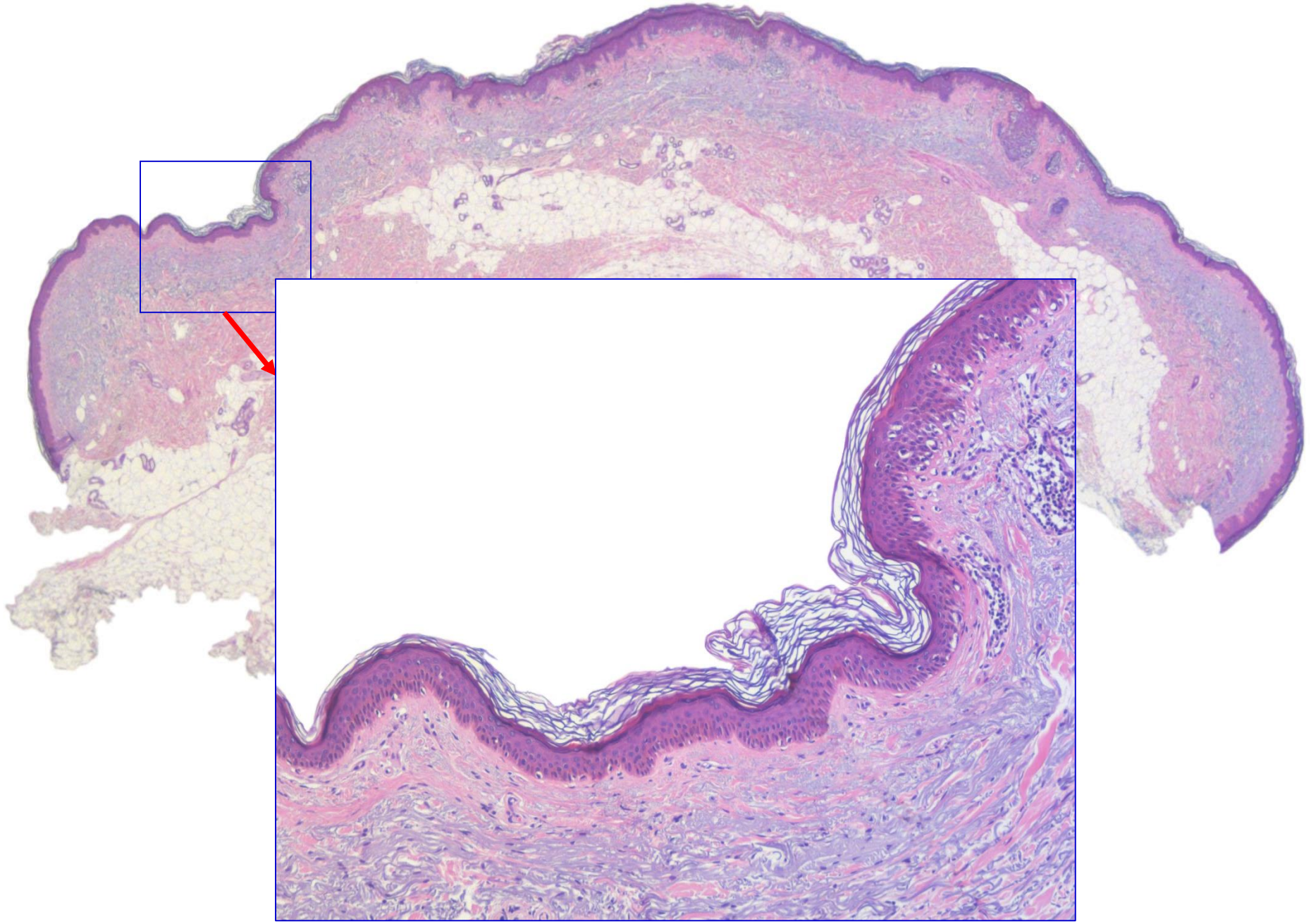
Melanomas with high proliferation and numerous mitotic figures acquire considerable thickness early-on, but they are sharply confined both, histopathologically



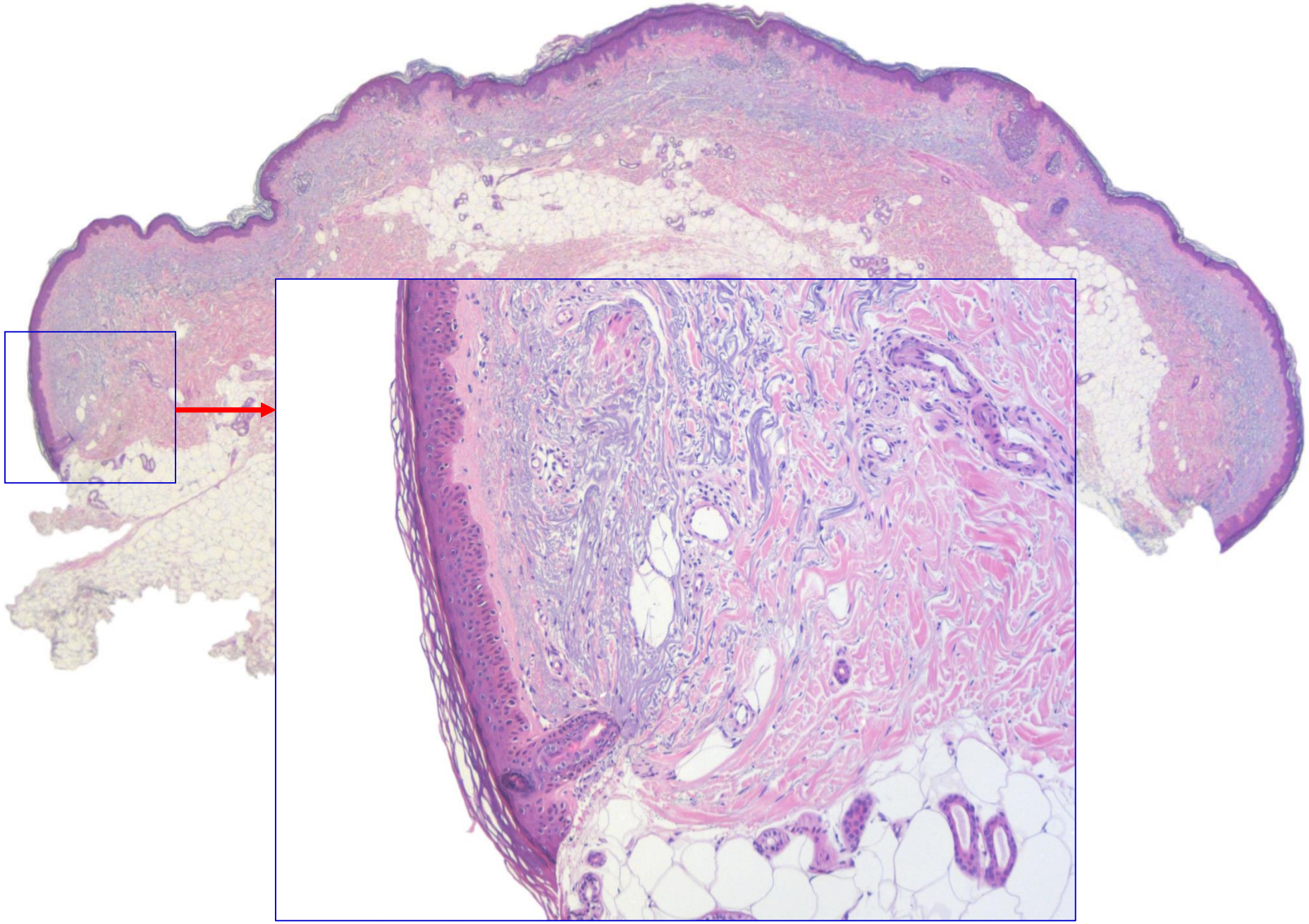
and clinically. Because they are often scarcely pigmented, they are overlooked easily; those domed nodules must be excised as early as possible, but a narrow margin is sufficient.



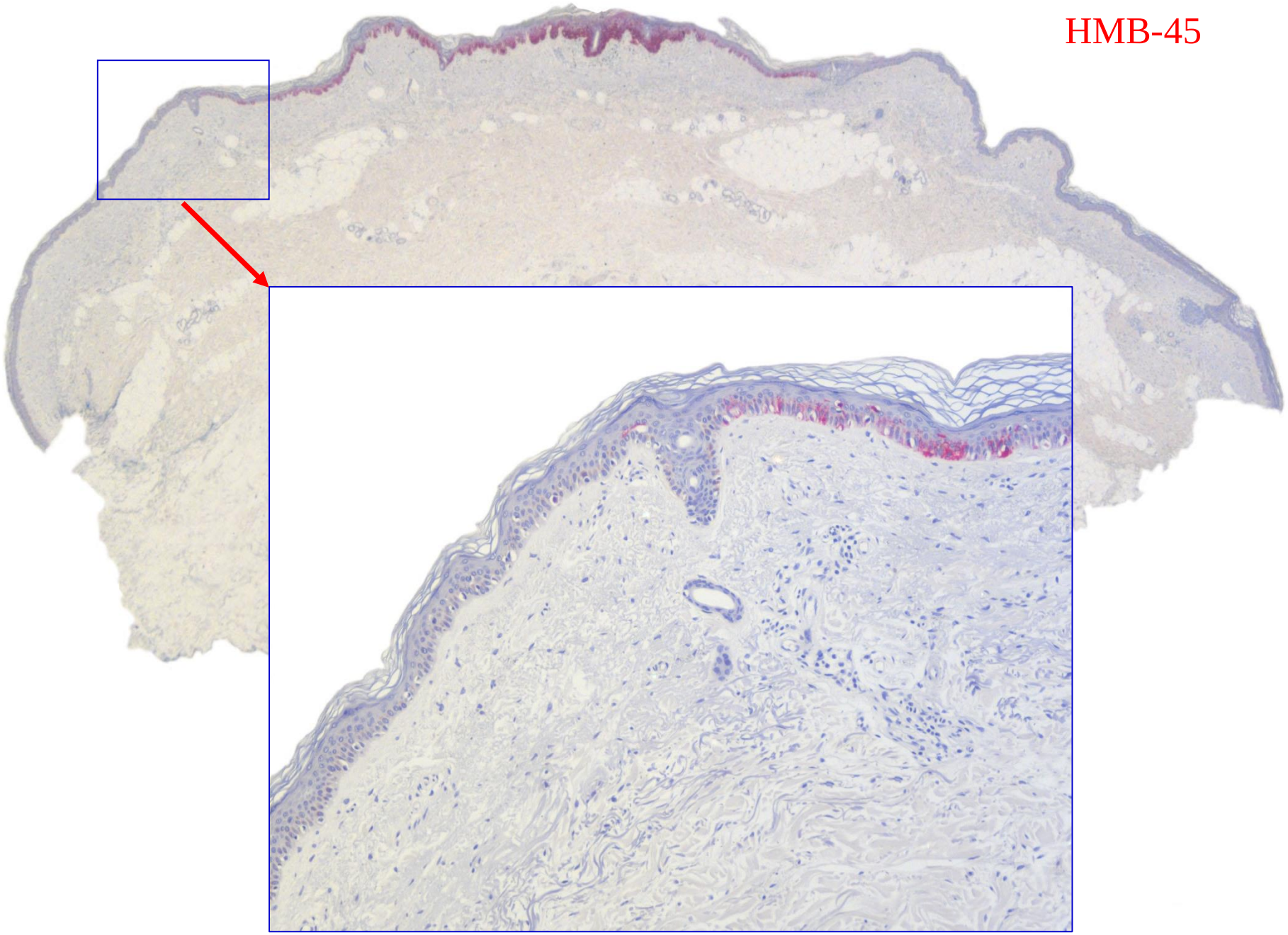
By contrast, cells of slow-growing melanomas, such as this melanoma in situ, have more time to spread,



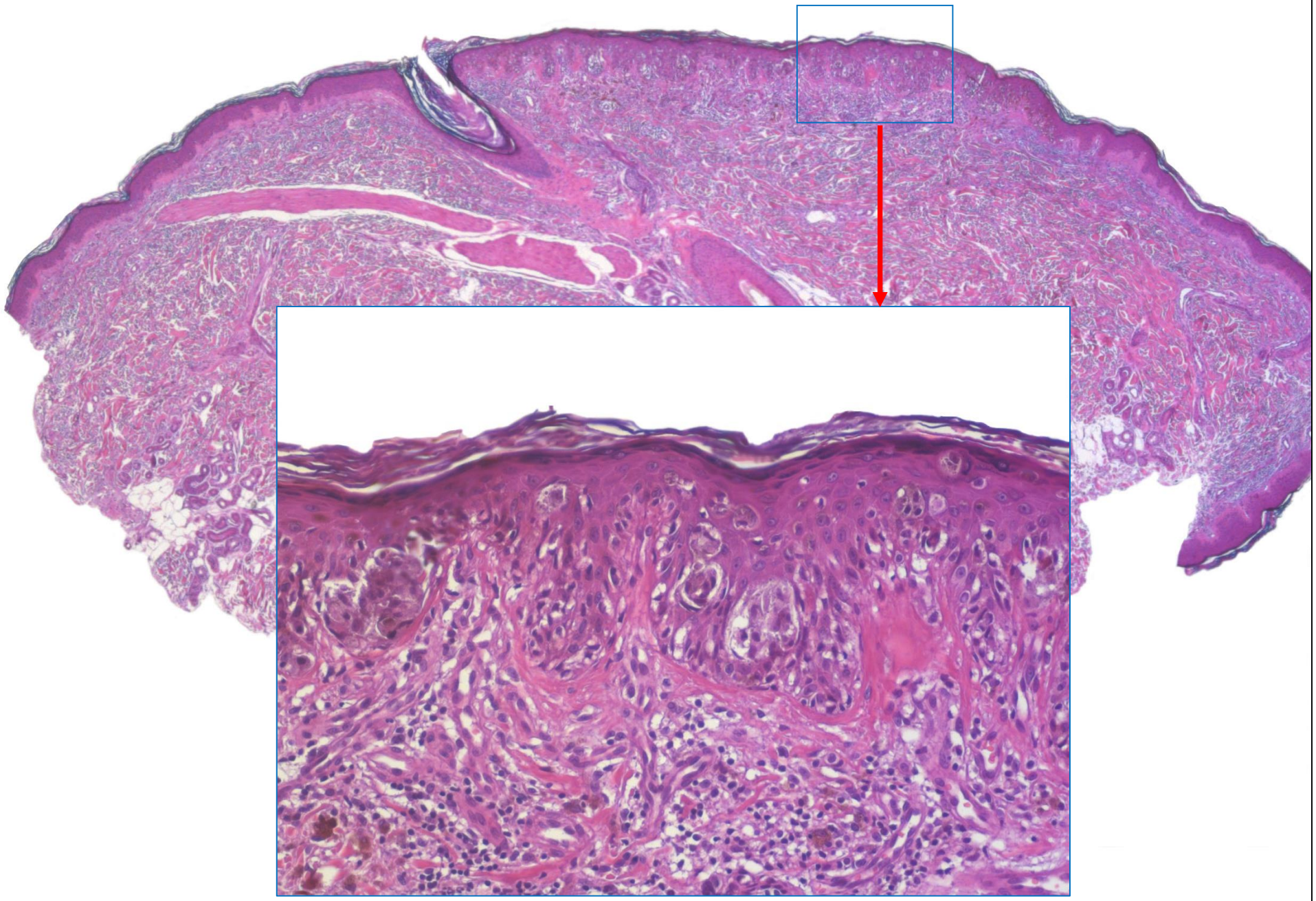
and the margin is often indistinct. Those cells clearly belong to the melanoma, but where the lesions ends is difficult to decide. The melanocytes in the periphery are still slightly increased in number and have somewhat prominent nuclei,



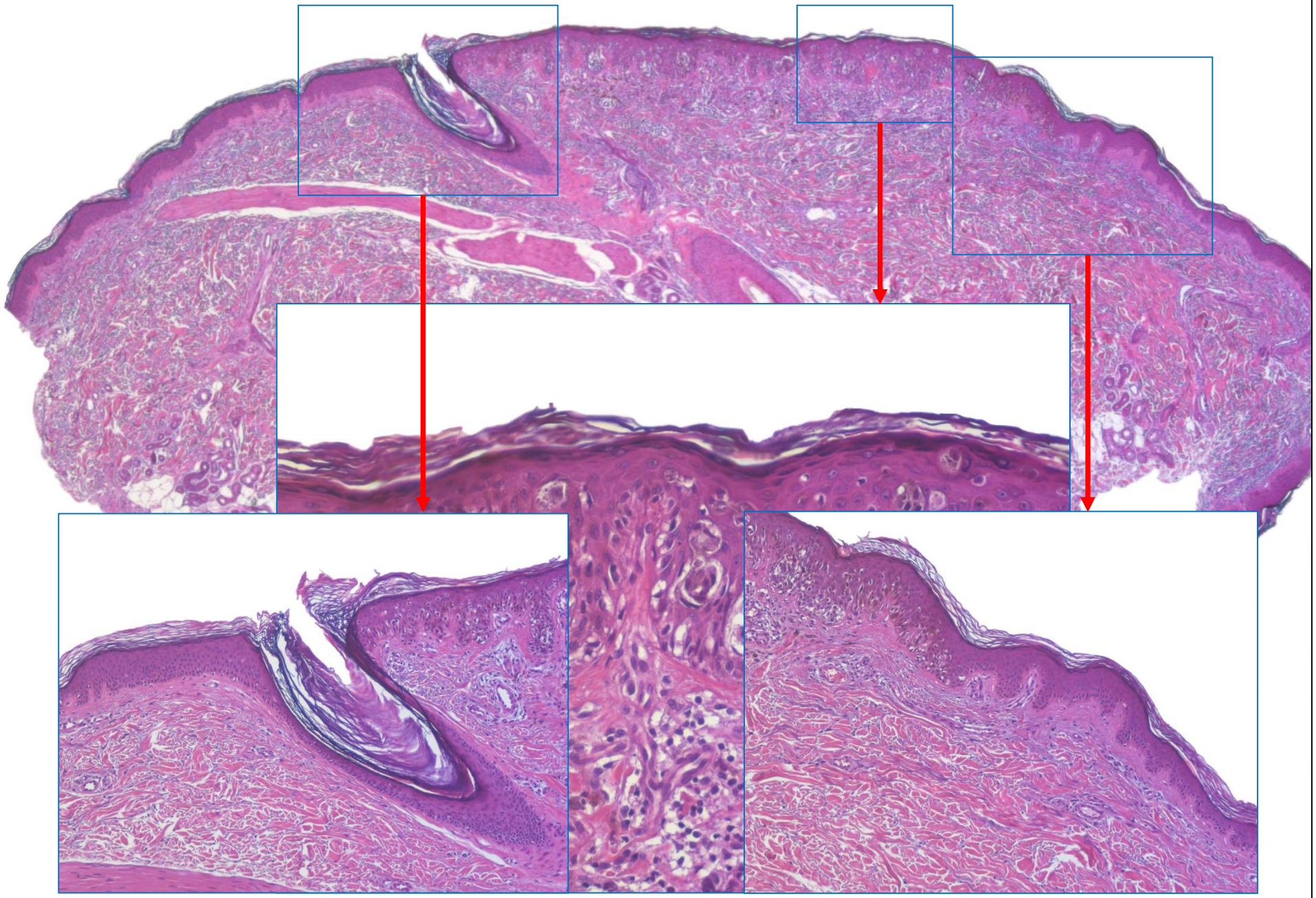
especially if compared to melanocytes at the far end of the specimen.



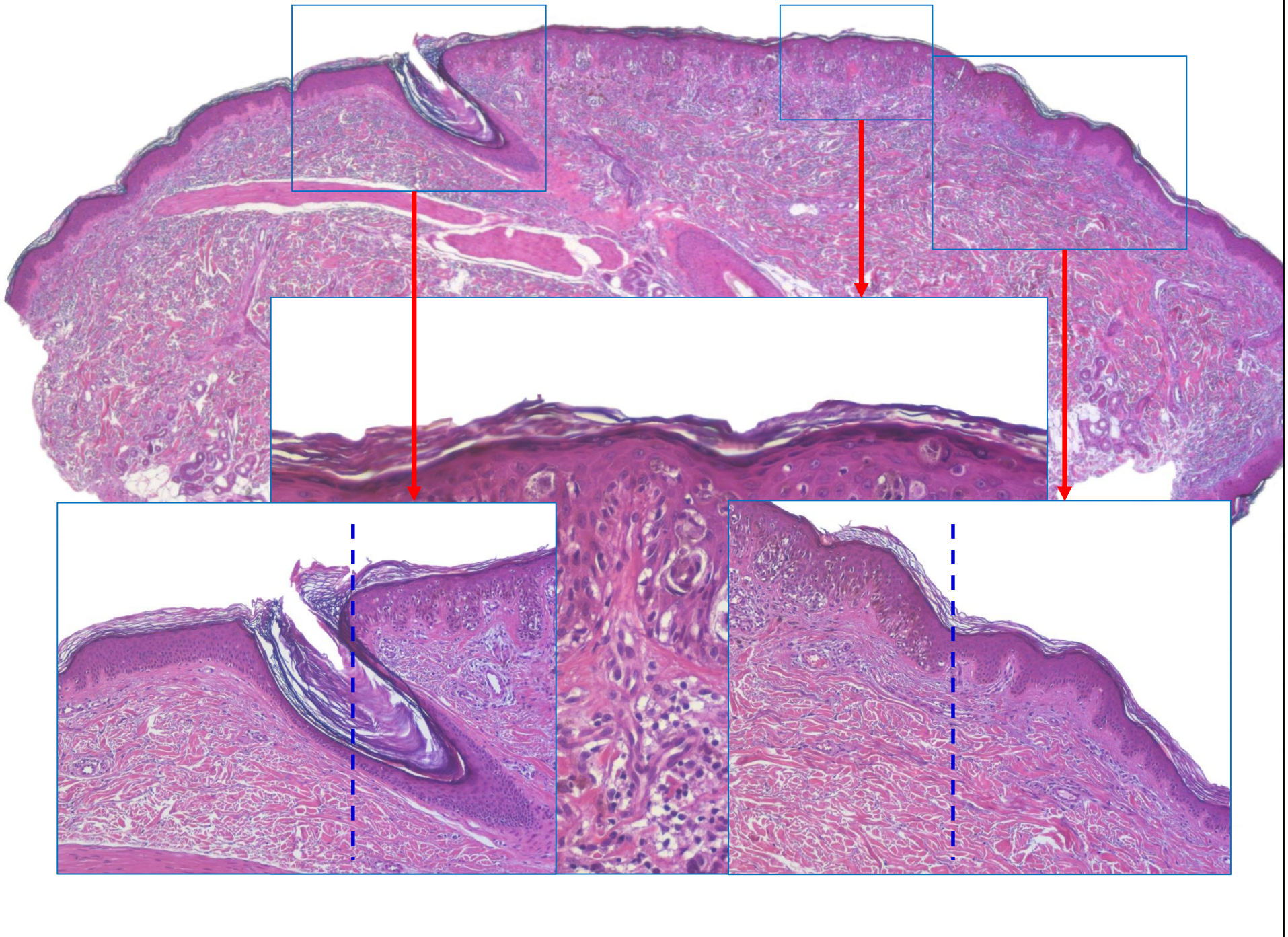
An HMB-45 stain for activated melanocytes may provide an additional clue, and in this instance, it indicates that the melanoma ends with the sudden decrease in the number of melanocytes. However, in a poorly circumscribed lesion such as this one, a histopathologic safety margin is warranted. 3 or 4 mm, as in this case, are enough.



They are not needed for many other melanomas that are more sharply confined, such as this melanoma in situ with solitary melanocytes and nests in all reaches of the epidermis.



In the periphery, there are only solitary melanocytes, but the borders are sharp



as if cut with a knife. No further surgery is necessary.

Human PATHOLOGY

VOLUME 14 September 1983 NUMBER 9

Current Topics

How Wide and Deep Is Wide and Deep Enough?

A Critique of Surgical Practice in Excisions of Primary Cutaneous Malignant Melanoma

A. BERNARD ACKERMAN, MD, AND AVERY M. SCHEINER, MD

For more than 75 years the standard surgical management of primary cutaneous malignant melanoma has been wide and deep excision, i.e., 5 cm of normal-appearing skin around the lesion and in depth to fascia. Most authors who have written about this matter refer to W. Sampson Handley's article of 1907 in *Lancet* entitled "The Pathology of Melanotic Growths in Relation to Their Operative Treatment"[1] as the authoritative source of this recommendation. Handley, Assistant Surgeon at Middlesex Hospital in England, had done a thorough study of the spread be "about an inch [2.5 cm] from the edge of the tumour." Nevertheless, as a consequence of Handley's publication, surgeons began to recommend 5-cm margins of excision around primary cutaneous malignant melanomas, and some continue to advocate this extent today[2].

In the past five years, modifications of this recommendation have been advocated. Among the most recent recommendations is that by Day et al.[3] of "no more than 1.5 cm of clinically normal skin bordering melanomas that rarely metastasize—namely, mela-

As early as 1983, Ackerman and Scheiner posed the question *"How deep and wide is deep and wide enough?"* and came to a very simple answer:

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The surgeon should excise what he or she judges clinically to be the entire neoplasm and only little more than that. The specimen should then be submitted for histologic assessment of all its margins; if no neoplastic melanocytes are found at the margins, no further surgery is warranted because there is nothing more of the primary neoplasm to excise.

England, had done a thorough study of the spread melanomas that rarely metastasize—namely, mela-

"The surgeon should excise what he or she judges clinically to be the entire neoplasm and only little more than that. The specimen should then be submitted for histologic assessment of all its margins; if no neoplastic melanocytes are found at the margins, no further surgery is warranted because there is nothing more of the primary neoplasm to excise."

This answer is simple enough, but it leads to three crucial questions:

Human PATHOLOGY

VOLUME 14 September 1983 NUMBER 9

Current Topics

How Wide and Deep Is Wide and Deep Enough?

A Critique of Surgical Practice in Excisions of Primary Cutaneous Malignant Melanoma

- How reliable is histopathologic assessment of margins of melanoma?
- Are there melanomas in which the reliability of histopathologic assessment of margins is reduced?
- What is the best method for histopathologic assessment of margins?

England, had done a thorough study of the spread of melanomas that rarely metastasize—namely, mela-

1.) How reliable is histopathologic assessment of margins of melanoma? 2.) Are there melanomas in which the reliability of histopathologic assessment of margins is reduced? 3.) What is the best method for histopathologic assessment of margins?

Research

JAMA Dermatology | Original Investigation

Outcomes of Melanoma In Situ Treated With Mohs Micrographic Surgery Compared With Wide Local Excision

Adi Nosrati, MD; Jacqueline G. Berliner, MD; Shilpa Goel, MD; Joseph McGuire, MD; Vera Morhenn, MD; Juliana R. de Souza, BSc; Yildiray Yenlay, MD; Rasnik Singh, BS; Kristina Lee, MS; Mio Nakamura, MD; Rachel R. Wu; Ann Griffin, PhD, CTR; Barbara Grimes, PhD; Eleni Linos, MD, DrPH; Mary Margaret Chren, MD; Roy Grekin, MD; Maria L. Wei, MD, PhD

Supplemental content

IMPORTANCE Melanoma in situ (MIS) is increasing in incidence, and expert consensus opinion recommends surgical excision for therapeutic management. Currently, wide local excision (WLE) is the standard of care. However, Mohs micrographic surgery (MMS) is now used to treat a growing subset of individuals with MIS. During MMS, unlike WLE, the entire cutaneous surgical margin is evaluated intraoperatively for tumor cells.

OBJECTIVE To assess the outcomes of patients with MIS treated with MMS compared with those treated with WLE.

DESIGN, SETTING, AND PARTICIPANTS Retrospective review of a prospective database. The study cohort consisted of 662 patients with MIS treated with MMS or WLE per standard of care in dermatology and surgery (general surgery, otolaryngology, plastics, oculoplastics, surgical oncology) at an academic tertiary care referral center from January 1, 1978, to December 31, 2013, with follow-up through 2015.

EXPOSURE Mohs micrographic surgery or WLE.

MAIN OUTCOMES AND MEASURES Recurrence, overall survival, and melanoma-specific survival.

RESULTS There were 277 patients treated with MMS (mean [SD] age, 64.0 [13.1] years; 62.1% male) and 385 treated with WLE (mean [SD] age, 58.5 [15.6] years; $P < .001$ for age; 54.8% male). Median follow-up was 8.6 (range, 0.2-37) years. Compared with WLE, MMS was used more frequently on the face (222 [80.2%] vs 141 [36.7%]) and scalp and neck (23 [8.3%] vs 26 [6.8%]; $P < .001$). The median (range) year of diagnosis was 2008 (1986-2013) for the MMS group vs 2003 (1978-2013) for the WLE group ($P < .001$). Overall recurrence rates were 5 (1.8%) in the MMS group and 22 (5.7%) in the WLE group ($P = .07$). Mean (SD) time to recurrence after MMS was 3.91 [illegible]
5-year recurrence rate was 1.1%
WLE-treated tumors, the surgi
compared with tumors that dic
92% and for WLE was 94% (P
vs 13 patients for the WLE grou
respectively ($P = .77$).

CONCLUSIONS AND RELEVANCE
overall survival, or melanoma-s
compared with WLE.

JAMA Dermatol. 2017;153(5):436-441
Published online February 22, 2017.

Mohs Micrographic Surgery Using MART-1 Immunostain in the Treatment of Invasive Melanoma and Melanoma In Situ

Sheila M. Valentín-Nogueras, MD, FAAD,* David G. Brodland, MD, FAAD, FACMS,†‡ John A. Zitelli, MD, FAAD, FACMS,†‡ Lorena González-Sepúlveda, MS,§ and Cruz M. Nazario, PhD‖

BACKGROUND Mohs micrographic surgery (MMS) with melanoma antigen recognized by T-cell (MART-1) immunostaining is an effective treatment of cutaneous melanoma.

OBJECTIVE To determine the efficacy of MMS with MART-1 immunostain in the management of invasive and in situ melanoma.

METHODS AND MATERIALS A retrospective cohort study evaluated 2,114 melanomas in 1,982 patients excised using MMS and MART-1 immunostain. The margins required for excision were calculated based on Breslow thickness, location, and size. Survival and local recurrence rates were calculated and compared with those of historical controls.

RESULTS The mean follow-up period was 3.73 years. Local recurrence was identified in 0.49% (7/1,419) of primary melanomas. Approximately 82% of melanomas were excised with ≤6-mm margins. The surgical margin was significantly related to tumor location and size but not to Breslow thickness. The five-year Kaplan–Meier local recurrence and disease-specific survival rates were 0.59 ± 0.30 and 98.53 ± 0.42, respectively. Mohs micrographic surgery with MART-1 immunostain achieved lower local recurrence rates and equivalent or higher Kaplan–Meier survival rates than conventional wide local excision.

CONCLUSION Mohs micrographic surgery with MART-1 immunostain is an effective treatment of melanoma as evidenced by low local recurrence rates. It offers the advantage of more tissue-conserving margins than those recommended for conventional excision.

SURGICAL DERMATOLOGY

BJD
British Journal of Dermatology

Recurrence rate of lentigo maligna after micrographically controlled staged surgical excision*

K. de Vries,[1,2] K. Greveling,[2] L.M. Prens,[2] K. Munte,[3] S. Koljenović,[4] M.B.A. van Doorn[2] and E.P. Prens[2]

[1]Department of Dermatology, University Medical Center Groningen, Groningen, the Netherlands
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Accepted for publication
18 November 2015

Funding sources
None.

Conflicts of interest
None declared.

*Plain language summary available online

DOI 10.1111/bjd.14325

Summary

Background Lentigo maligna is a slowly growing melanoma in situ. Current guidelines advise wide local excision with a margin of 5 mm as the treatment of first choice, which has recurrence rates ranging from 6% to 20%.
Objectives To determine retrospectively the recurrence rate of lentigo maligna after staged surgical excision.
Methods Records of all patients with lentigo maligna treated with our method of staged surgical excision between 2002 and 2011 were retrieved. To identify recurrences we used the computer program Sympathy, which is linked to PALGA, a nationwide network and registry of histo- and cytopathology in the Netherlands.
Results We identified 100 patients, who were treated with staged surgical excision with 100% immunohistopathological control of lateral margins. Digital pictures were used to facilitate orientation during the several stages of surgery. After a mean follow-up of 60 months, four patients had a recurrence, after 37, 58, 74 and 77 months of follow-up.
Conclusions Staged surgical excision is superior in clearance and recurrence rates to wide local excision for lentigo maligna and should be considered as the treatment of first choice in national and international guidelines.

The use of Mohs micrographic surgery (MMS) for melanoma in situ (MIS) of the trunk and proximal extremities

Landon E. Stigall, MD, David G. Brodland, MD, and John A. Zitelli, MD
Pittsburgh, Pennsylvania

Background: Evaluation of the entire surgical margin results in high rates of complete excision, low local recurrence rates, and maximal tissue conservation. Although well recognized for melanoma of the head and neck, few studies have focused exclusively on the trunk and proximal extremities.

Objective: We sought to evaluate the efficacy of Mohs micrographic surgery for melanoma in situ (MIS) of the trunk and proximal extremities, and determine adequate excision margins for MIS when total margin evaluation is not used.

Methods: Long-term outcomes in 882 cases of MIS treated with Mohs micrographic surgery were analyzed and compared with historical controls. Rates of complete excision were determined for increasing surgical margin intervals.

Results: One local recurrence occurred in our cohort (0.1%). Only 83% of MIS were excised with a 6-mm margin. Margins of 9 mm were needed to excise 97% of MIS, statistically equivalent to thin melanomas.

Limitations: We used a nonrandomized, single-institution, retrospective design.

Conclusion: Mohs micrographic surgery may cure the 17% of MIS that exceed traditional excision margins of 5 mm and is a valuable option for these patients. Surgical margins of at least 0.9 cm should be considered for MIS of the trunk and extremities when total margin evaluation is not used. (J Am Acad Dermatol 2016;75:1015-21.)

The first question has been addressed in numerous studies performed chiefly by Mohs surgeons. The recurrence rate was usually around 1% and better than the one achieved with the standard strategy of “wide local extension.” Of course, the low rate of recurrence rate may be caused, in part, by spontaneous regression of small remnants of melanoma, just as in basal-cell and squamous cell carcinoma, but all evidence suggest that, if done thoroughly, histopathologic assessment of margins works.

Research

JAMA Dermatology | Original Investigation

Outcomes of Melanoma In Situ Treated With Mohs Micrographic Surgery Compared With Wide Local Excision

Adi Nosrati, MD; Jacqueline G. Berliner, MD; Shilpa Goel, MD; Joseph McGuire, MD; Vera Morhenn, MD; Juliana R. de Souza, BSc; Yildiray Yenlay, MD; Rasnik Singh, BS; Kristina Lee, MS; Mio Nakamura, MD; Rachel R. Wu; Ann Griffin, PhD, CTR; Barbara Grimes, PhD; Eleni Linos, MD, DrPH; Mary Margaret Chren, MD; Roy Grekin, MD; Maria L. Wei, MD, PhD

Supplemental content

IMPORTANCE Melanoma in situ (MIS) is increasing in incidence, and expert consensus opinion recommends surgical excision for therapeutic management. Currently, wide local excision (WLE) is the standard of care. However, Mohs micrographic surgery (MMS) is now used to treat a growing subset of individuals with MIS. During MMS, unlike WLE, the entire cutaneous surgical margin is evaluated intraoperatively for tumor cells.

Research

JAMA Dermatology | Original Investigation

Efficacy of Staged Excision With Permanent Section Margin Control for Cutaneous Head and Neck Melanoma

Jeffrey S. Moyer, MD; Shannon Rudy, MD; Philip S. Boonstra, PhD; Casey Kraft, MD; Steven B. Chinn, MD; Shan R. Baker, MD; Jennifer L. Schwartz, MD; Christopher K. Bichakjian, MD; Douglas Fullen, MD; Alison B. Durham, MD; Lori Lowe, MD; Timothy M. Johnson, MD

RESULTS There were 277 patients treated with MMS (mean [SD] age, 64.0 [13.1] years; 62.1% male) and 385 treated with WLE (mean [SD] age, 58.5 [15.6] years; $P < .001$ for age; 54.8% male). Median follow-up was 8.6 (range, 0.2-37) years. Compared with WLE, MMS was used more frequently on the face (222 [80.2%] vs 141 [36.7%]) and scalp and neck (23 [8.3%] vs 26 [6.8%]; $P < .001$). The median (range) year of diagnosis was 2008 (1986-2013) for the MMS group vs 2003 (1978-2013) for the WLE group ($P < .001$). Overall recurrence rates were 5 (1.8%) in the MMS group and 22 (5.7%) in the WLE group ($P = .07$). Mean (SD) time to recurrence after MMS was 3.91 [illegible]
5-year recurrence rate was 1.1%
WLE-treated tumors, the surgi
compared with tumors that dic
92% and for WLE was 94% (P
vs 13 patients for the WLE grou
respectively ($P = .77$).

CONCLUSIONS AND RELEVANCE
overall survival, or melanoma-s
compared with WLE.

JAMA Dermatol. 2017;153(5):436-441
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Mohs Micrographic Surgery Using MART-1 Immunostain in the Treatment of Invasive Melanoma and Melanoma In Situ

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BACKGROUND Mohs micrographic surgery (MMS) with melanoma antigen recognized by T-cell (MART-1) immunostaining is an effective treatment of cutaneous melanoma.

OBJECTIVE To determine the efficacy of MMS with MART-1 immunostain in the management of invasive and in situ melanoma.

METHODS AND MATERIALS A retrospective cohort study evaluated 2,114 melanomas in 1,982 patients excised using MMS and MART-1 immunostain. The margins required for excision were calculated based on Breslow thickness, location, and size. Survival and local recurrence rates were calculated and compared with those of historical controls.

RESULTS The mean follow-up period was 3.73 years. Local recurrence was identified in 0.49% (7/1,419) of primary melanomas. Approximately 82% of melanomas were excised with ≤6-mm margins. The surgical margin was significantly related to tumor location and size but not to Breslow thickness. The five-year Kaplan–Meier local recurrence and disease-specific survival rates were 0.59 ± 0.30 and 98.53 ± 0.42, respectively. Mohs micrographic surgery with MART-1 immunostain achieved lower local recurrence rates and equivalent or higher Kaplan–Meier survival rates than conventional wide local excision.

CONCLUSION Mohs micrographic surgery with MART-1 immunostain is an effective treatment of melanoma as evidenced by low local recurrence rates. It offers the advantage of more tissue-conserving margins than those recommended for conventional excision.

Recurrence rate of lentigo maligna after micrographically controlled staged surgical excision*

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Conflicts of interest
None declared.

*Plain language summary available online

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Summary

Background Lentigo maligna is a slowly growing melanoma in situ. Current guidelines advise wide local excision with a margin of 5 mm as the treatment of first choice, which has recurrence rates ranging from 6% to 20%.
Objectives To determine retrospectively the recurrence rate of lentigo maligna after staged surgical excision.
Methods Records of all patients with lentigo maligna treated with our method of staged surgical excision between 2002 and 2011 were retrieved. To identify recurrences we used the computer program Sympathy, which is linked to PALGA, a nationwide network and registry of histo- and cytopathology in the Netherlands.
Results We identified 100 patients, who were treated with staged surgical excision with 100% immunohistopathological control of lateral margins. Digital pictures were used to facilitate orientation during the several stages of surgery. After a mean follow-up of 60 months, four patients had a recurrence, after 37, 58, 74 and 77 months of follow-up.
Conclusions Staged surgical excision is superior in clearance and recurrence rates to wide local excision for lentigo maligna and should be considered as the treatment of first choice in national and international guidelines.

The use of Mohs micrographic surgery (MMS) for melanoma in situ (MIS) of the trunk and proximal extremities

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Pittsburgh, Pennsylvania

Background: Evaluation of the entire surgical margin results in high rates of complete excision, low local recurrence rates, and maximal tissue conservation. Although well recognized for melanoma of the head and neck, few studies have focused exclusively on the trunk and proximal extremities.

Objective: We sought to evaluate the efficacy of Mohs micrographic surgery for melanoma in situ (MIS) of the trunk and proximal extremities, and determine adequate excision margins for MIS when total margin evaluation is not used.

Methods: Long-term outcomes in 882 cases of MIS treated with Mohs micrographic surgery were analyzed and compared with historical controls. Rates of complete excision were determined for increasing surgical margin intervals.

Results: One local recurrence occurred in our cohort (0.1%). Only 83% of MIS were excised with a 6-mm margin. Margins of 9 mm were needed to excise 97% of MIS, statistically equivalent to thin melanomas.

Limitations: We used a nonrandomized, single-institution, retrospective design.

Conclusion: Mohs micrographic surgery may cure the 17% of MIS that exceed traditional excision margins of 5 mm and is a valuable option for these patients. Surgical margins of at least 0.9 cm should be considered for MIS of the trunk and extremities when total margin evaluation is not used. (J Am Acad Dermatol 2016;75:1015-21.)

Recurrence rates in those studies were higher with melanomas on the head and neck. This corresponds to findings by conventional surgery.

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DOI 10.1245/s10434-015-4942-0

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ORIGINAL ARTICLE – MELANOMAS

The Association Between Excision Margins and Local Recurrence in 11,290 Thin (T1) Primary Cutaneous Melanomas: A Case–Control Study

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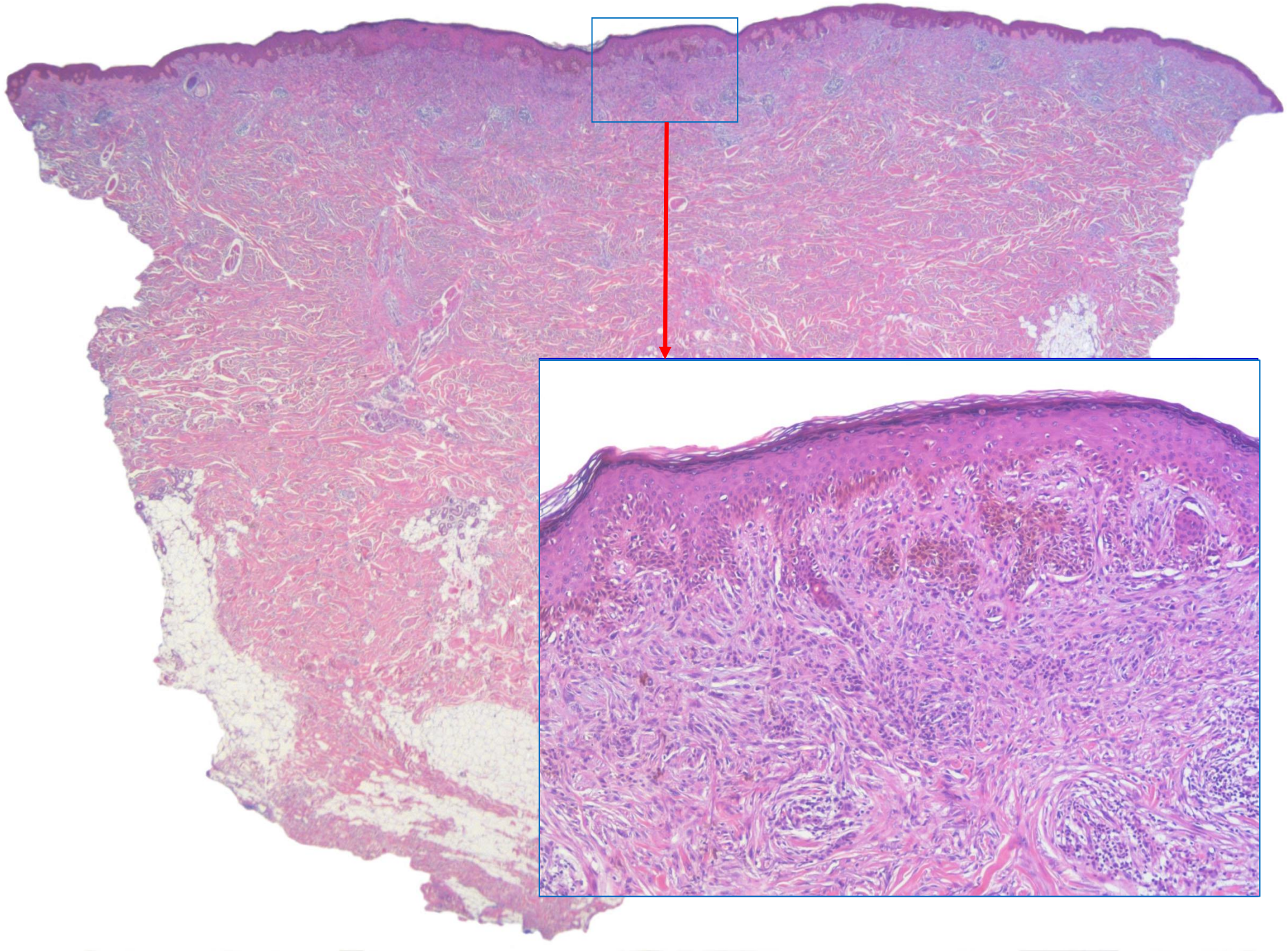
ABSTRACT

Background. At presentation, most primary cutaneous melanomas are "thin" (Breslow thickness ≤1 mm, designated T1 in the American Joint Committee on Cancer staging system) and local recurrence (LR) is rare. Most current management guidelines recommend 1 cm surgical excision margins for T1 melanomas, but evidence to support this recommendation is sparse. We sought to identify clinical and pathologic factors associated with LR in patients with T1 melanomas that might guide primary tumor management.

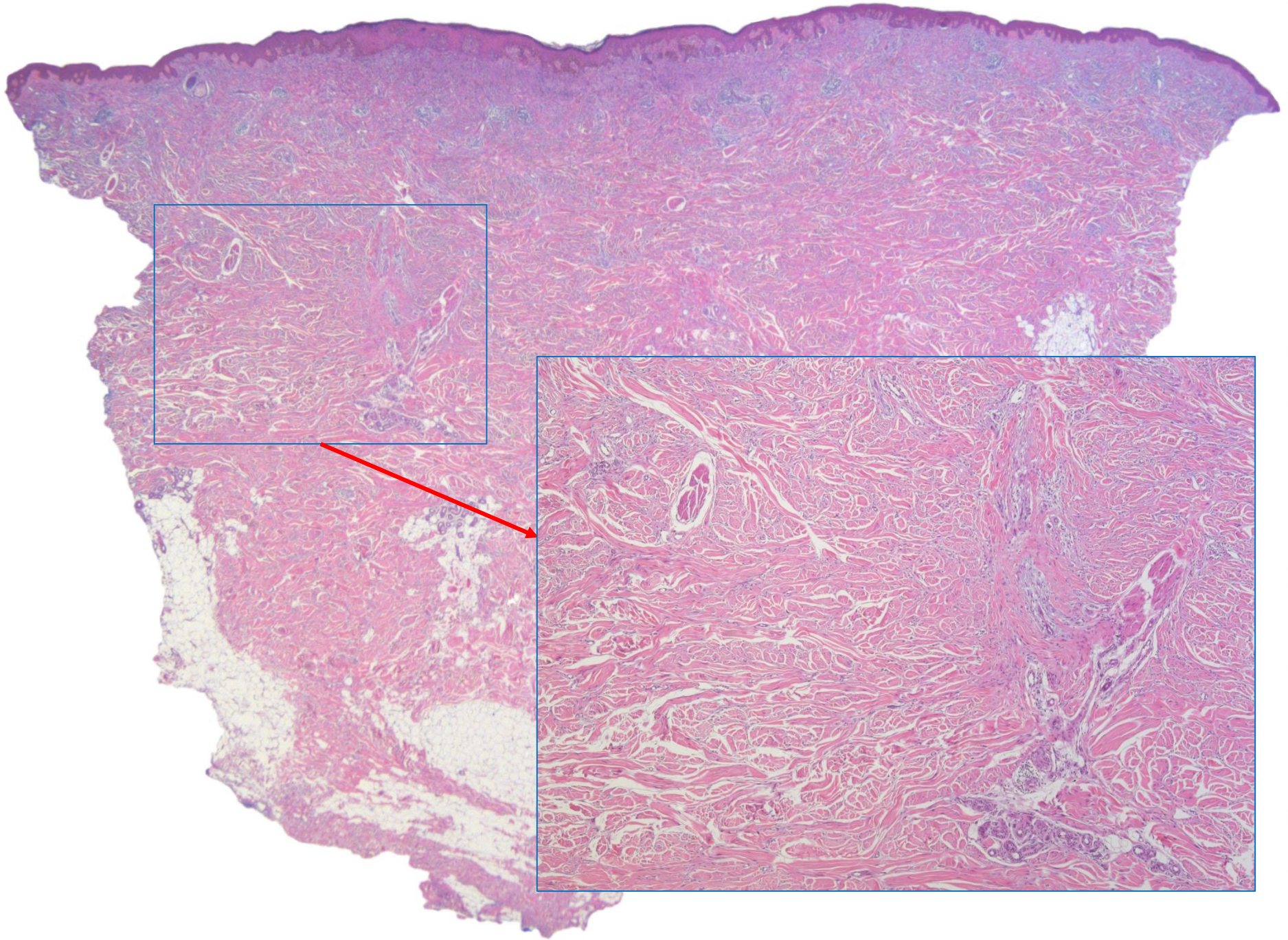
melanoma subtypes ($p = 0.008$), and melanomas composed predominantly of spindle cells ($p = 0.005$). However, Breslow thickness, Clark level, ulceration, mitotic rate, regression, and lymphovascular invasion were not.

Conclusions. LR was associated with <8 mm histologic excision margins (corresponding to <1 cm margins in vivo) and desmoplastic, acral, and lentigo maligna melanoma subtypes. This study provides evidence that a ≥1 cm clinical excision margin for thin (T1) primary melanomas reduces the risk of LR.

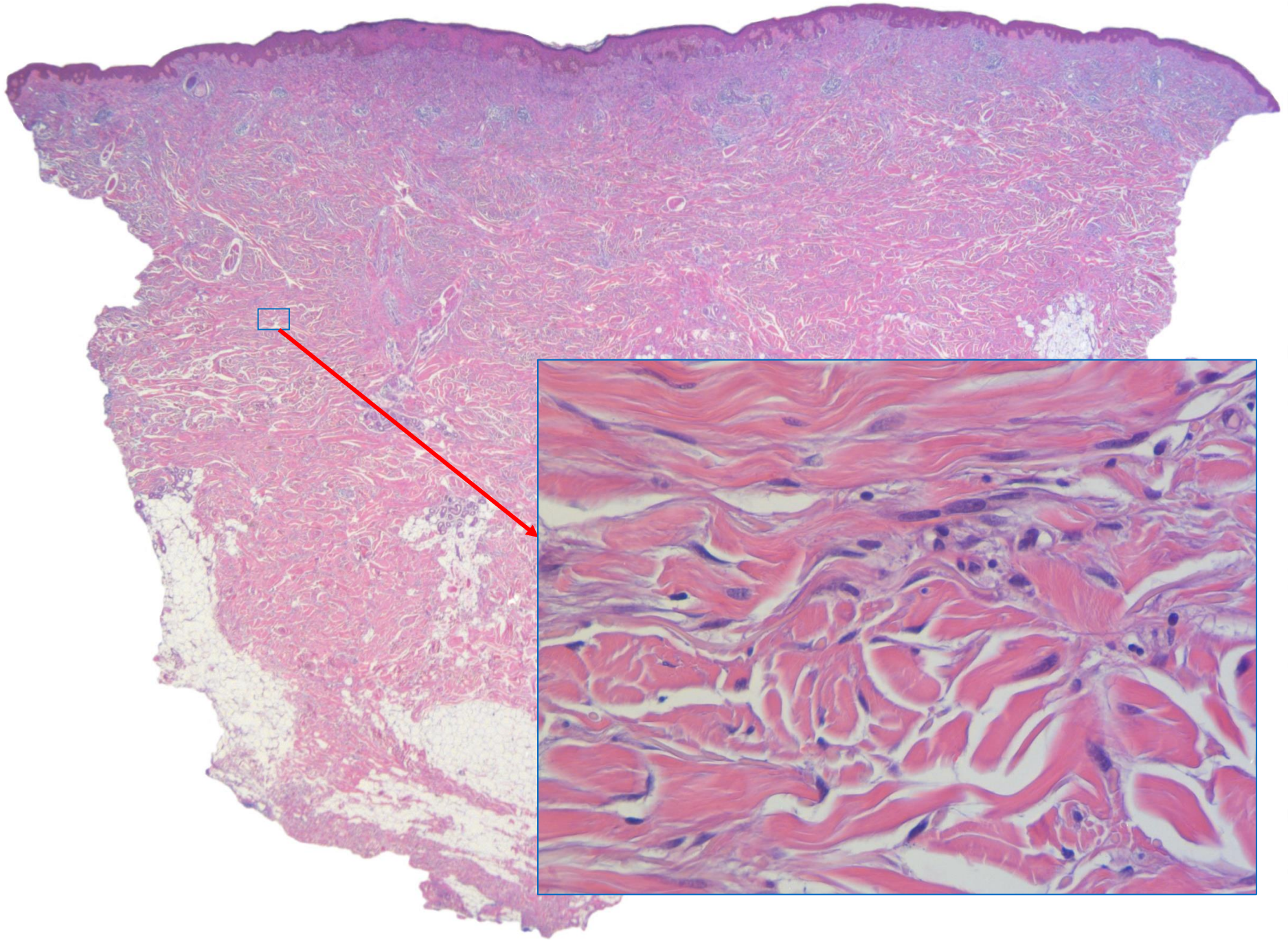
For example, MacKenzie-Ross and co-workers found higher rates of local recurrence in *"desmoplastic, acral and lentigo maligna melanoma subtypes."* The reason is that those melanomas tend to be poorly confined and that their margins are difficult to recognize.



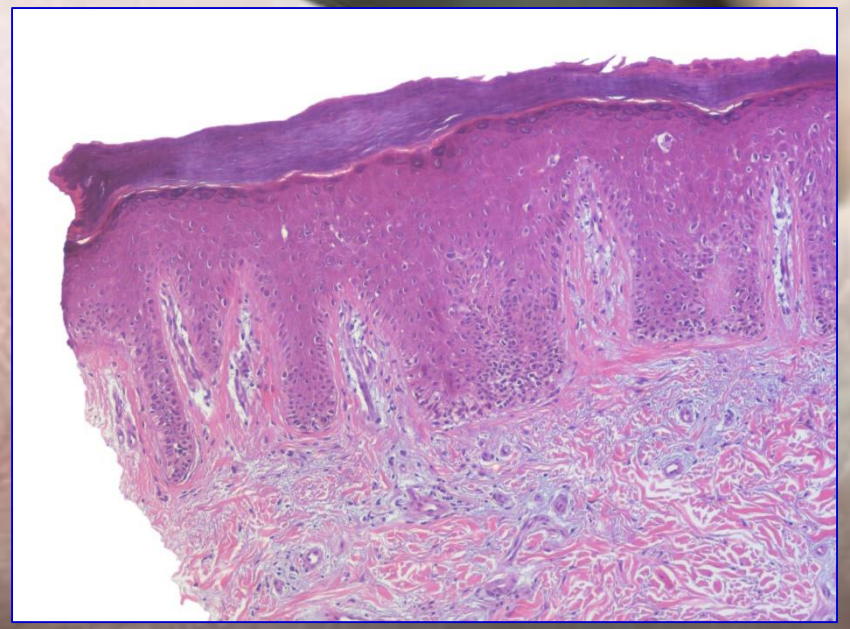
In desmoplastic melanoma, difficulties are caused by cytological features: neoplastic melanocytes in the dermis are spindled and can be confused easily with fibrocytes.



Moreover, desmoplastic melanomas often have narrow, pauci-cellular extensions that are difficult to distinguish from the surrounding connective tissue.



The cells in those extension have largish nuclei but are not markedly atypical. Moreover, they often have lost antigens of melanocytes, such as the one recognized by Melan-A. If tiny extensions of desmoplastic melanoma are overlooked and left in place, recurrences are inevitable.



On palms and soles, poor circumscription is caused chiefly by spread of neoplastic cells as solitary units along skin ridges.

ORIGINAL ARTICLE

Distribution and Significance of Occult Intraepidermal Tumor Cells Surrounding Primary Melanoma

Jeffrey P. North[1,2], Toshiro Kageshita[3], Daniel Pinkel[4,5], Philip E. LeBoit[4,6] and Boris C. Bastian[4,6]

Primary melanoma can recur at the excision site if not excised with a safety margin of surrounding uninvolved skin. To characterize the nature of residual melanoma in the skin surrounding primary tumors targeted by safety margins, we used array comparative genomic hybridization and fluorescent *in situ* hybridization to detect and spatially map aberrations in the skin adjacent to acral melanomas. Melanocytic cells with genetic amplifications in histopathologically normal skin (field cells) were detected exclusively in the epidermis in 84% of 19 cases, with a mean extension of 6.1 mm (*in situ* melanomas) and 4.5 mm (invasive melanomas) beyond the histopathological margin. Genetic profiling of these field cells indicated that they represent an early phase of disease preceding melanoma *in situ*. The extent of field cells did not correlate with tumor depth or diameter, indicating that tumor depth is not suited to predict the extent of field cells. These results demonstrate that, on acral sites, melanoma field cells extend significantly into seemingly normal skin. These field cells provide a plausible explanation for the tendency of certain melanoma types to recur locally despite apparently having undergone complete excision.

Journal of Investigative Dermatology (2008) **128,** 2024–2030; doi:10.1038/jid.2008.41; published online 6 March 2008

Molecular studies have shown that *" occult intraepidermal tumor cells surrounding primary melanoma"* in acral skin *"provide a plausible explanation for the tendency of certain melanoma types to recur locally despite apparently having undergone complete excision."*

ORIGINAL ARTICLE

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Journal of Investigative Dermatology (2008) **128,** 2024–2030; doi:10.1038/jid.2008.41; published online 6 March 2008

The mean extension of those cells beyond the histopathological margin was 6.1 mm for in-situ melanomas and 4.5 mm for invasive melanomas. The wider spread of in-situ melanomas may have been by chance but it is clear, from this and other studies, that *"tumor depth is not suited to predict the extent of field cells."*

Guidelines of the Brazilian Dermatology Society for diagnosis, treatment and follow up of primary cutaneous melanoma - Part I*

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Walter Loureiro[5]
João Pedreira Duprat Neto[7]
Flávia Vasques Bittencourt[8]
Sérgio Schrader Serpa[10]
Gabriel Gontijo[8]
Maria Cristina Messina[1,2,3,4]
Ricardo Silvestre Macarenco[1,6]
Thais Helena Bello Di Giacomo[1,2,3]
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Hamilton Ometto Stolf[11]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20154707

Abstract: The last Brazilian guidelines on melanoma were published in 2002. Development in diagnosis and treatment made updating necessary. The coordinators elaborated ten clinical questions, based on PICO system. A Medline search, according to specific MeSH terms for each of the 10 questions was performed and articles selected were classified from A to D according to level of scientific evidence. Based on the results, recommendations were defined and classified according to scientific strength. The present Guidelines were divided in two parts for editorial and publication reasons. In the first part, the following clinical questions were answered: 1) The use of dermoscopy for diagnosis of primary cutaneous melanoma brings benefits for patients when compared with clinical examination? 2) Does dermoscopy favor diagnosis of nail apparatus melanoma? 3) Is there a prognostic difference when incisional or excisional biopsies are used? 4) Does revision by a pathologist trained in melanoma contribute to diagnosis and treatment of primary cutaneous melanoma? What margins should be used to treat lentigo maligna melanoma and melanoma in situ?

Keywords: Dermoscopy; Diagnostic imaging; Diagnostic techniques and procedures; Guideline; Histology; Melanoma; Practice guideline; Sentinel lymph node biopsy; Therapeutics

TABLE 1: Surgical Margins for the treatment of primary cutaneous melanoma

Breslow thickness (mm)	Surgical margin (cm)	Level of evidence
In situ	0.5 #	A
Up to 1.00	1.0	A
From 1.01 to 2. 00	1.0 to 2.0 *	B
More than 2.00	2.0	A

t-test

* The surgical margins can be modified to contemplate anatomical, functional or aesthetic needs. Experts agree that margins between 1cm and 2 cm are acceptable in areas where margins of 2 cm would cause significant aesthetic, functional or anatomical losses. The patient should be informed and agree with the doctor about the best option.

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[11] Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP) – Botucatu (SP), Brazil.

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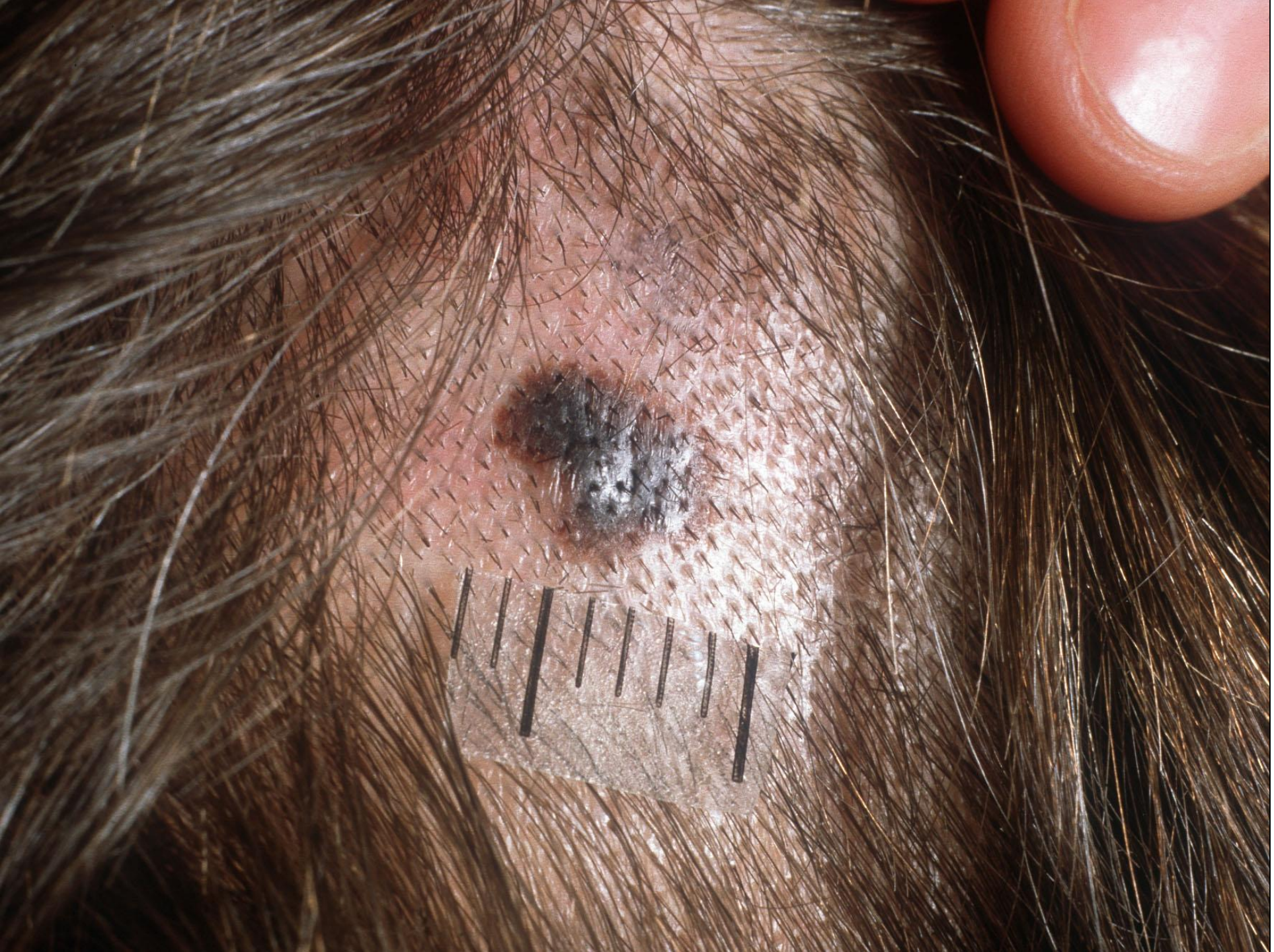
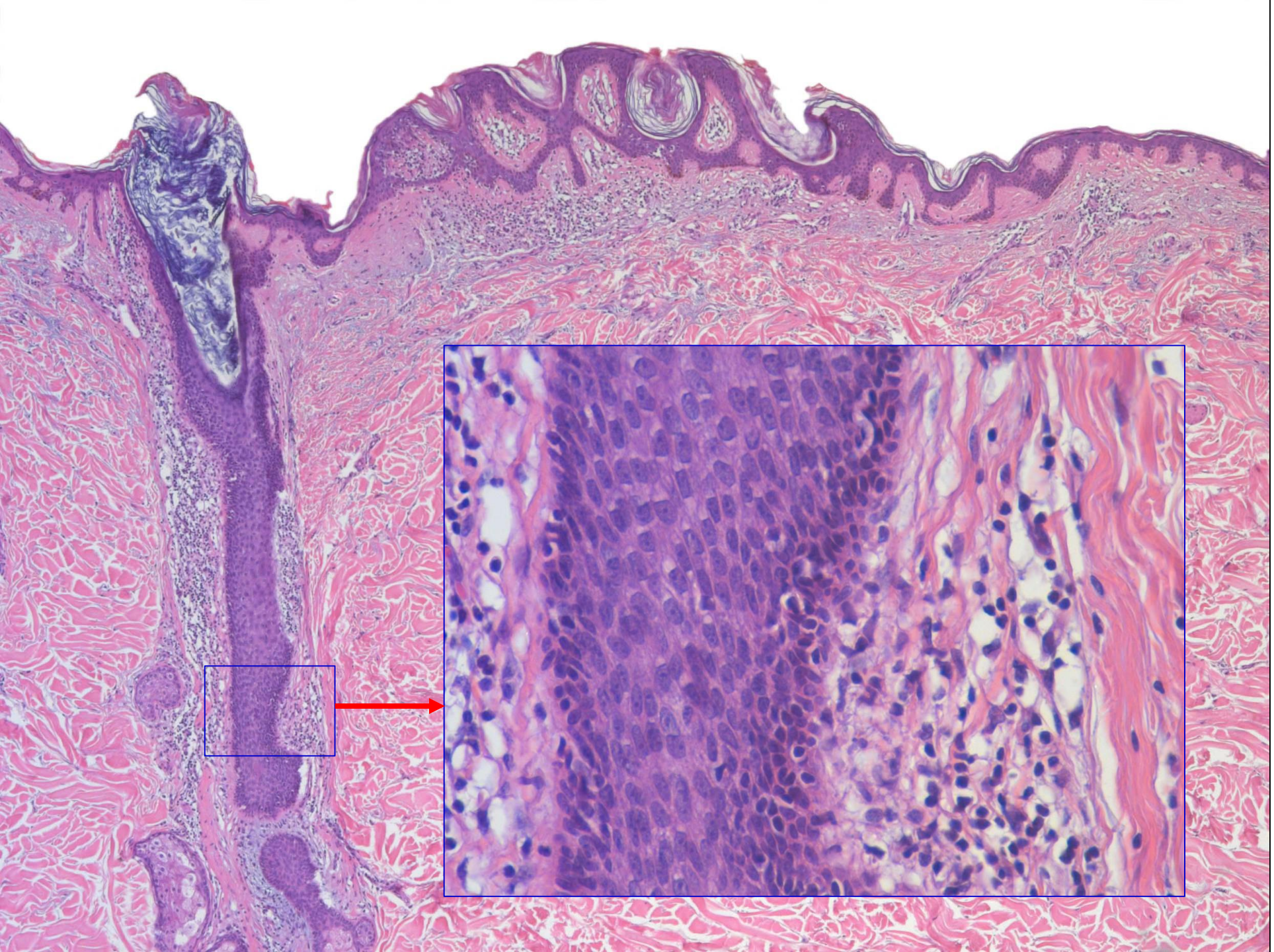
An Bras Dermatol. 2015;90(6):851-61.

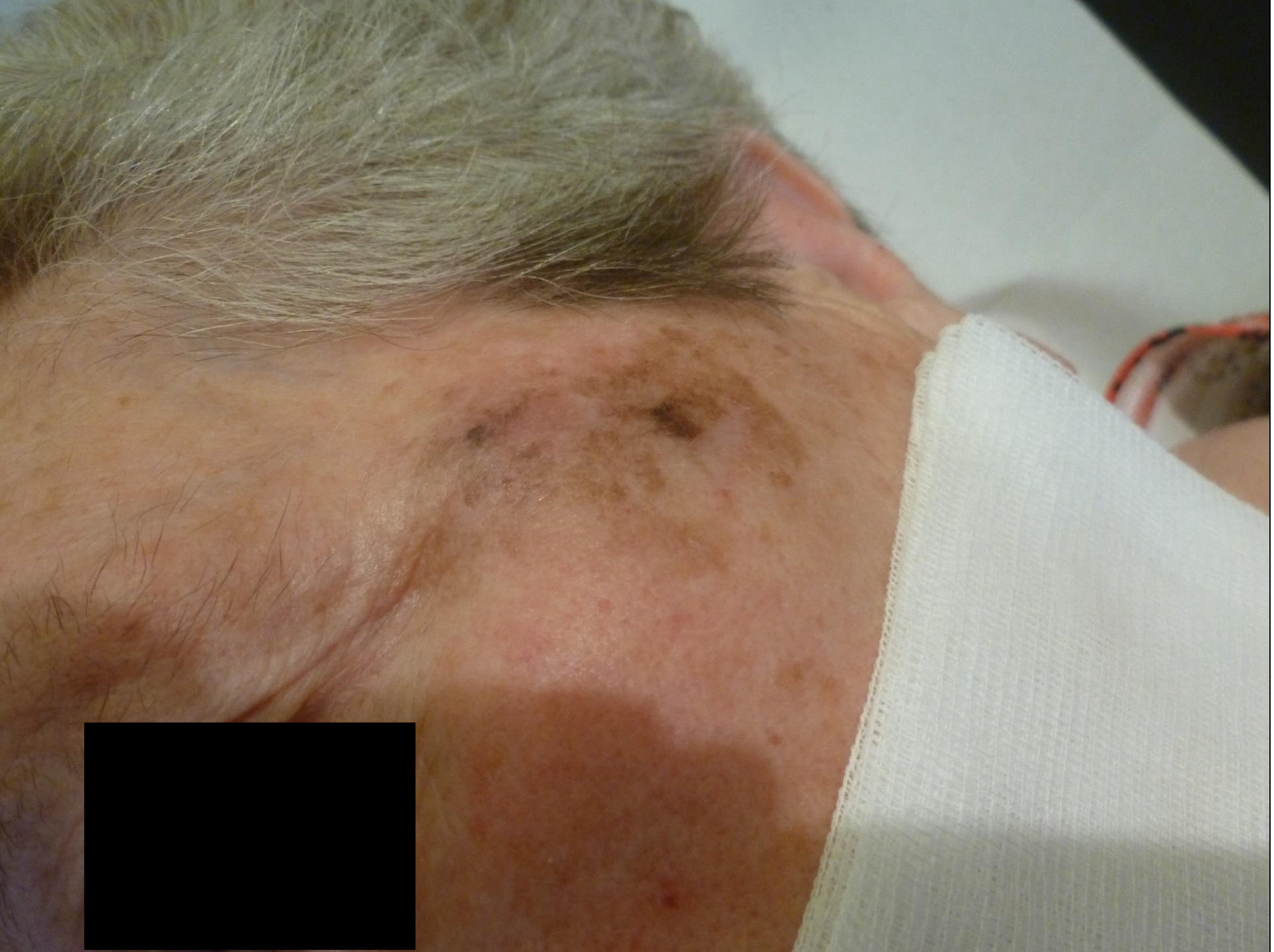
Nevertheless, most guidelines for treatment of melanoma, including those of Brazil, still maintain that melanoma in situ be excised with a narrower margin than invasive melanoma.



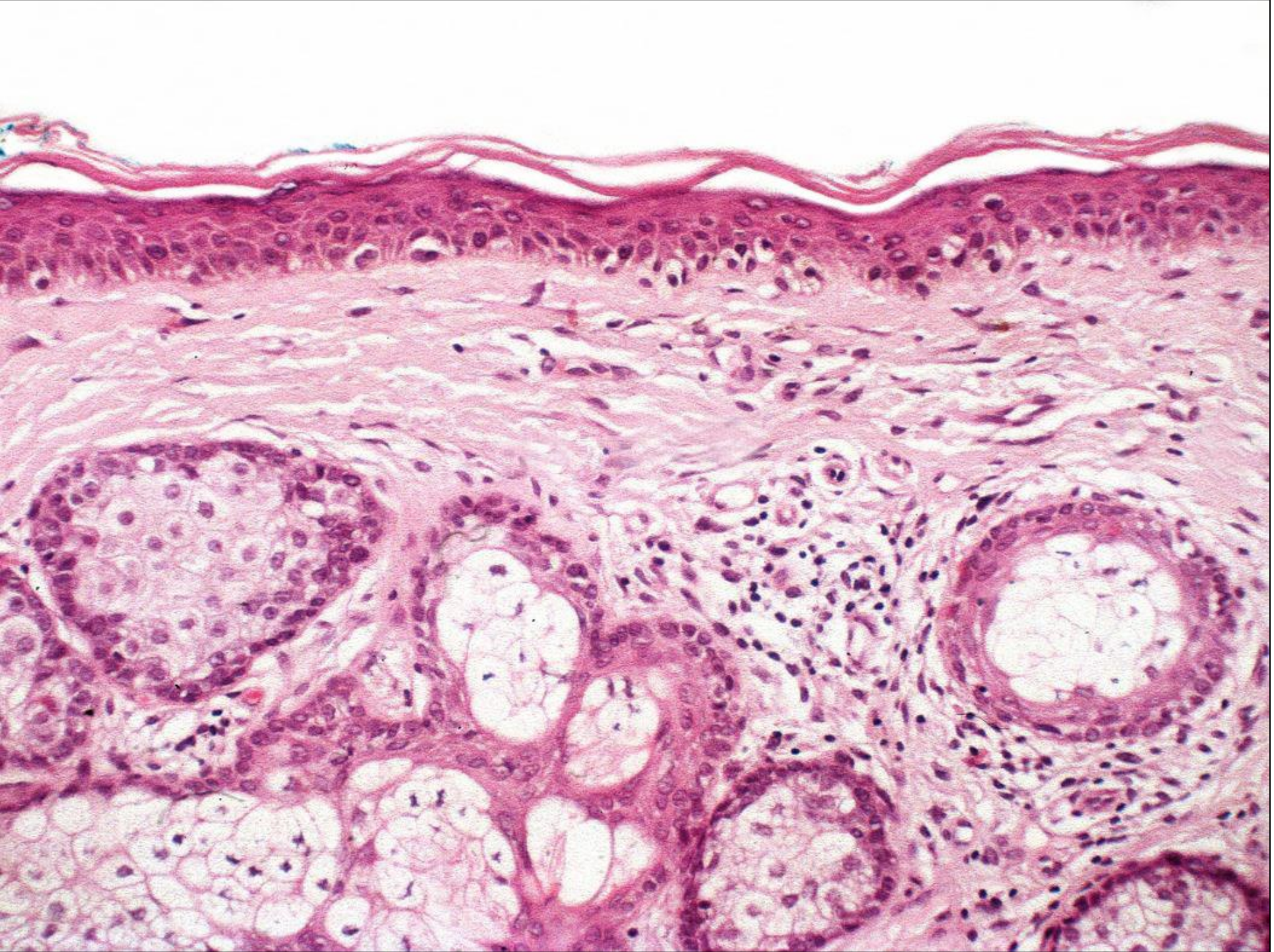
In melanomas from the head and neck, determination of borders is impeded by the fact that neoplastic cells may reside in hair follicles where they are difficult to recognize. This melanoma, for example, consists not only of the nodule but also of an irregularly shaped macular component, and nothing seems to be present in-between,



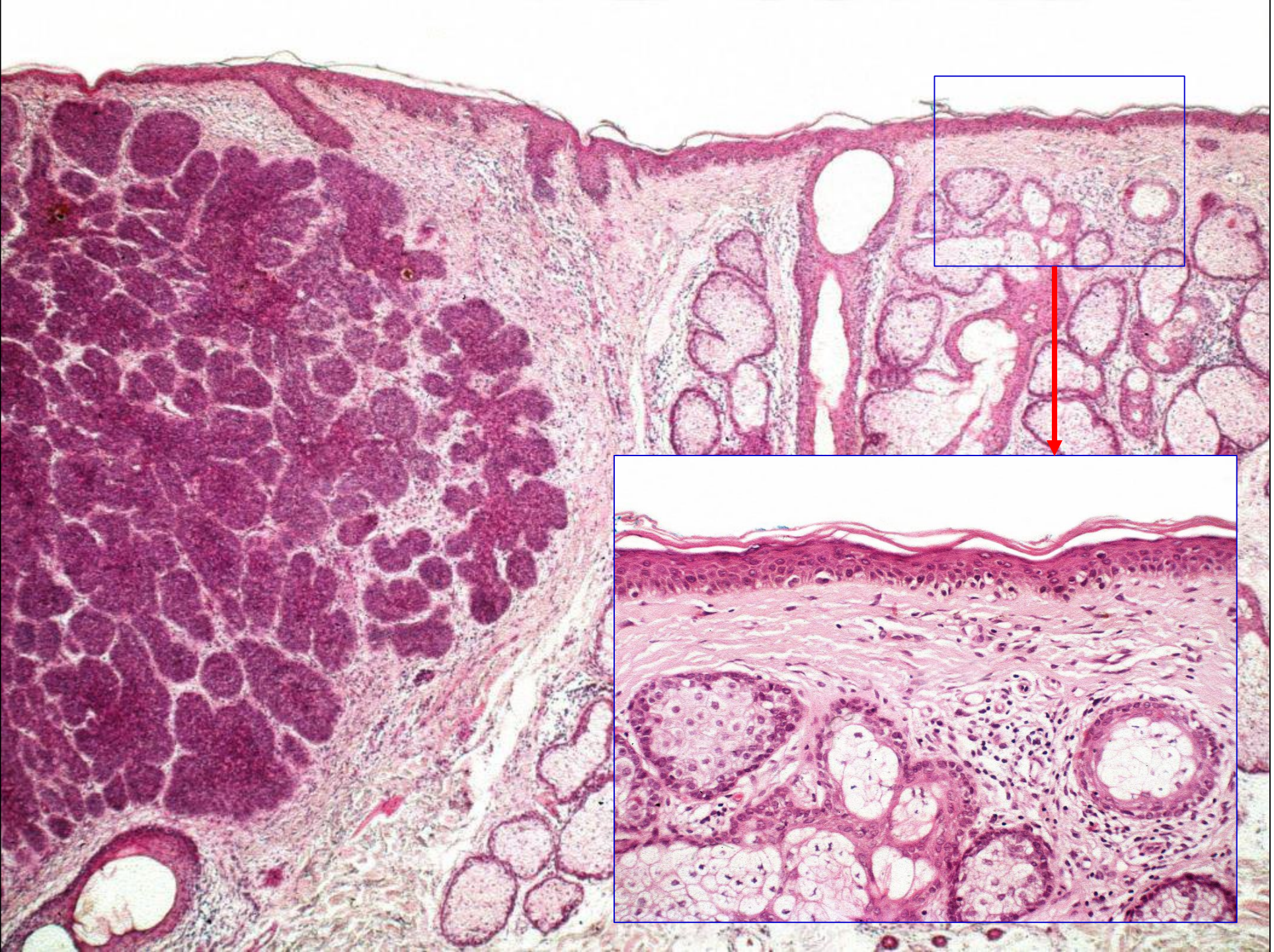
the reason being a pauci-cellular component with neoplastic melanocytes as solitary units chiefly in hair follicles where they may also be overlooked histopathologically.



Another problem in sun-damaged skin of the face and neck is distinction of extensions of melanoma from melanocytic hyperplasia.



In skin damaged severely by sunlight, melanocytes may be increased number and size and may be arranged slightly irregularly. This is not an example of melanoma in situ



but melanocytic hyperplasia adjacent to a basal-cell carcinoma. Those factors combined

DERMATOLOGIC SURGERY

Clinical factors associated with subclinical spread of in situ melanoma

Thuzar M. Shin, MD, PhD, Jeremy R. Etzkorn, MD, Joseph F. Sobanko, MD, David J. Margolis, MD, PhD, Joel M. Gelfand, MD, MSCE, Emily Y. Chu, MD, PhD, Rosalie Elenitsas, MD, Waqas R. Shaikh, MD, MPH, and Christopher J. Miller, MD
Philadelphia, Pennsylvania

Background: Subclinical spread of in situ melanoma occurs at a wide frequency, ranging from 12% to 71%.

Objective: To identify clinical factors associated with subclinical spread of in situ melanoma.

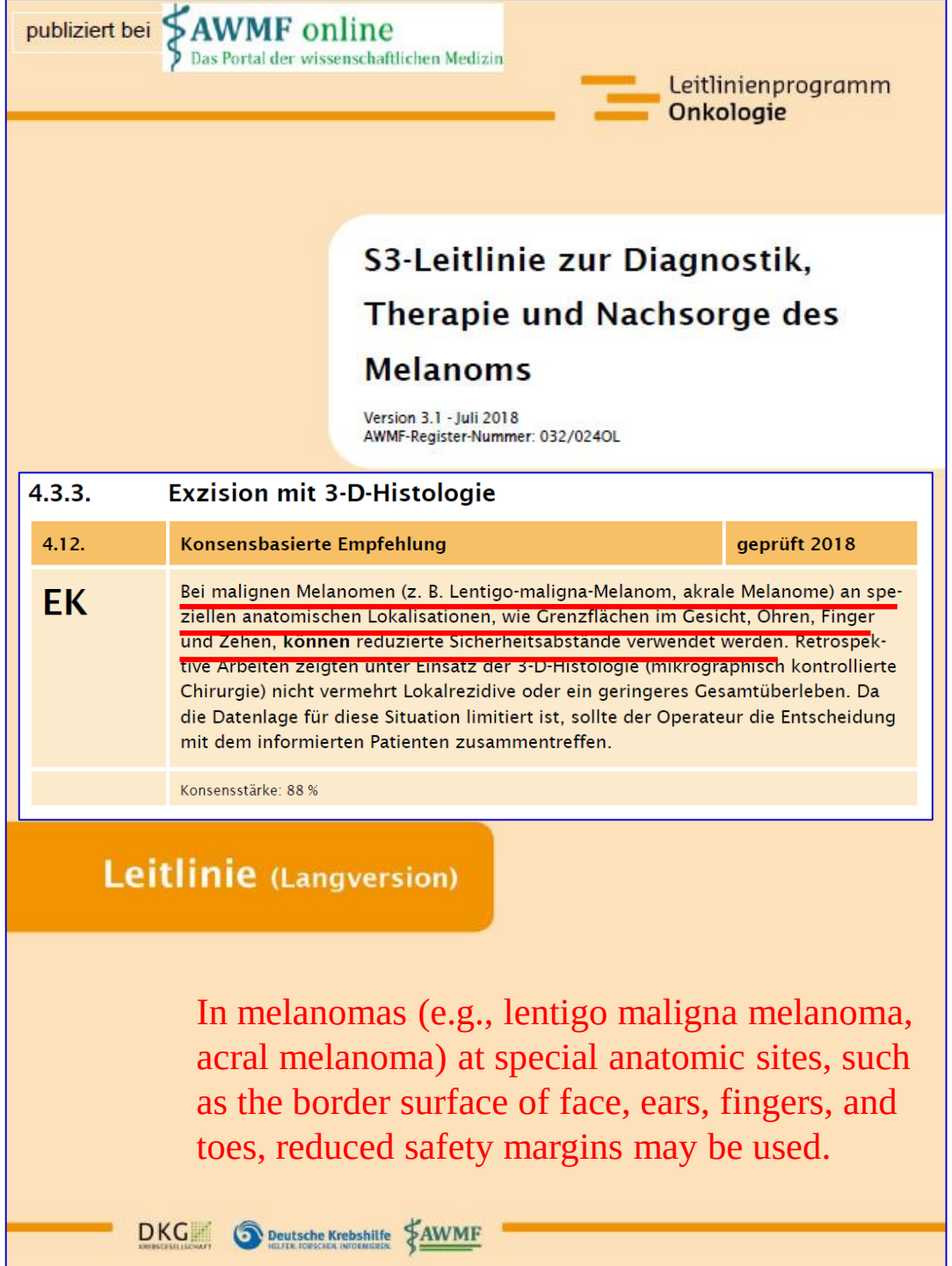
Methods: We used a retrospective, cross-sectional study of 674 consecutive in situ melanomas to examine 627 patients treated with Mohs surgery and melanoma antigen recognized by T cells 1 immunostaining. The presence of subclinical spread was correlated with clinical characteristics. Univariate and multivariate logistic regression analyses were performed to generate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Both univariate and multivariate analyses demonstrated significantly increased odds for subclinical spread of in situ melanomas when they were located on the head or neck, at acral sites, or on the pretibial leg (OR 1.97, 95% CI 1.41-3.40); in persons with a history of prior treatment (OR 2.77, 95% CI 1.74-4.420); melanomas of preoperative size >1 cm (OR 1.74, 95% CI 1.23-2.46, P = .002); or in persons ≥60 years old (OR 1.47, 95% CI 1.01-2.13, P = .042). A count prediction model demonstrated that the risk for subclinical spread increased with the number of clinical risk factors.

Limitation: We used a single-site, retrospective study design.

Conclusion: Clarifying the risk factors for subclinical spread might help to refine triage of in situ melanomas to the appropriate surgical techniques for margin assessment prior to reconstruction. (J Am Acad Dermatol 2017;76:707-13.)

are responsible for *"increased odds for subclinical spread of in situ melanomas when they are located on the head and neck or acral sites."*



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Leitlinienprogramm Onkologie

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms

Version 3.1 - Juli 2018
AWMF-Register-Nummer: 032/024OL

4.3.3. Exzision mit 3-D-Histologie

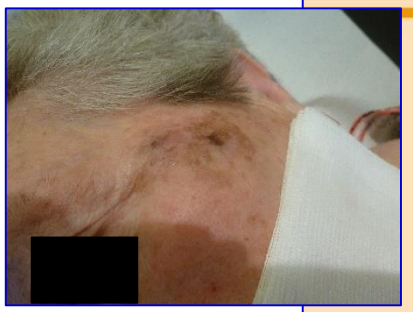
4.12.	Konsensbasierte Empfehlung	geprüft 2018
EK	Bei malignen Melanomen (z. B. Lentigo-maligna-Melanom, akrale Melanome) an speziellen anatomischen Lokalisationen, wie Grenzflächen im Gesicht, Ohren, Finger und Zehen, **können** reduzierte Sicherheitsabstände verwendet werden. Retrospektive Arbeiten zeigten unter Einsatz der 3-D-Histologie (mikrographisch kontrollierte Chirurgie) nicht vermehrt Lokalrezidive oder ein geringeres Gesamtüberleben. Da die Datenlage für diese Situation limitiert ist, sollte der Operateur die Entscheidung mit dem informierten Patienten zusammentreffen.	
	Konsensstärke: 88 %	

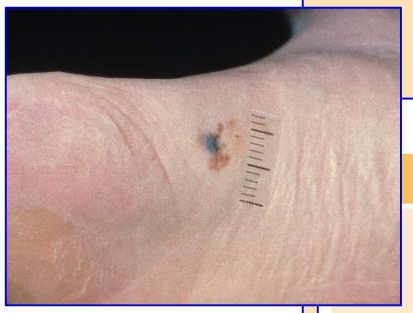
Leitlinie (Langversion)

In melanomas (e.g., lentigo maligna melanoma, acral melanoma) at special anatomic sites, such as the border surface of face, ears, fingers, and toes, reduced safety margins may be used.

DKG Deutsche Krebshilfe AWMF

Given those circumstances, it is curious that some guidelines for melanoma management, including the German one of July 2018, give the following advise: *"In melanomas (e.g., lentigo maligna melanoma, acral melanoma) at special anatomic sites, such as the border surface of face, ears, fingers, and toes, reduced safety margins may be used."* In other words, reduced safety margins are accepted exclusively for those melanomas that are most poorly confined. Logic is turned upside down.





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Leitlinienprogramm Onkologie

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms

Version 3.1 - Juli 2018
AWMF-Register-Nummer: 032/024OL

Exzision mit 3-D-Histologie

	Konsensbasierte Empfehlung	geprüft 2018
	Bei malignen Melanomen (z. B. Lentigo-maligna-Melanom, akrale Melanome) an speziellen anatomischen Lokalisationen, wie Grenzflächen im Gesicht, Ohren, Finger und Zehen, **können** reduzierte Sicherheitsabstände verwendet werden. Retrospektive Arbeiten zeigten unter Einsatz der 3-D-Histologie (mikrographisch kontrollierte Chirurgie) nicht vermehrt Lokalrezidive oder ein geringeres Gesamtüberleben. Da die Datenlage für diese Situation limitiert ist, sollte der Operateur die Entscheidung mit dem informierten Patienten zusammentreffen.	
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Leitlinie (Langversion)

In melanomas (e.g., lentigo maligna melanoma, acral melanoma) at special anatomic sites, such as the border surface of face, ears, fingers, and toes, reduced safety margins may be used.

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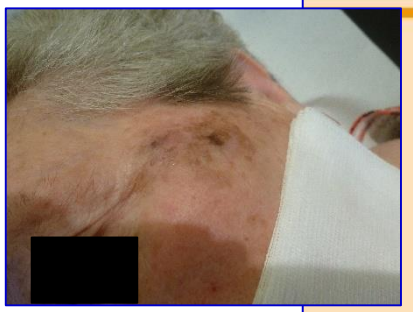
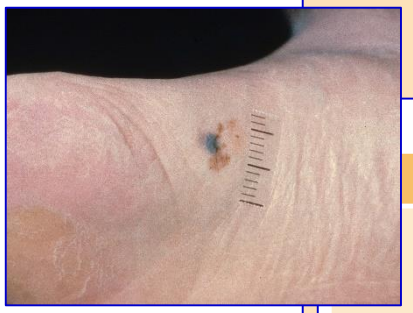
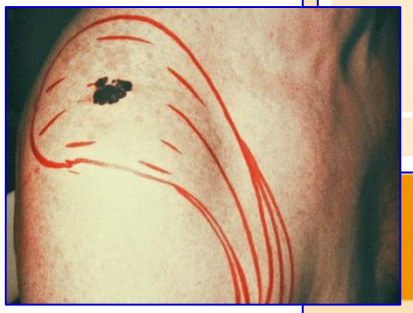
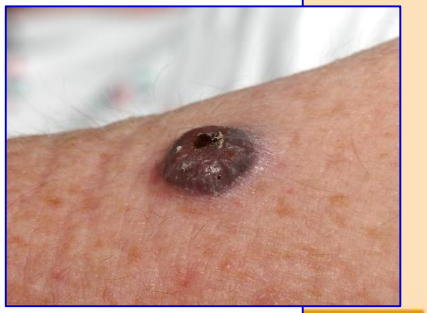
Of course, the reason for that stipulation is clear, namely, functional necessity, but if reduced safety margins are accepted for lentigo maligna melanoma and acral melanoma,









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Leitlinienprogramm Onkologie

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms

Version 3.1 - Juli 2018
AWMF-Register-Nummer: 032/024OL

Exzision mit 3-D-Histologie

	Konsensbasierte Empfehlung	geprüft 2018
	Bei malignen Melanomen (z. B. Lentigo-maligna-Melanom, akrale Melanome) an speziellen anatomischen Lokalisationen, wie Grenzflächen im Gesicht, Ohren, Finger und Zehen, **können** reduzierte Sicherheitsabstände verwendet werden. Retrospektive Arbeiten zeigten unter Einsatz der 3-D-Histologie (mikrographisch kontrollierte Chirurgie) nicht vermehrt Lokalrezidive oder ein geringeres Gesamtüberleben. Da die Datenlage für diese Situation limitiert ist, sollte der Operateur die Entscheidung mit dem informierten Patienten zusammentreffen.	
	Konsensstärke: 88 %	

Leitlinie (Langversion)

In melanomas (e.g., lentigo maligna melanoma, acral melanoma) at special anatomic sites, such as the border surface of face, ears, fingers, and toes, reduced safety margins may be used.

DKG Deutsche Krebshilfe AWMF

why not for melanomas more sharply confined, namely, melanomas on the trunk and proximal extremities that are usually referred to as “superficial spreading” and “nodular”?

The American Journal of Surgical Pathology 23(12): 1493–1498, 1999
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Patterns of Local Horizontal Spread of Melanomas

Consequences for Surgery and Histopathologic Investigation

Helmut Breuninger, Bettina Schlagenhauff, Waltraud Stroebel,
Gundula Schaumburg-Lever, and Gernot Rassner

Understanding local spreading patterns of melanomas is a precondition for the localized surgical treatment and histopathologic investigation. We used hematoxylin and eosin–stained paraffin sections for a two-phase, cellular and microscopic study of patterns of lateral spread in superficial spreading melanomas (SSMs), nodular melanomas (NMs), lentigo maligna melanomas (LMMs), and acral lentiginous melanomas (ALMs). Complete histologic examination of vertical excisional margins was carried out with paraffin sections 5 mm beyond the clinical tumor border of 1395 SSMs, 376 NMs, 179 LMMs, 46 ALMs, and 37 acrally located SSMs or NMs. Further sections of embedded material were analyzed when tumor-positive margins were found. In case of continuous tumor spread, reoperations were continued until the tissue was free of tumor cells. In case of noncontinuity, a final excision was made to a minimum safety margin of 10 to 20 mm. Concentrically consecutive, 5-μm thick hematoxylin and eosin–stained sections were taken from the outside of a 10-mm safety margin inward to the clinical borders of 34 SSMs, five NMs, 10 LMMs, and five ALMs. Noncontinuous subclinical spread was found in all SSMs and NMs in the form of few isolated cell nests at the epidermis–dermis junction. Ninety-two percent of these were located within 6 mm of the central tumor. All LMMs and ALMs showed a clearly demonstrable, uninterrupted spread into the periphery at the epidermis–dermis junction, too, usually in groups of outgrowths. The probability of finding these outgrowths 5 mm beyond the clinical tumor border was 54% in LMM and ALM. Complete histologic examination of vertical excisional margins (micrographic surgery) is therefore the therapy of choice only for LMM and ALM and is inefficient for SSM and NM.

Surgical excision followed by histopathologic investigation is the treatment of choice for melanoma.[17] Currently, local resection is recommended with a safety margin of 10 to 30 mm, depending on tumor thickness.

Micrographic surgery, based on a complete histologic examination of excisional margins by frozen sections, is recommended for localized surgical treatment of melanomas and has been shown to yield good results. A precondition for this procedure, however, is that the lateral, subclinical parts of the central tumor continue to spread uninterrupted. We therefore investigated the immediate surroundings of superficial spreading melanomas (SSMs), nodular melanomas (NMs), lentigo maligna melanomas (LMMs), and acral lentiginous melanomas (ALMs) to determine their patterns of lateral spread.

MATERIALS AND METHODS

We used complete histologic evaluation of excisional margins with paraffin sections of skin from the tumor margins in a two-phase histopathologic and clinical trial to identify different subclinical patterns of spread by central tumors. This method was first introduced by us in 1982 and reported in 1984 and 1988.[2,3] It has been used for the treatment of melanomas since 1985 (Fig. 1).

In the literature, it has been claimed that the latter types have a different pattern of *"local horizontal spread."* In 1999, Breuninger and co-workers studied more than 2000 melanomas of different types and asserted that *"noncontinuous subclinical spread was found in all SSMs and NMs,"* whereas *"all LMMs and ALMs showed a clearly demonstrable, uninterrupted spread."* They concluded that *"complete histological examination of vertical excision margins (micrographic surgery) is therefore the therapy of choice only for LMM and ALM and is inefficient for SSM and NM."*

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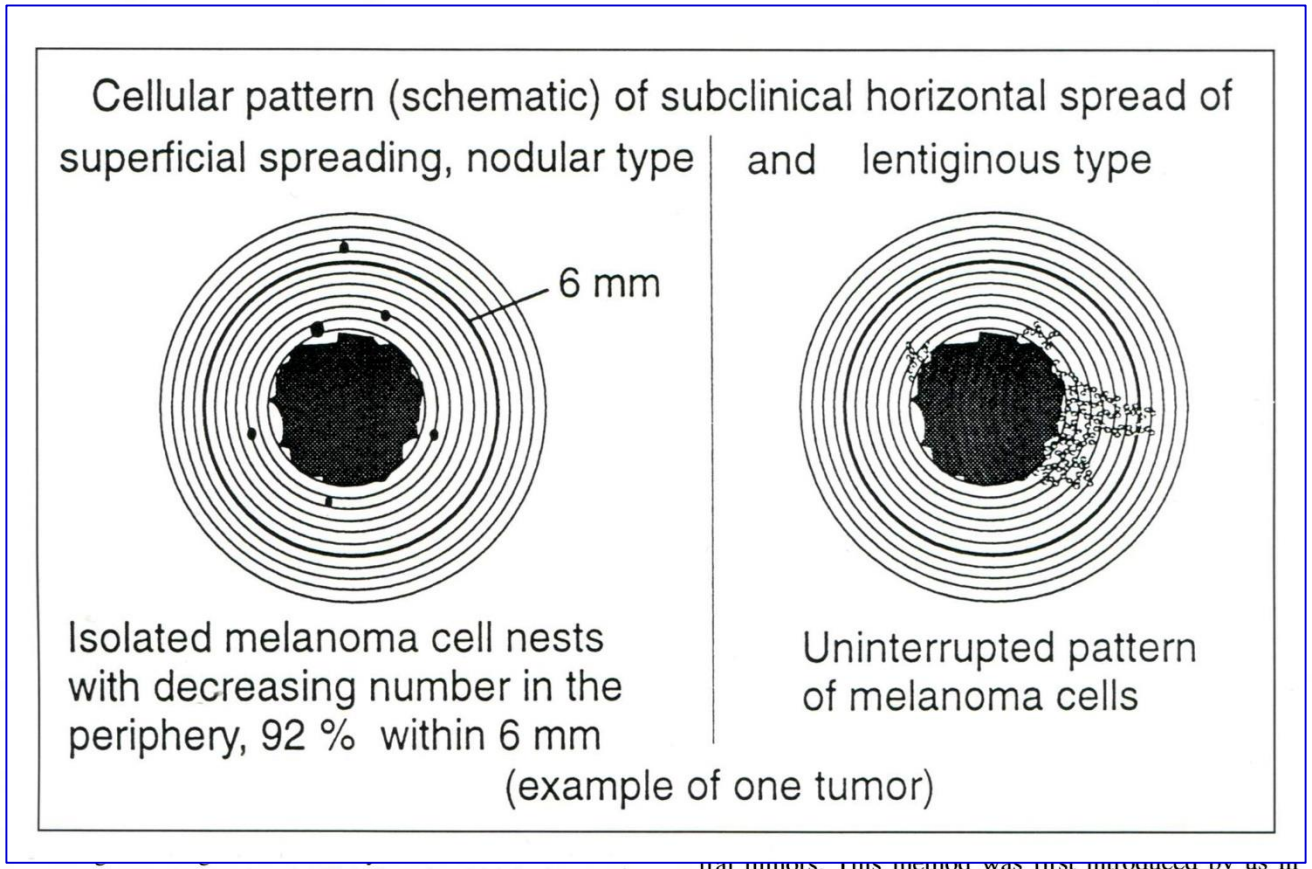

der was 54% in LMM and ALM. Complete histologic examination of vertical excisional margins (micrographic surgery) is therefore the therapy of choice only for LMM and ALM and is inefficient for SSM and NM.

1982 and reported in 1984 and 1988.[2,3] It has been used for the treatment of melanomas since 1985 (Fig. 1).

This was their result: *"Isolated melanoma cell nests"* in the superficial and nodular type and an *"uninterrupted pattern of melanoma cells"* in the *"lentiginous type."* It looks pretty convincing and would justify their conclusion as long as one takes no closer look at the pictures in this article.

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Patterns of Local Horizontal Spread of Melanomas

Consequences for Surgery and Histopathologic Investigation

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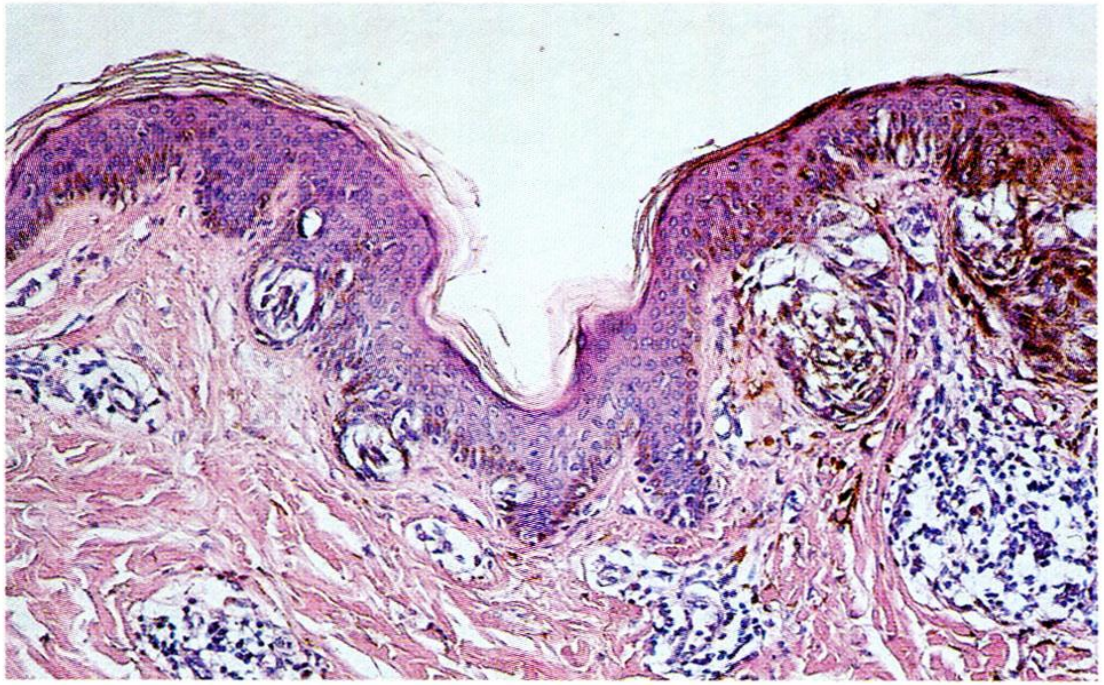
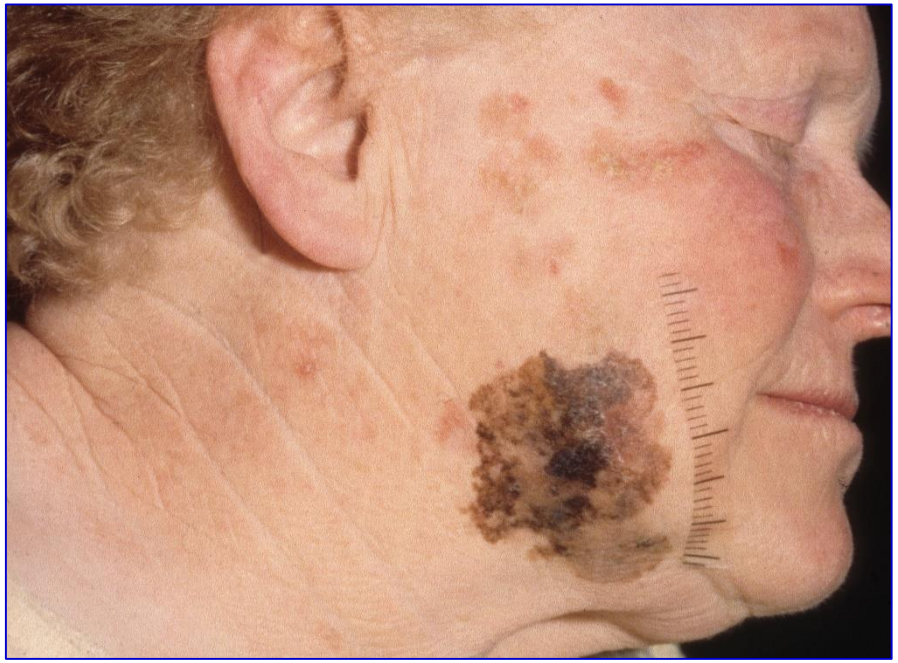


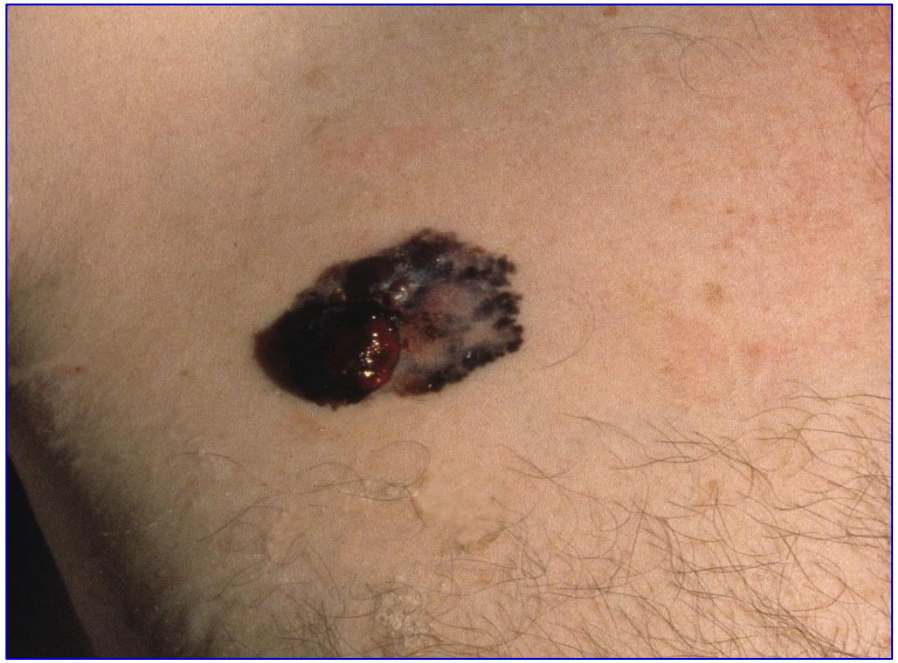
FIG. 6. Scattered cell nests at the lateral border of a superficial spreading melanoma, similar to Fig. 5, cut in a transverse direction.

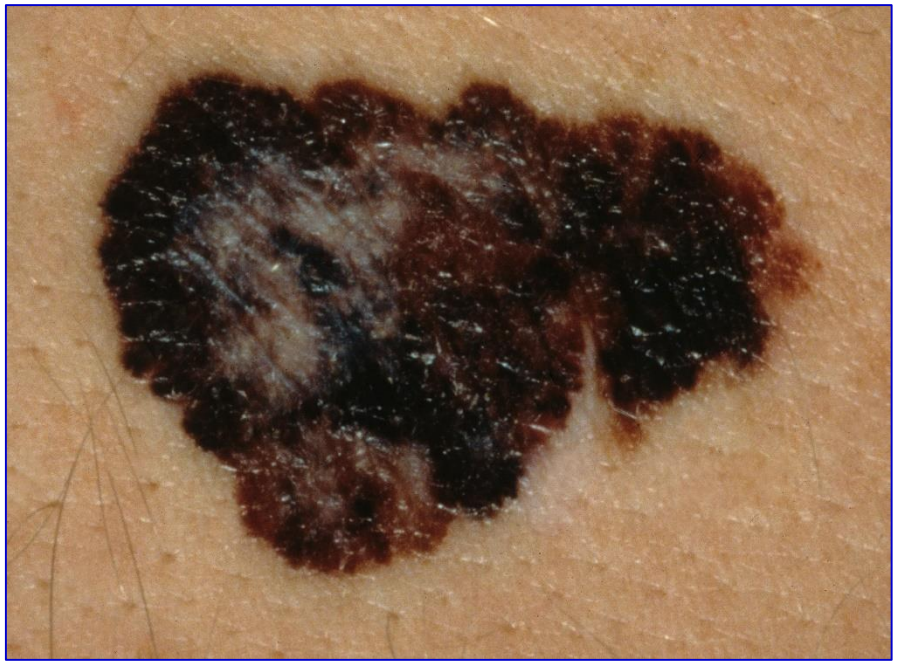
der was 54% in LMM and ALM. Complete histologic examination of vertical excisional margins (micrographic surgery) is therefore the therapy of choice only for LMM and ALM and is inefficient for SSM and NM.

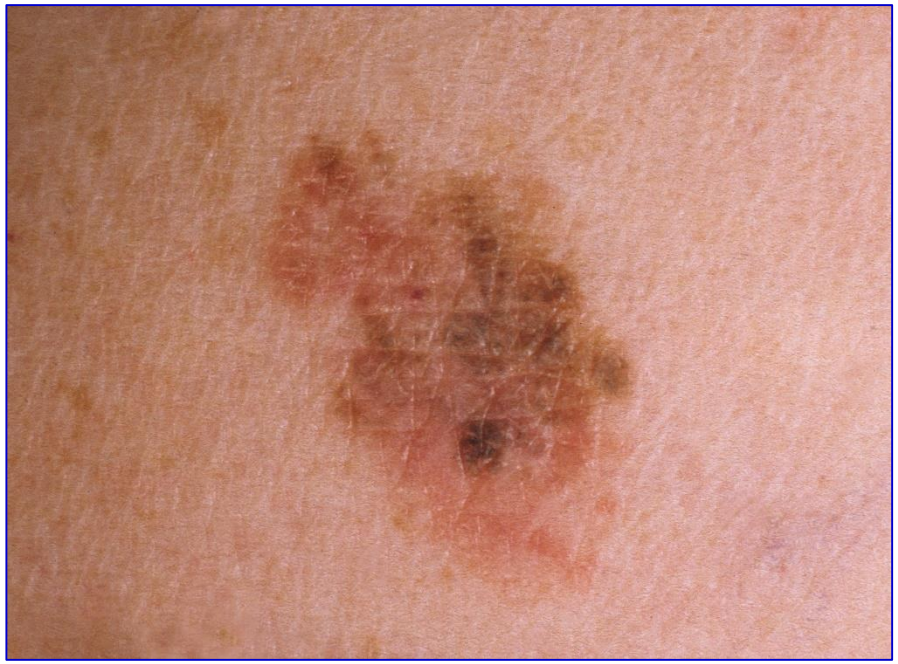
1982 and reported in 1984 and 1988.[2,3] It has been used for the treatment of melanomas since 1985 (Fig. 1).

This picture, for example, serves to illustrate *"scattered cell nests at the lateral border of a superficial spreading melanoma,"* but those nests are closely approximated with one another, and there are many melanocytes as solitary units around and between them. This type of spread is not "noncontinuous."

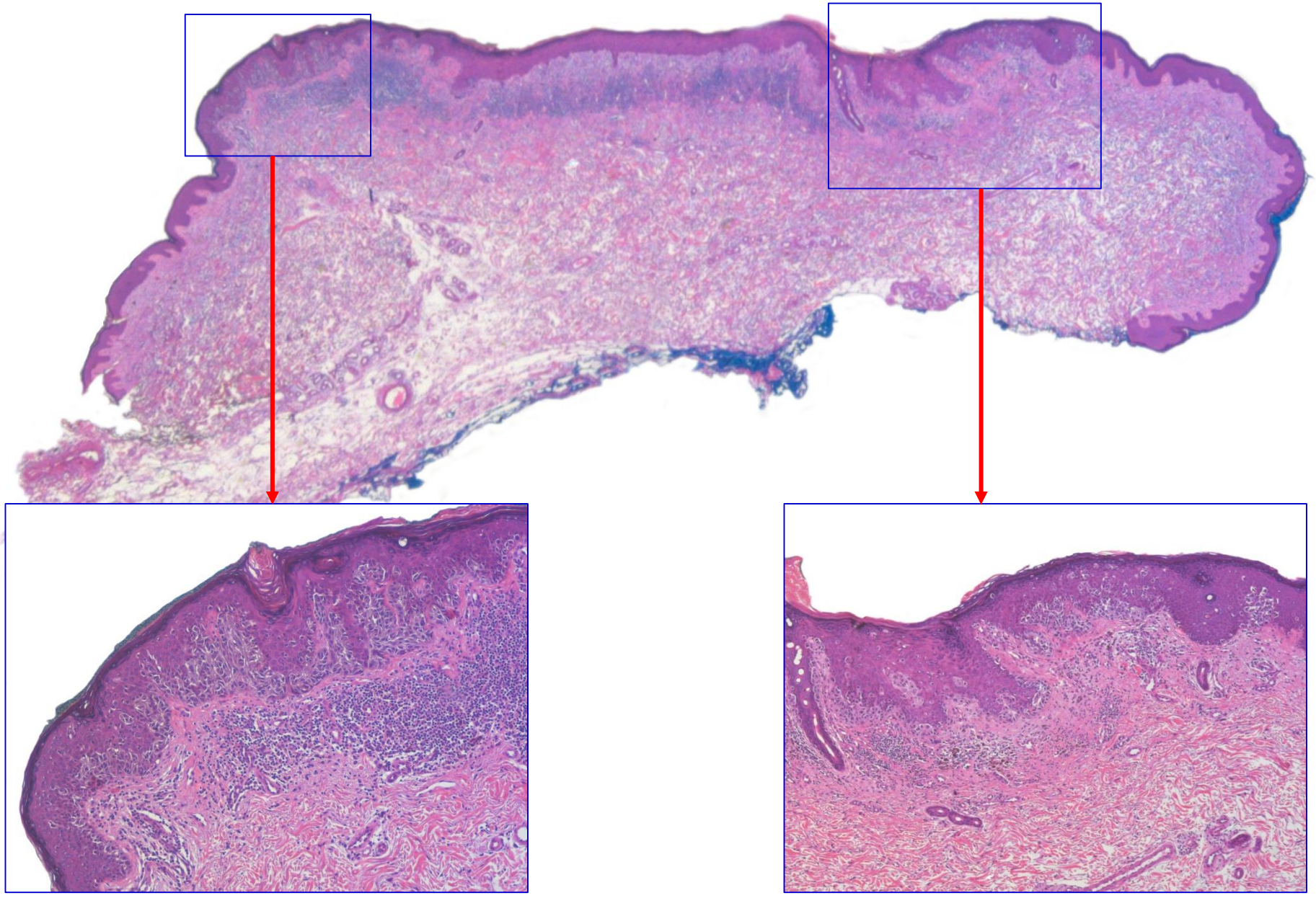




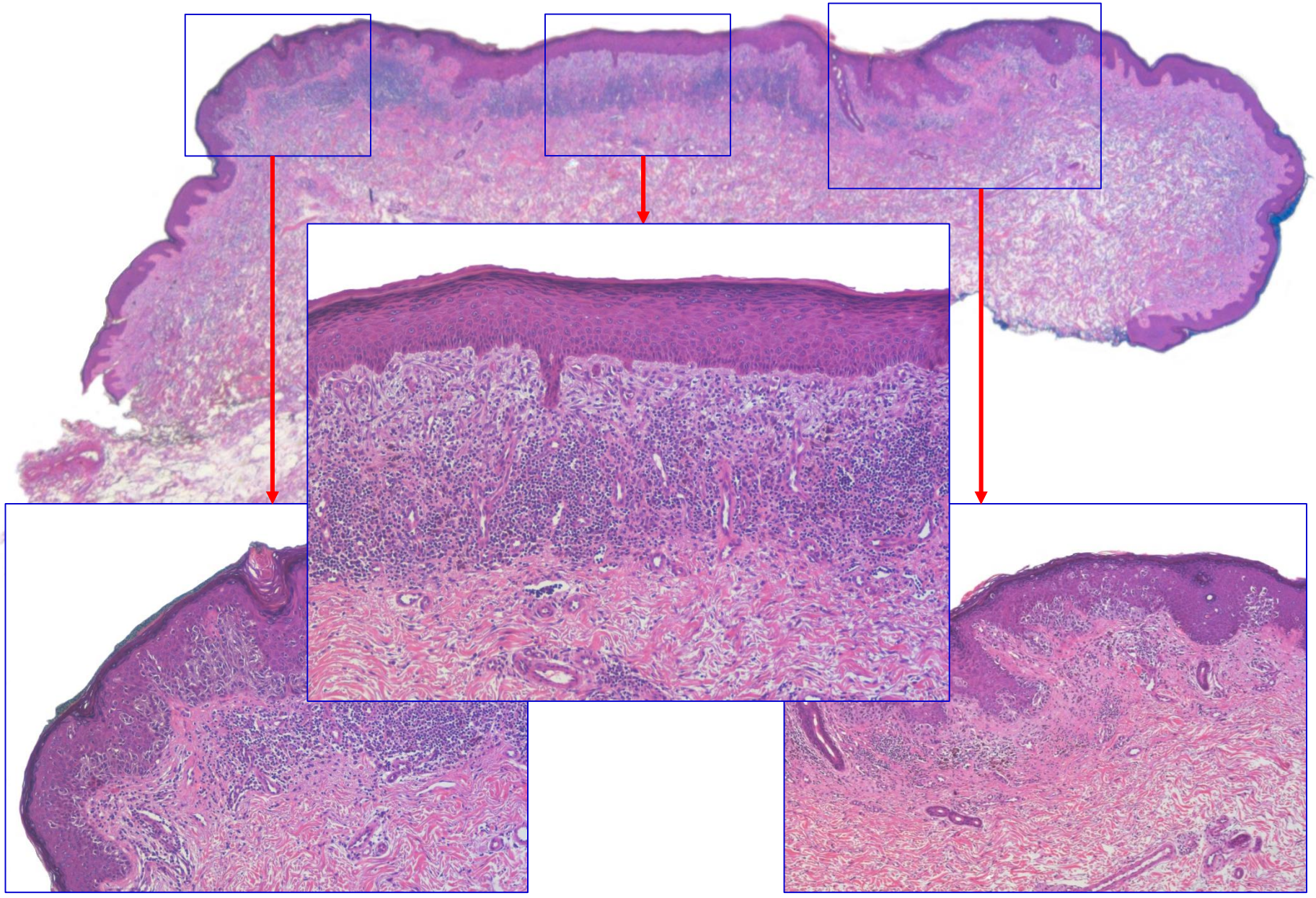




Nonetheless, a noncontinuous pattern may occur in melanomas, the reason being partial regression. As in all other neoplasms, regression diminuishes the utility of histopathologic control of margins, and it is relatively common in melanomas. Clinically, zones of regression usually presents themselves as areas of depigmentation in the center or at the edge of the lesion, but they may also be pigmented if there are many melanophages and, in that instance, they may be very inconspicuous.

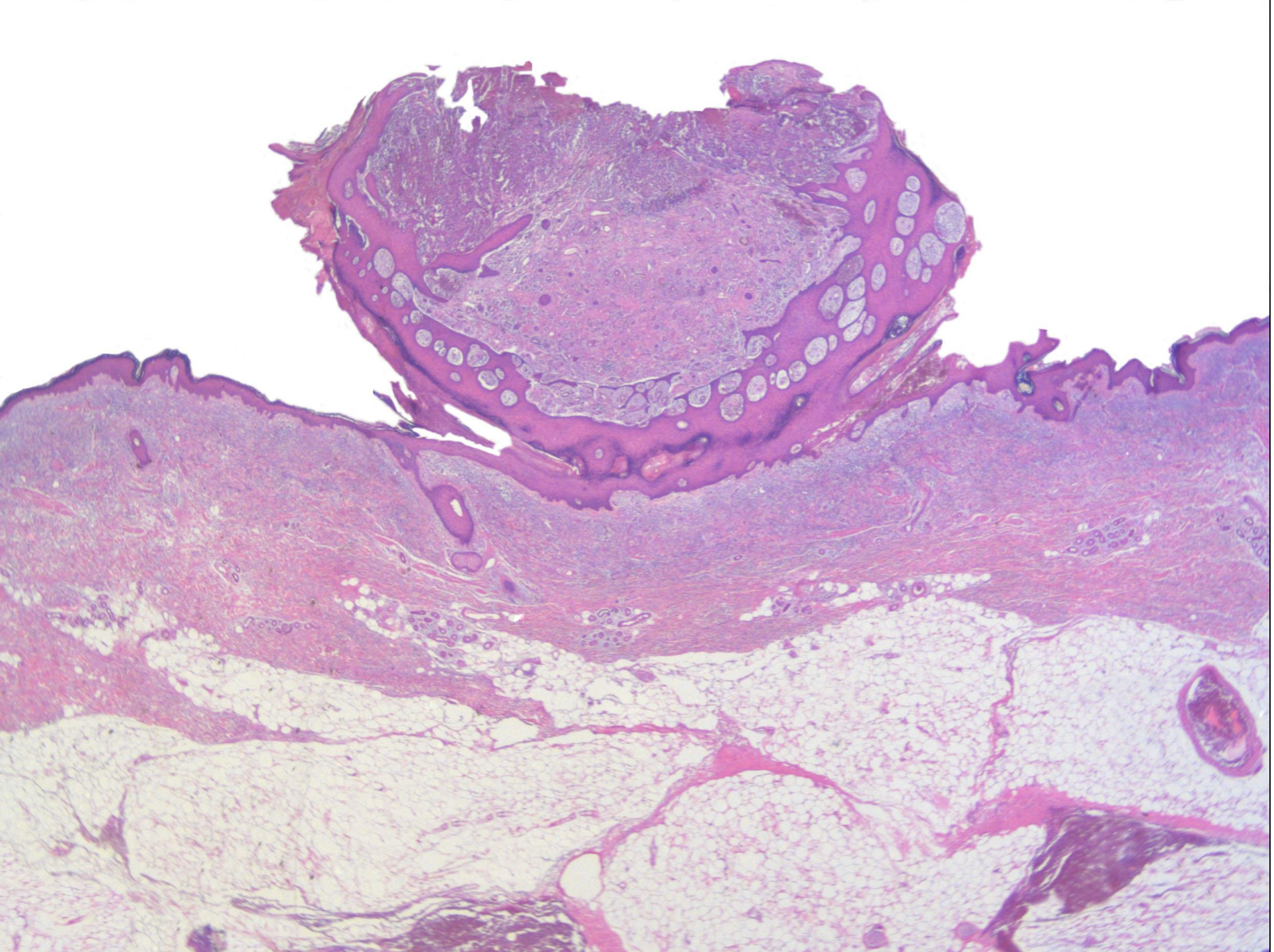


The same applies to the histopathologic presentation of regression. In some cases, such as this one, it is visible clearly: The edges of the lesion are replete with melanocytes scattered through all levels of the epidermis,

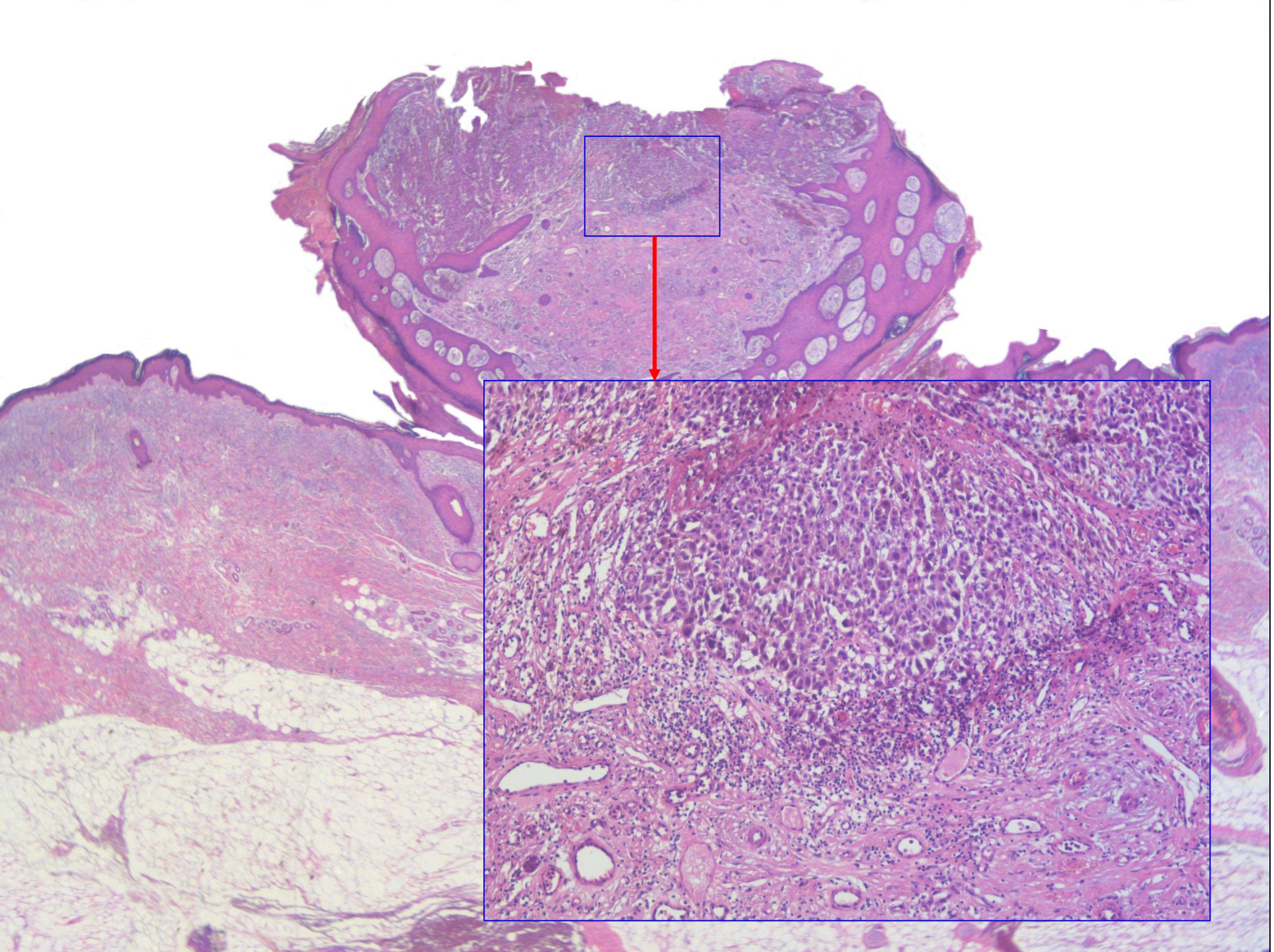


but the center is free of melanocytes; they have been wiped away by the immune response. There is still a dense lichenoid lymphocytic infiltrate beneath a thickened fibrotic papillary dermis with numerous melanophages and prominent blood vessels arranged perpendicular to the skin surface. If a surgeon cuts through such a zone of regression, there may be no melanocytes at the margin, but the neoplasm may continue in the periphery of it.

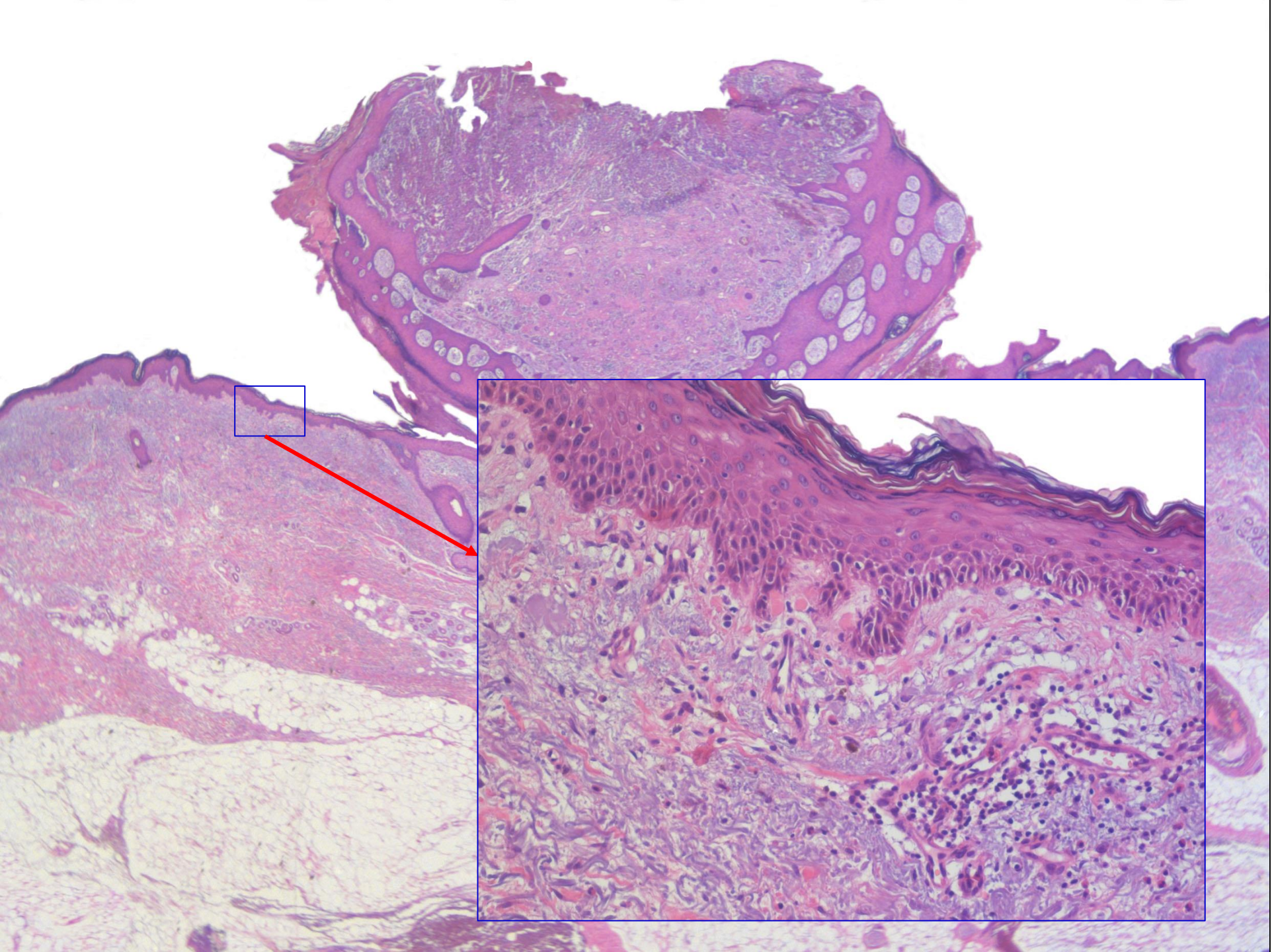
In this case, regression is discerned easily,



but it may also be very inconspicuous. In this example of a thick papillomatous melanoma, all that has remained of the neoplasm



are aggregates of neoplastic cells in the exophytic nodule that are still under the attack of lymphocytes; the rest has been wiped out and substituted by fibrosis. There is also subtle fibrosis in the adjacent papillary dermis,



and a closer look reveals remnants of the preceding inflammatory process, some lymphocytes, necrotic keratocytes, and dilated blook vessels. Those signs of regression are non-specific and may be overlooked easily.

DERMATOLOGIC SURGERY

Risk factors for positive or equivocal margins after wide local excision of 1345 cutaneous melanomas

Christopher J. Miller, MD,[a] Thuzar M. Shin, MD, PhD,[a] Joseph F. Sobanko, MD,[a] John M. Sharkey, BA,[a] John W. Grunyk, BA,[b] Rosalie Elenitsas, MD,[a] Emily Y. Chu, MD, PhD,[a] Brian C. Capell, MD, PhD,[a] Michael E. Ming, MD,[a] and Jeremy R. Etzkorn, MD[a]

Philadelphia, Pennsylvania

Background: Positive or equivocal margins after wide local excision (WLE) complicate surgical management of cutaneous melanoma.

Objective: To identify the frequency of and risk factors for positive or equivocal margins after WLE of cutaneous melanoma.

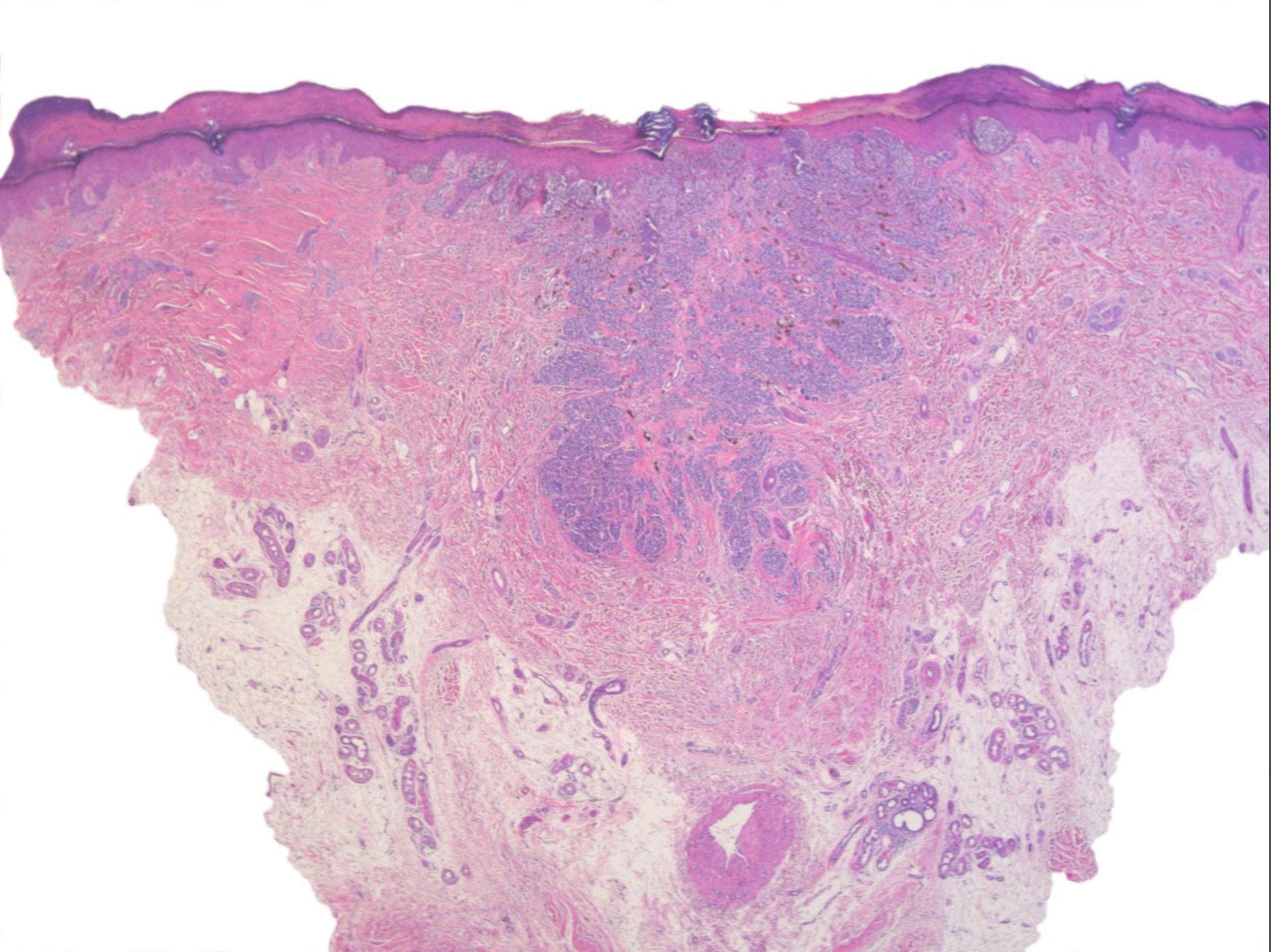
Methods: Retrospective, single-center, cross-sectional study of 1345 consecutive melanomas treated with WLE.

Results: The overall frequency of positive or equivocal margins was 4.2% (56/1345), ranging from 2.2% to 22.6%, depending on the size of the surgical margins, patient characteristics, biopsy history, and the clinicopathology of the melanoma. In descending order, independent risk factors associated with the greatest odds for positive or equivocal margins after multivariate analysis were noncompliance with recommended surgical margins (odds ratio [OR] 5.57, $P = .002$); anatomic location on the head, neck, hands, feet, genitals, or pretibial leg (OR 5.07, $P < .001$); histologic regression (OR 2.78, $P = .007$); in situ melanoma (OR 2.27, $P = .011$); multiple biopsies at the tumor site before WLE (OR 1.92 [per biopsy], $P = .004$); and increasing age (OR 1.049 [per year], $P < .001$).

Limitations: This was a single-site, retrospective observational study.

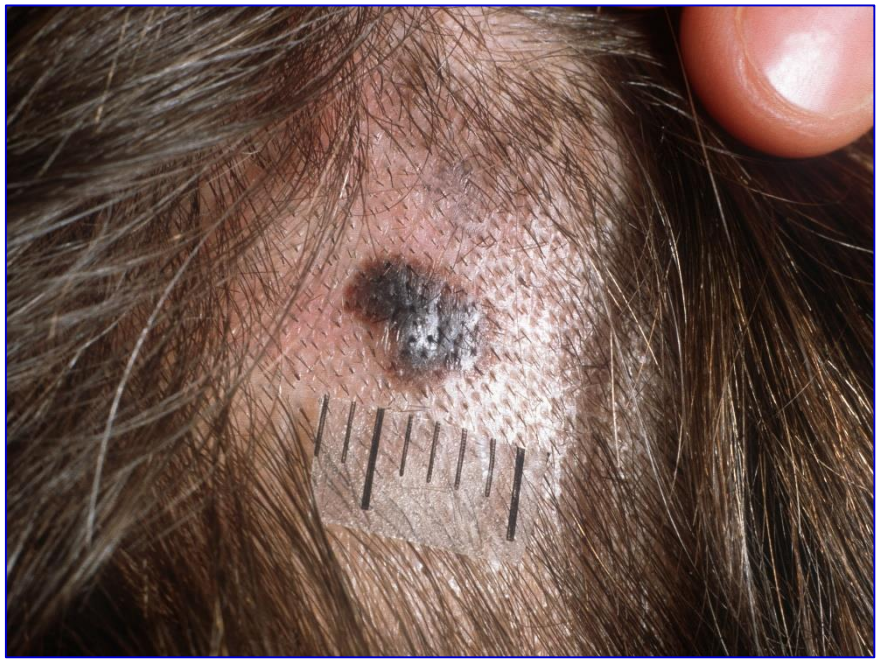
Conclusions: Clinicopathologic factors, especially location in cosmetically or functionally sensitive areas and noncompliance with recommended surgical margins, identified melanomas at increased risk for positive or equivocal margins after WLE. (J Am Acad Dermatol 2017;77:333-40.)

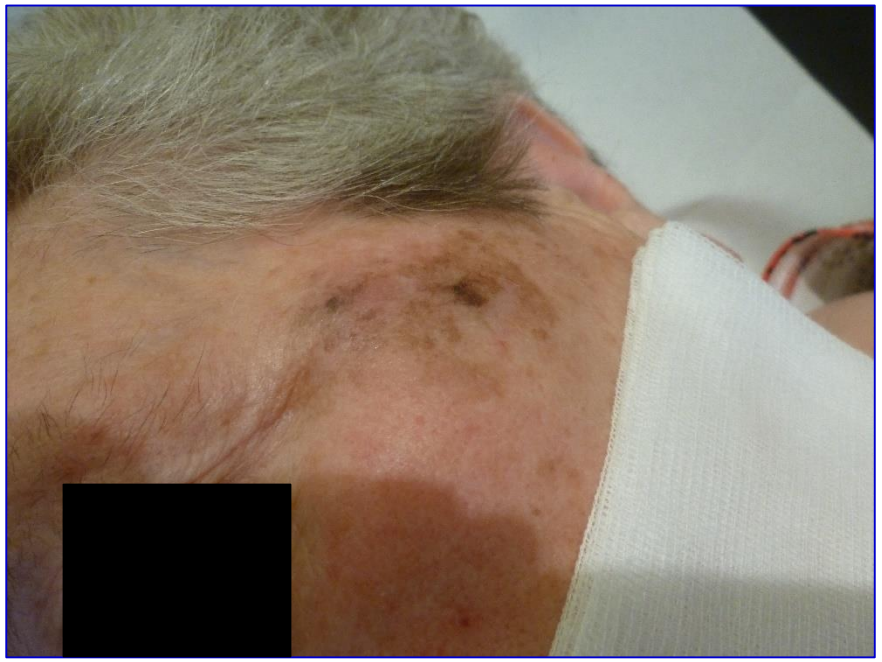
Hence, it is not surprising that, among *"risk factors for positive or equivocal margins after wide excision,"* not only *"anatomic location on the head, neck, hands, feet, genitals, or pretibial leg"* has been noted, but also *"histologic regression."* Yet another risk factor is *"multiple biopsies at the tumor site,"* and it is clear why the latter may contribute to local recurrence.

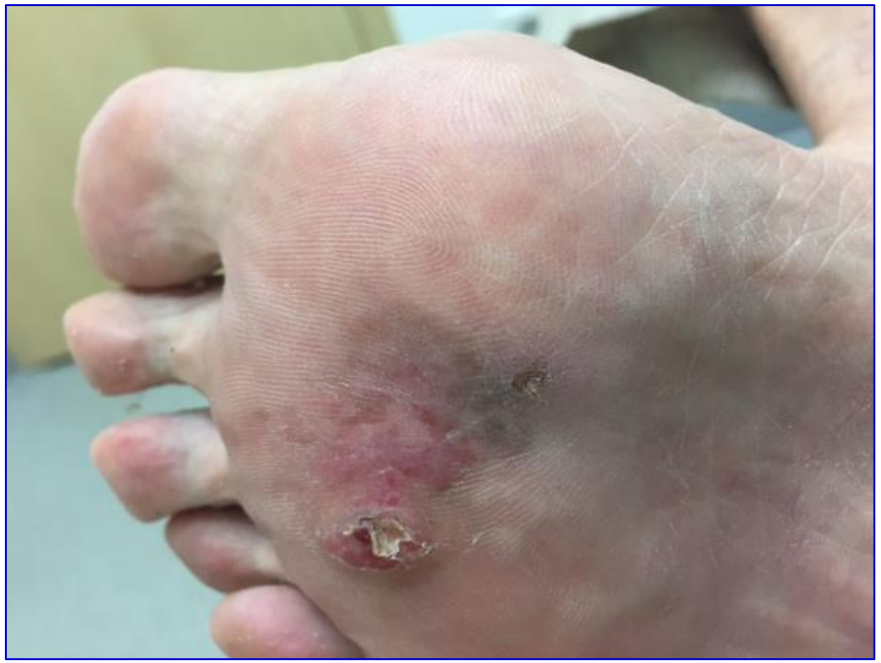


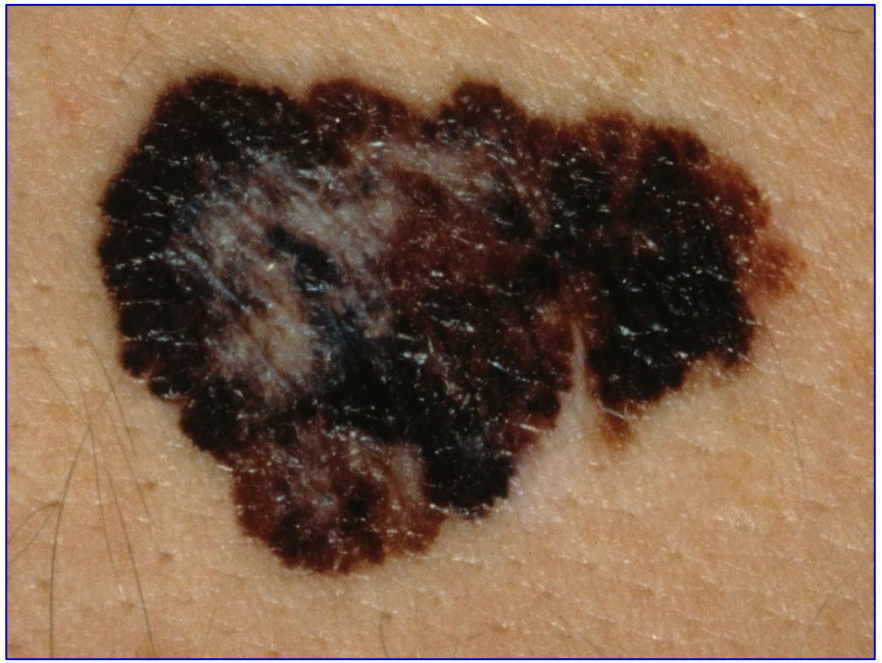
If there is a scar at the surgical margin, the melanoma may go on in the periphery of it.

For the forementioned reasons, histopathologic control of margins is not always dependable.

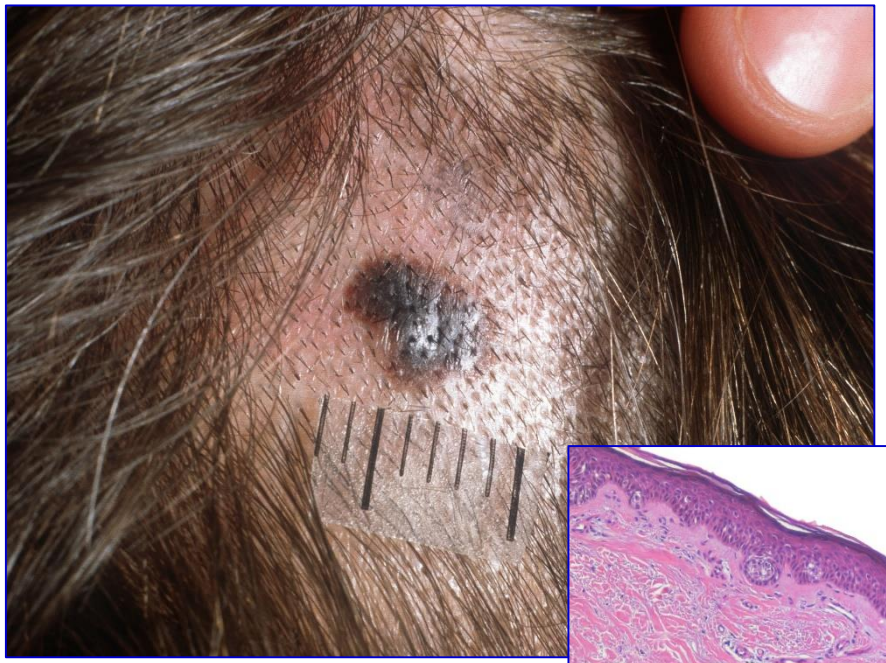


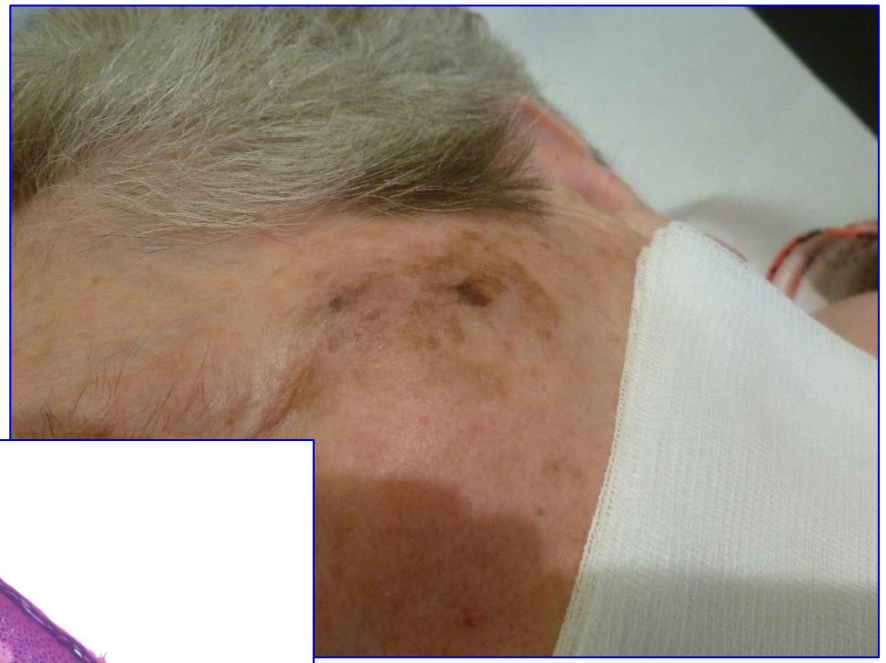


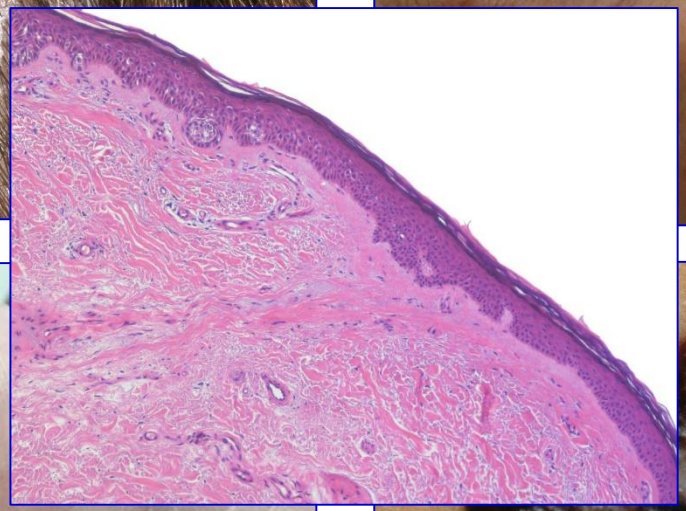


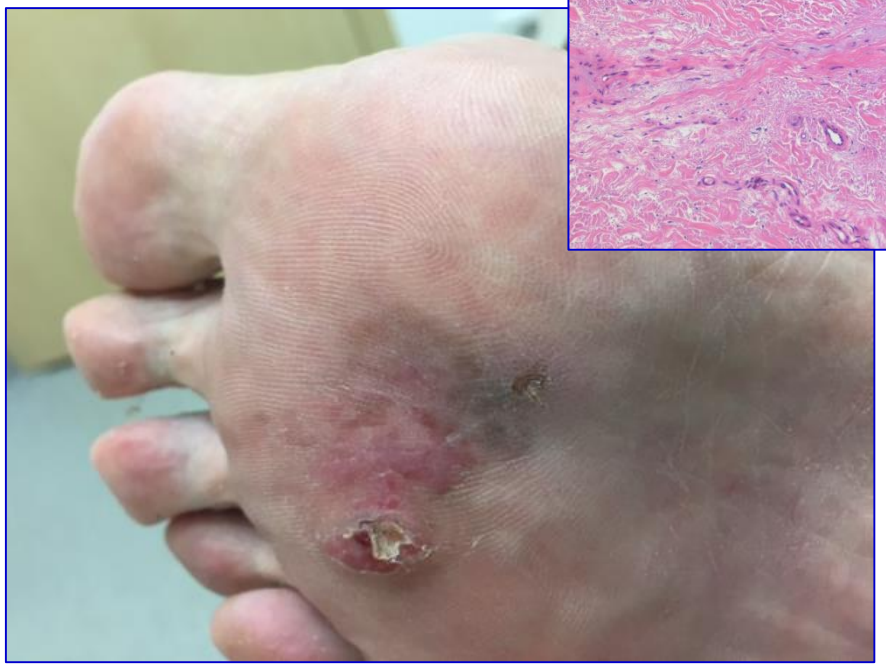


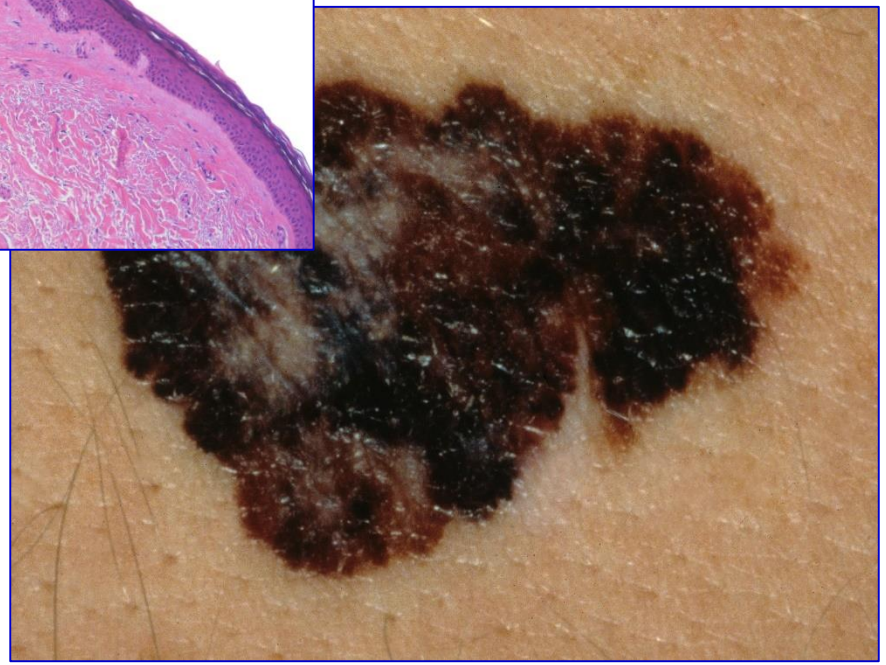
Melanomas known to be associated with an increased risk of misjudgment, namely, melanomas on the head and neck, especially those on the scalp and in chronically sun-damaged skin of the face, acral melanomas, desmoplastic melanomas, and melanomas with signs of regression, should be excised with a slightly extended histopathologic safety margin.



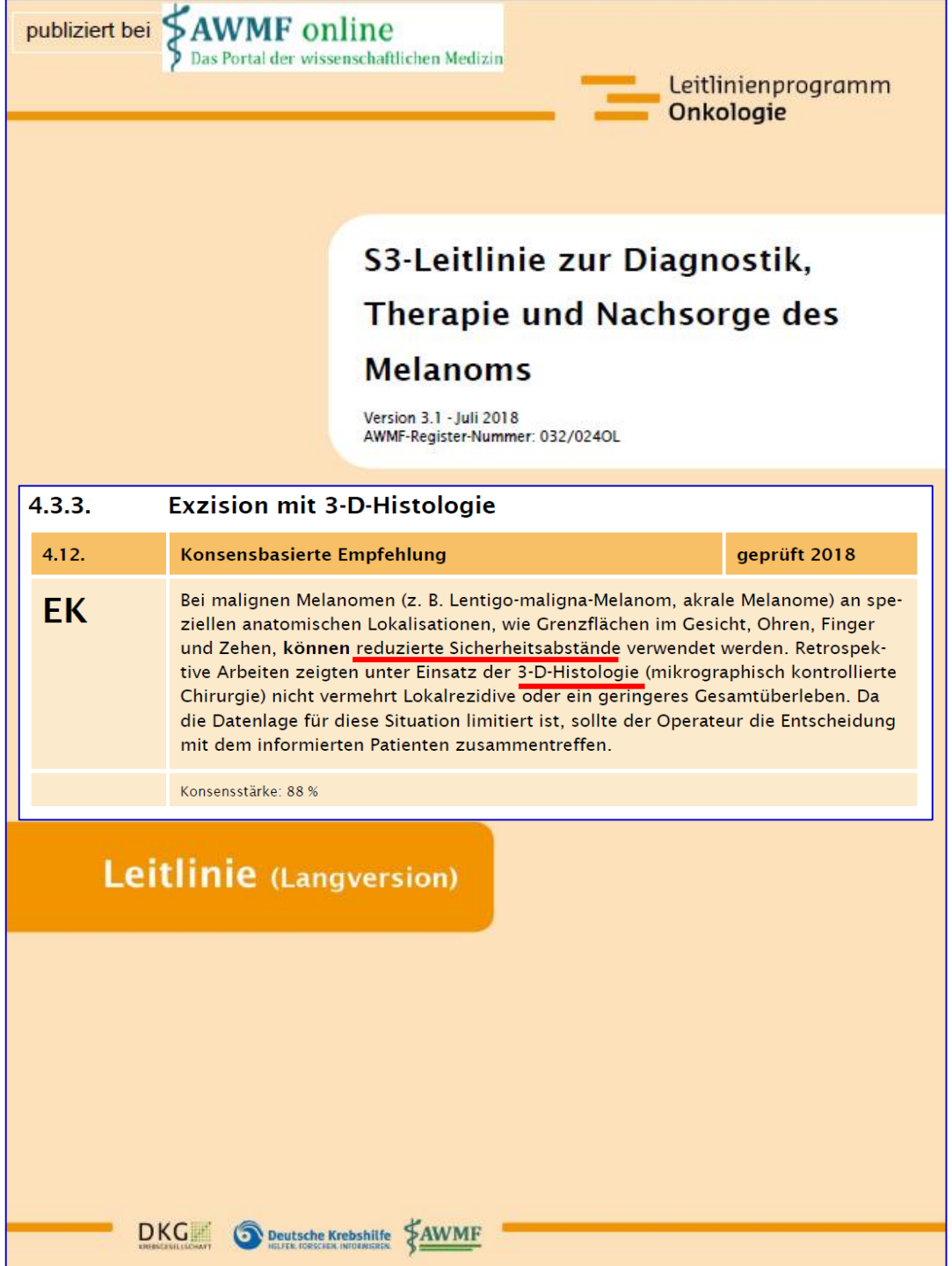








Overall, however, histopathologic control of margins is a safe method and allows margins to be reduced for most melanomas, often abrogating the necessity of re-excisions and skin grafts. But which method of margin control should be used?



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Leitlinienprogramm Onkologie

S3-Leitlinie zur Diagnostik, Therapie und Nachsorge des Melanoms

Version 3.1 - Juli 2018
AWMF-Register-Nummer: 032/024OL

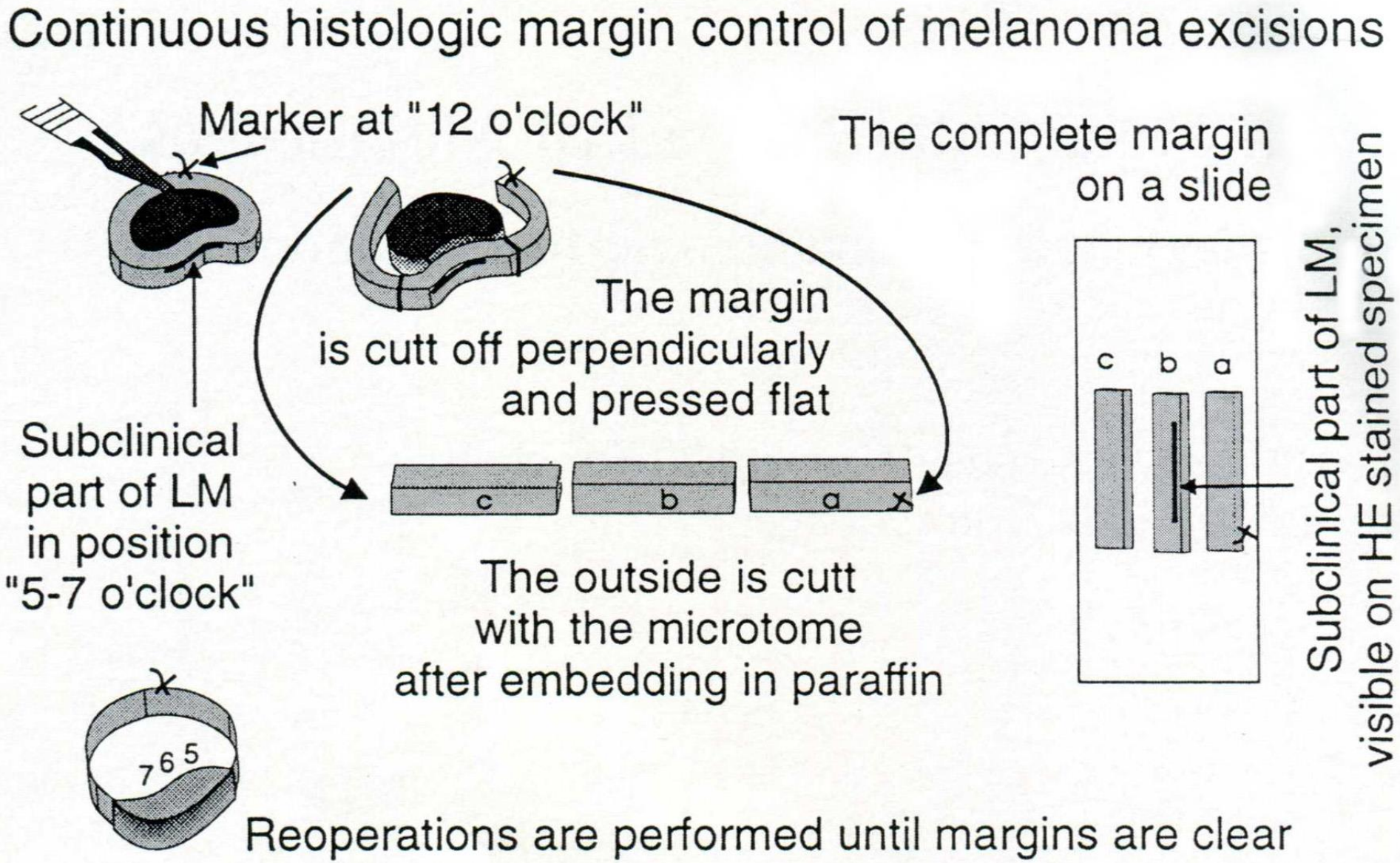
4.3.3. Exzision mit 3-D-Histologie

4.12.	Konsensbasierte Empfehlung	geprüft 2018
EK	Bei malignen Melanomen (z. B. Lentigo-maligna-Melanom, akrale Melanome) an speziellen anatomischen Lokalisationen, wie Grenzflächen im Gesicht, Ohren, Finger und Zehen, **können** reduzierte Sicherheitsabstände verwendet werden. Retrospektive Arbeiten zeigten unter Einsatz der 3-D-Histologie (mikrographisch kontrollierte Chirurgie) nicht vermehrt Lokalrezidive oder ein geringeres Gesamtüberleben. Da die Datenlage für diese Situation limitiert ist, sollte der Operateur die Entscheidung mit dem informierten Patienten zusammentreffen.	
	Konsensstärke: 88 %	

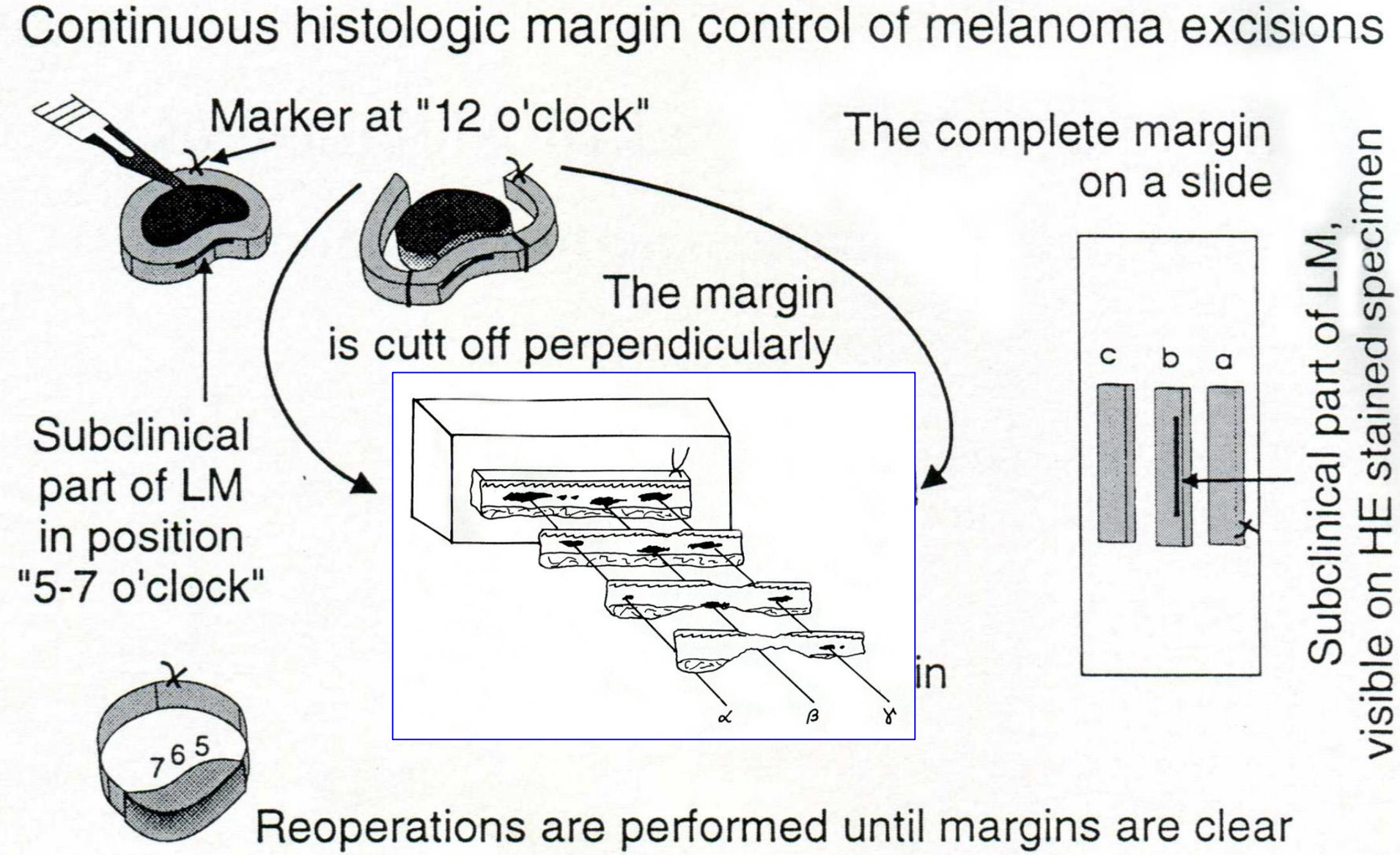
Leitlinie (Langversion)

DKG Deutsche Krebshilfe AWMF

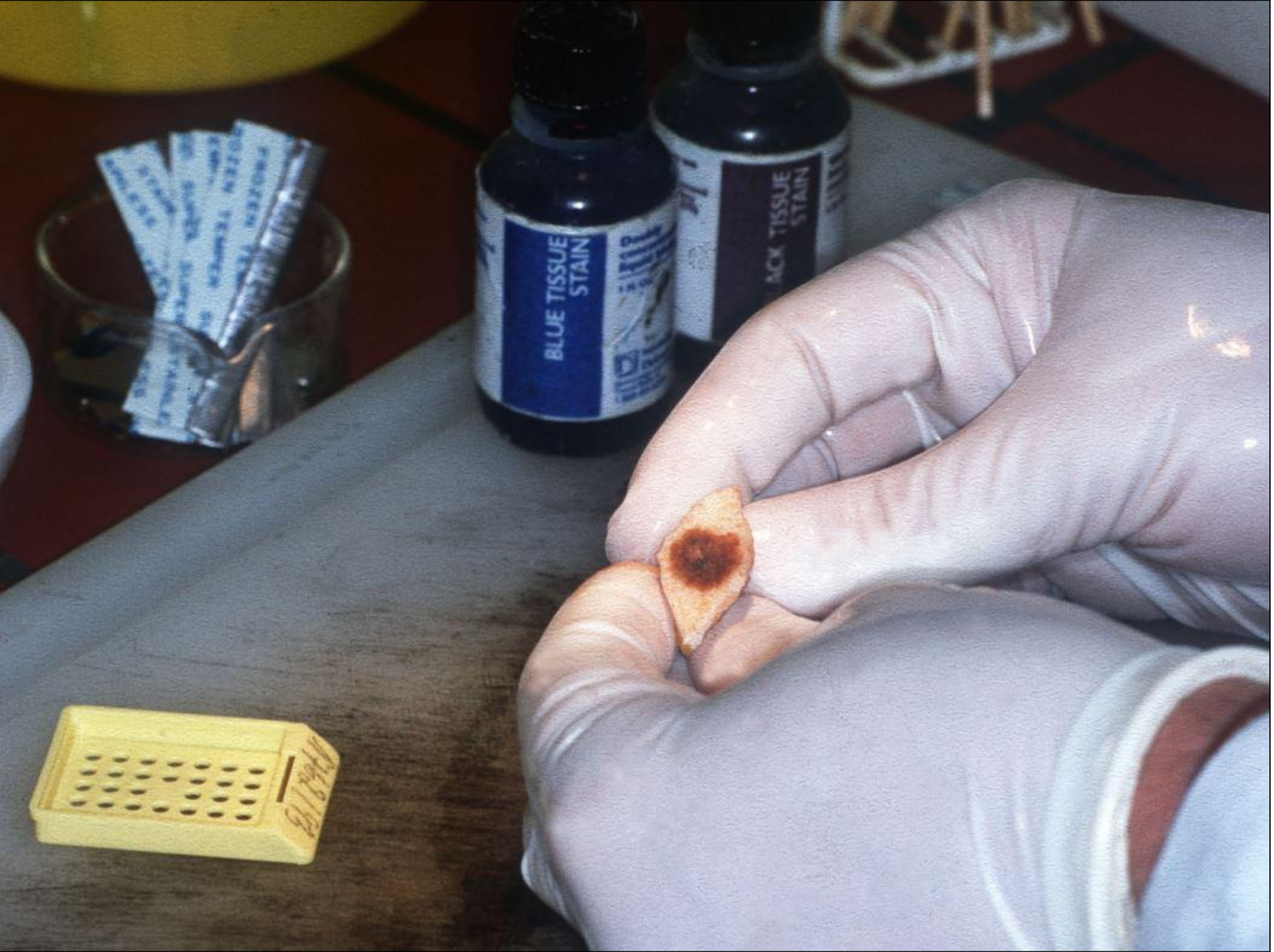
In the German guidelines, *"reduced safety margins"* are accepted only in conjunction with so-called *"three-dimensional histology,"* a method with permanent sections corresponding to Mohs surgery.



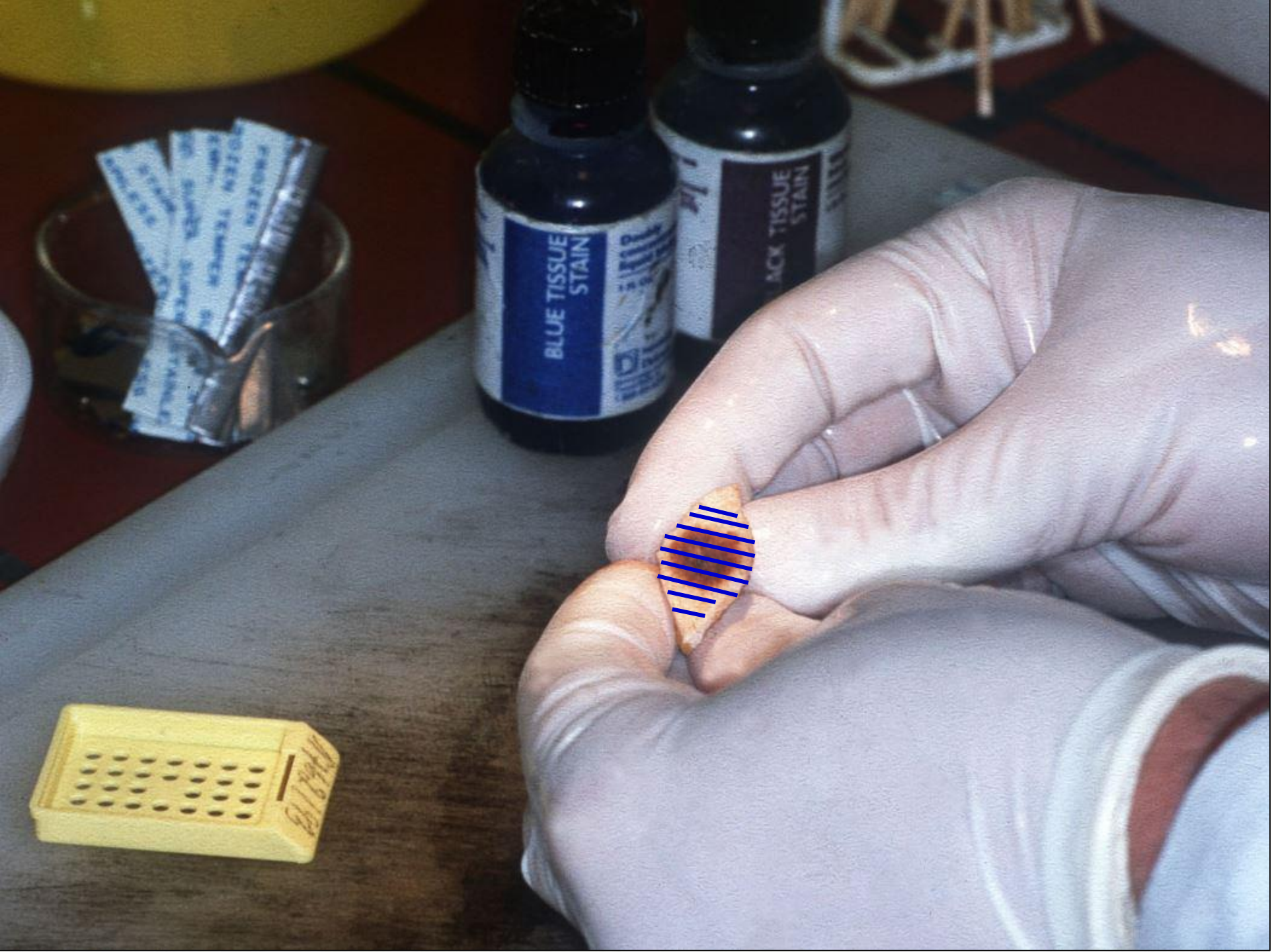
Following excision, a peripheral rim of the specimen is cut off and embedded en face. Histopathologic sections are then cut from the outside so that the complete border of the specimen can be assessed. That technique is valuable but has its limitations.



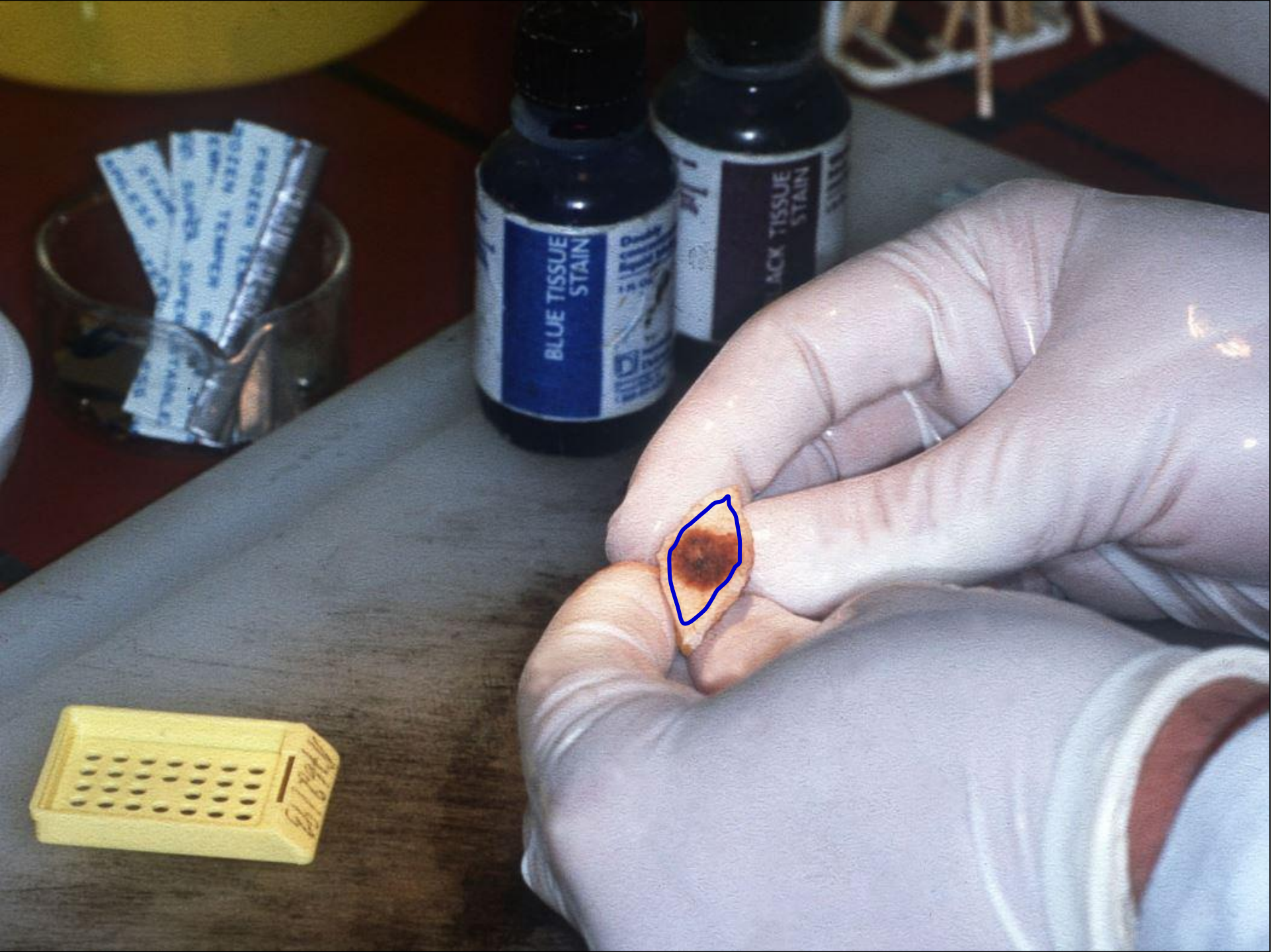
If the outer surface of the specimen is slightly irregular, one must cut into the block in order to get a plane section, and it may be difficult to decide whether or not findings are really at the surgical margin.



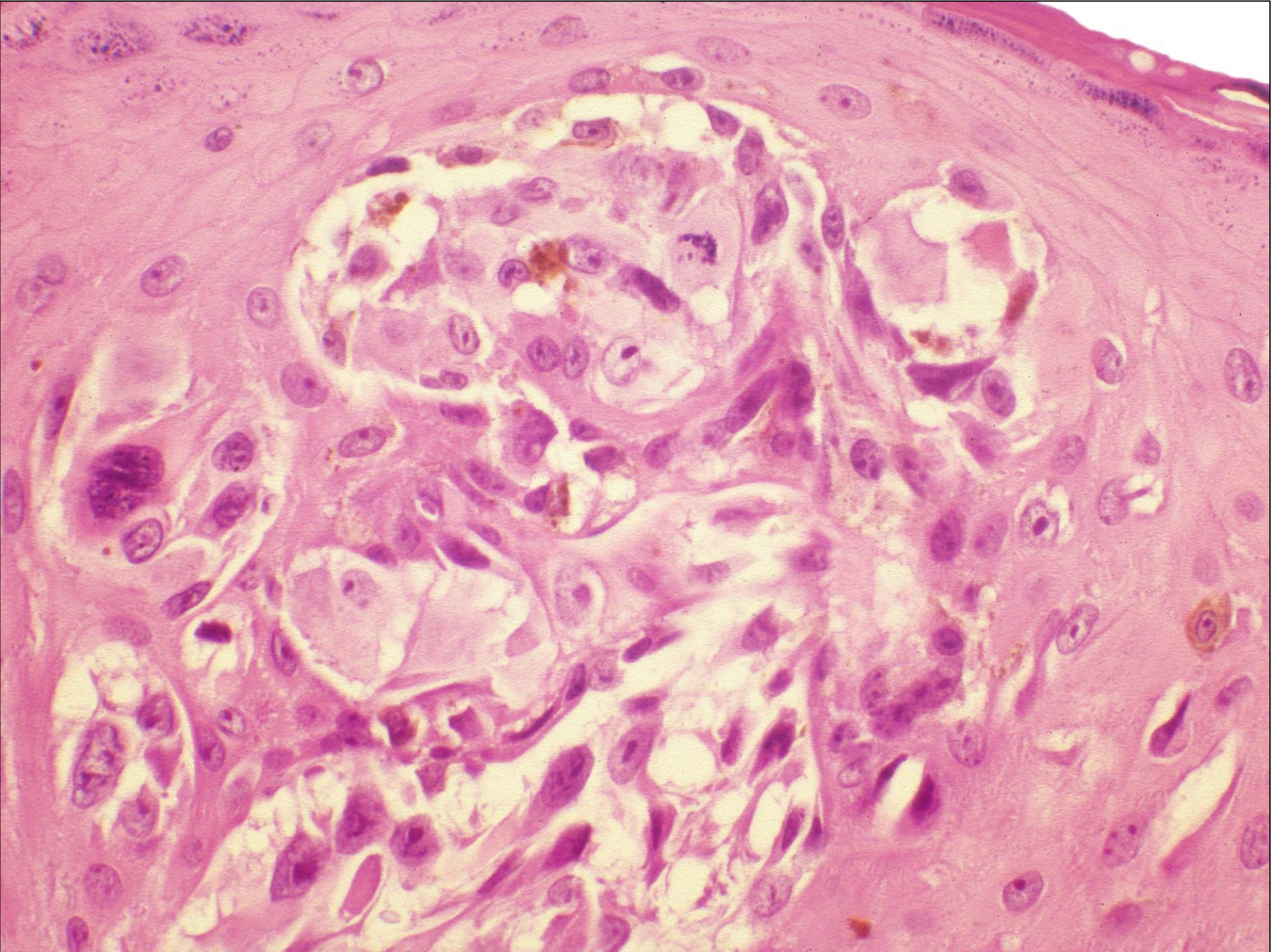
Moreover, in regard to melanocytic neoplasms, the assessment of architectural features – symmetry, circumscription, and distribution of melanocytes – is crucial for diagnosis.



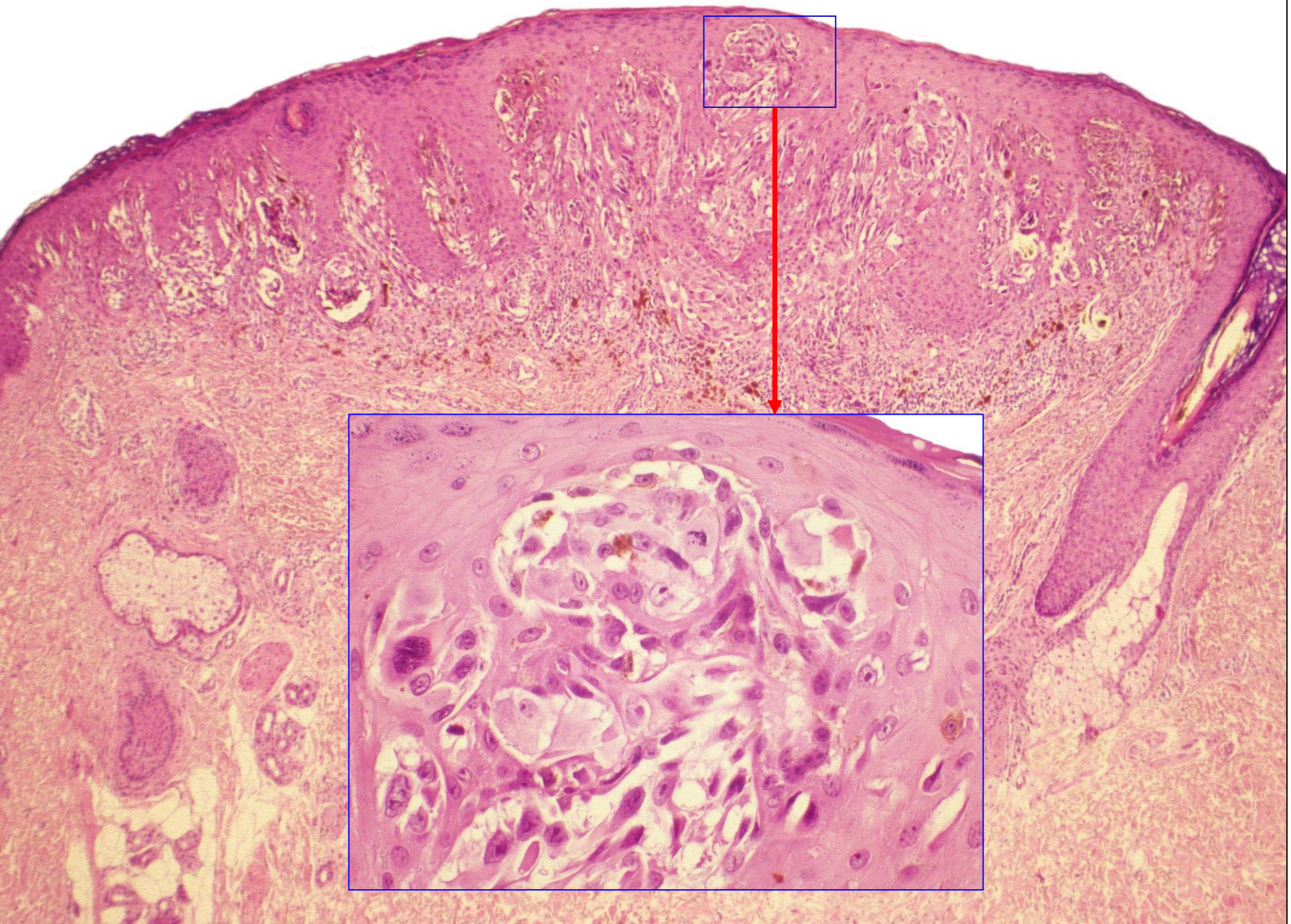
The architecture can be appreciated best in traverse sections through the block. Those sections do not allow for complete assessment of margins but they provide a dependable representation of margins if they are close enough.



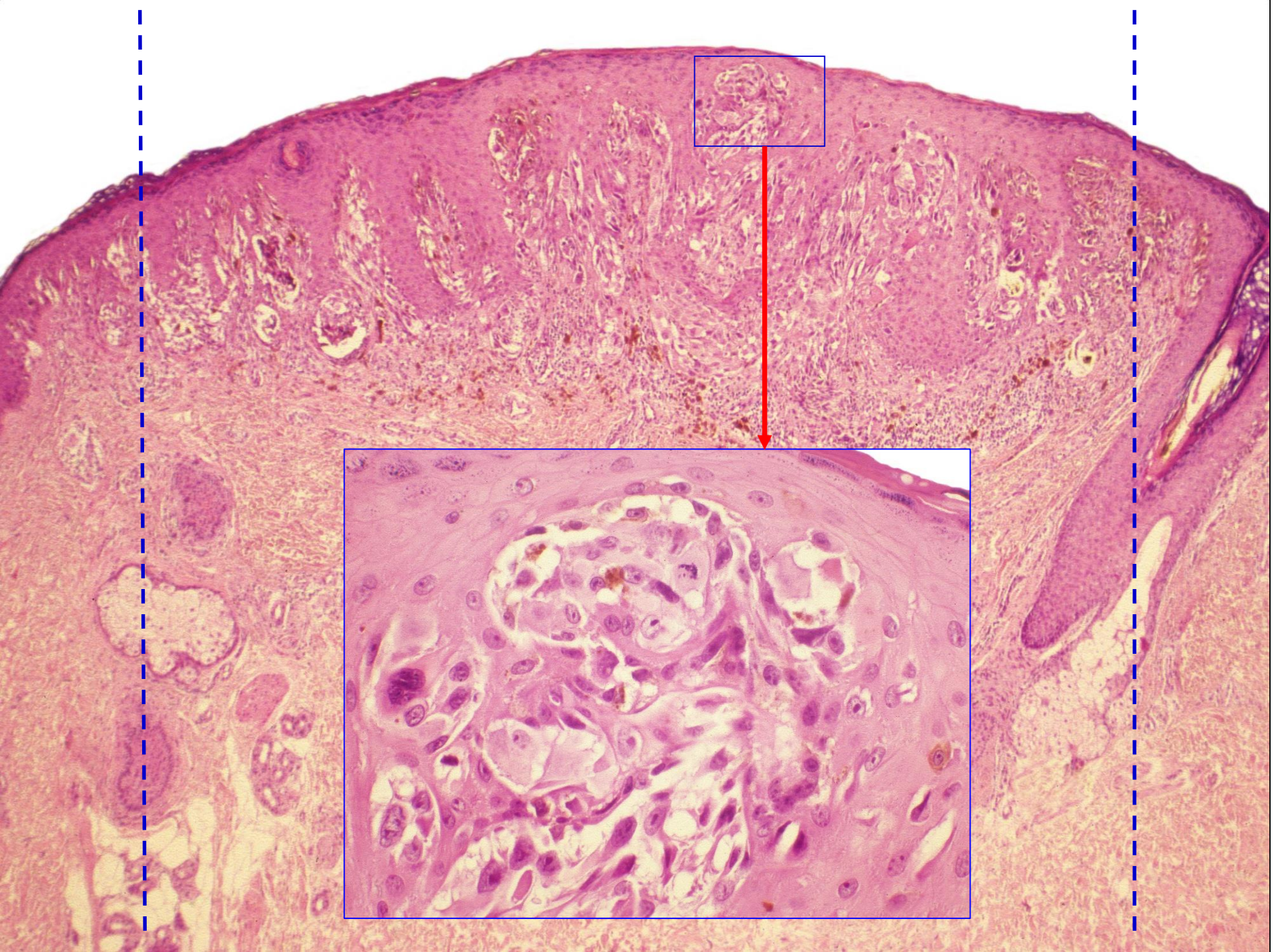
If, on the other hand, a peripheral rim of the specimen is cut off for margin control, one may cut into the tumor and sacrifice criteria that are crucial for histopathologic diagnosis.



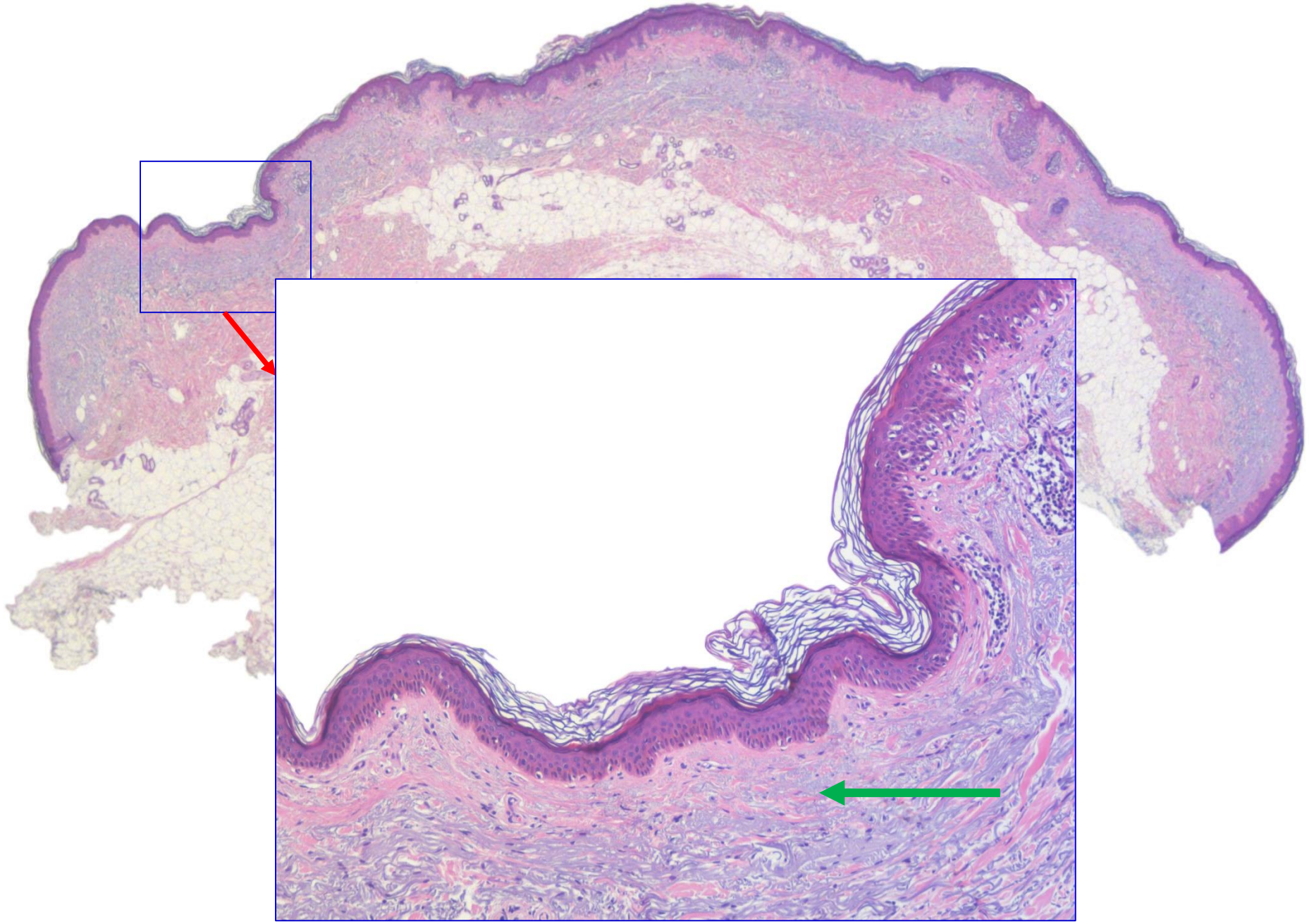
This is especially damaging in Spitzoid lesions because Spitz's nevi, such as this one, are composed of atypical melanocytes with mitotic figures scattered throughout the epidermis.



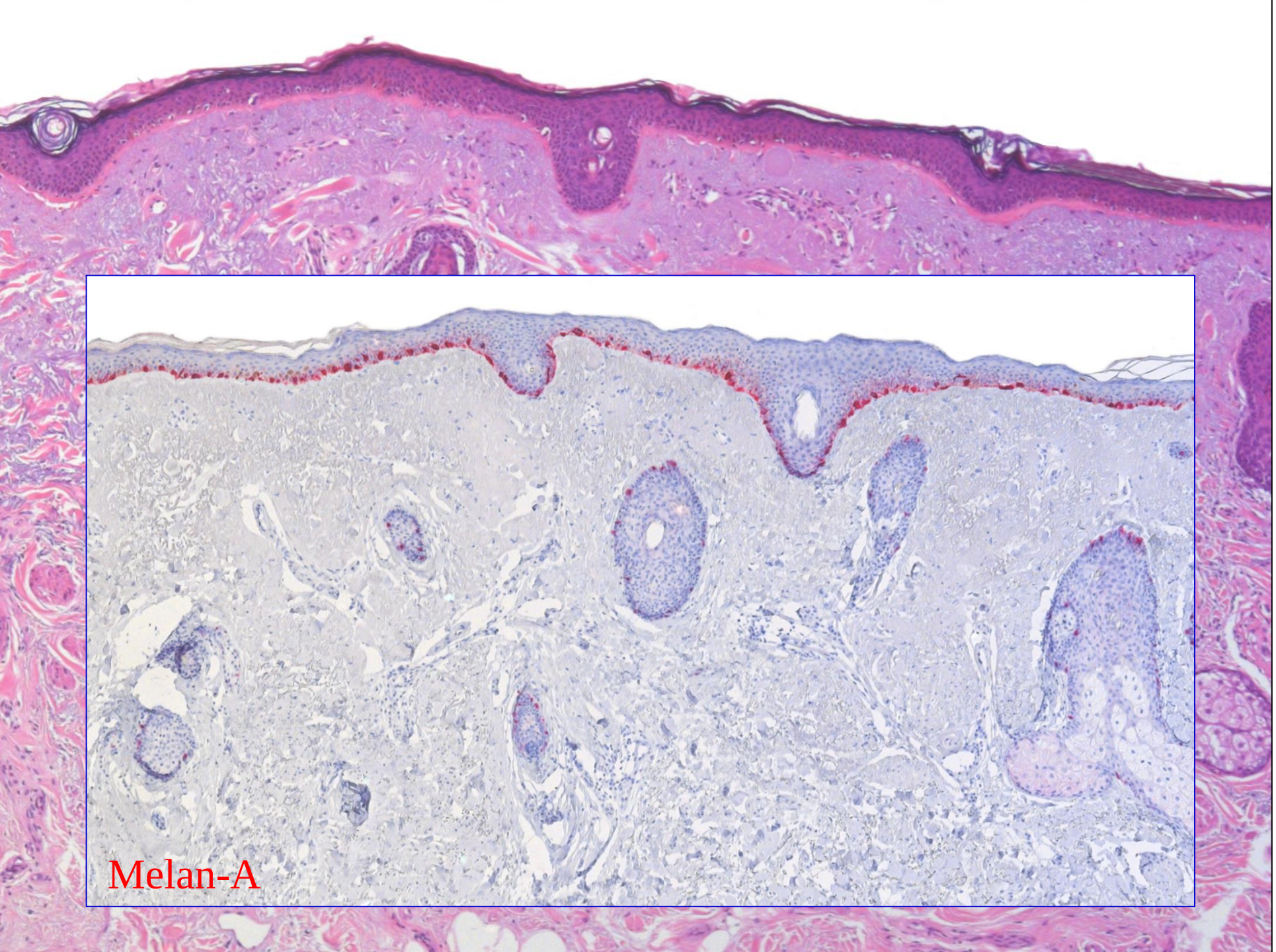
Only architectural features – small size, symmetry, and sharp circumscription – allow this lesion to be recognized as a nevus.



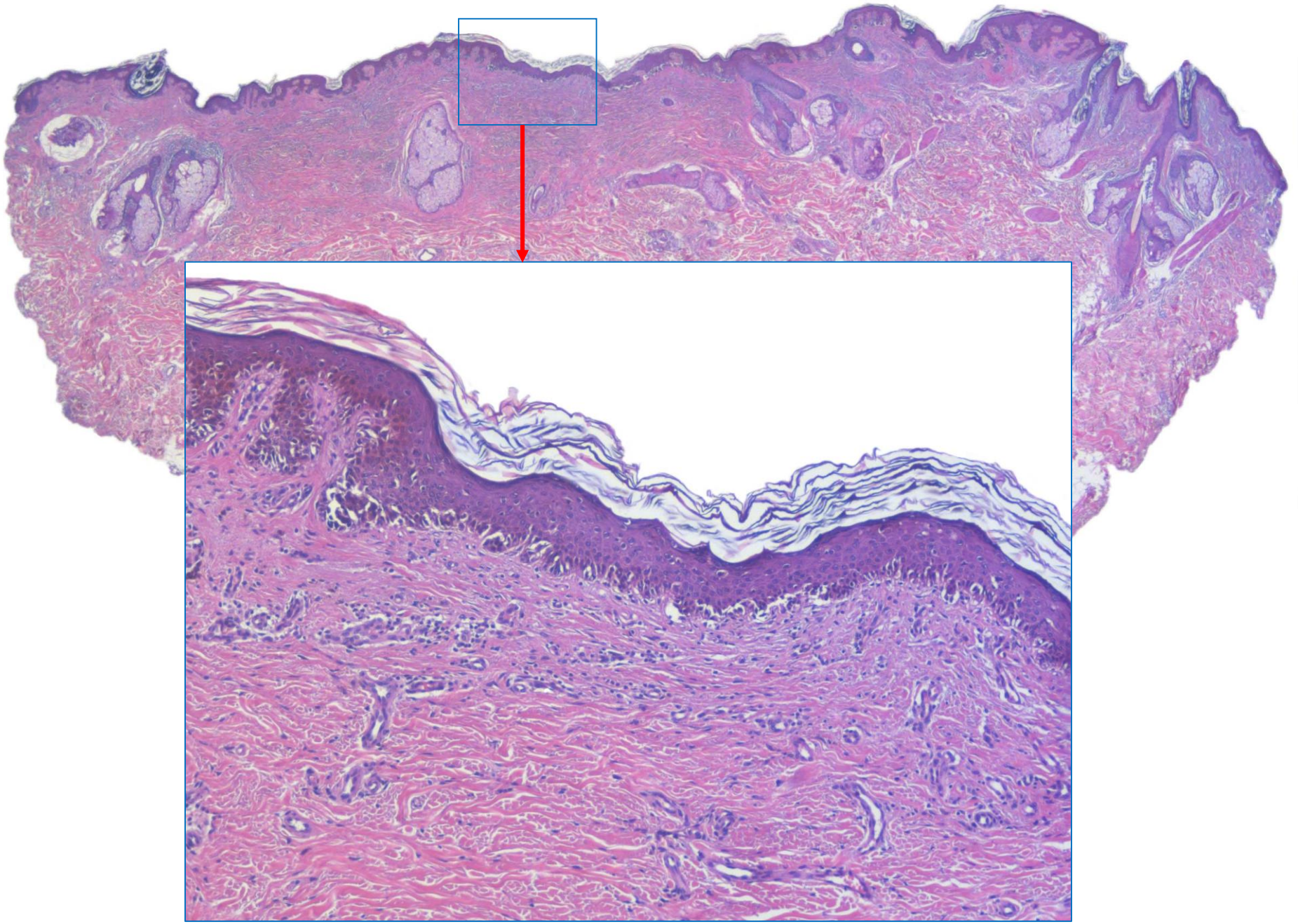
If the periphery had been sacrificed, it would probably have been diagnosed as melanoma.



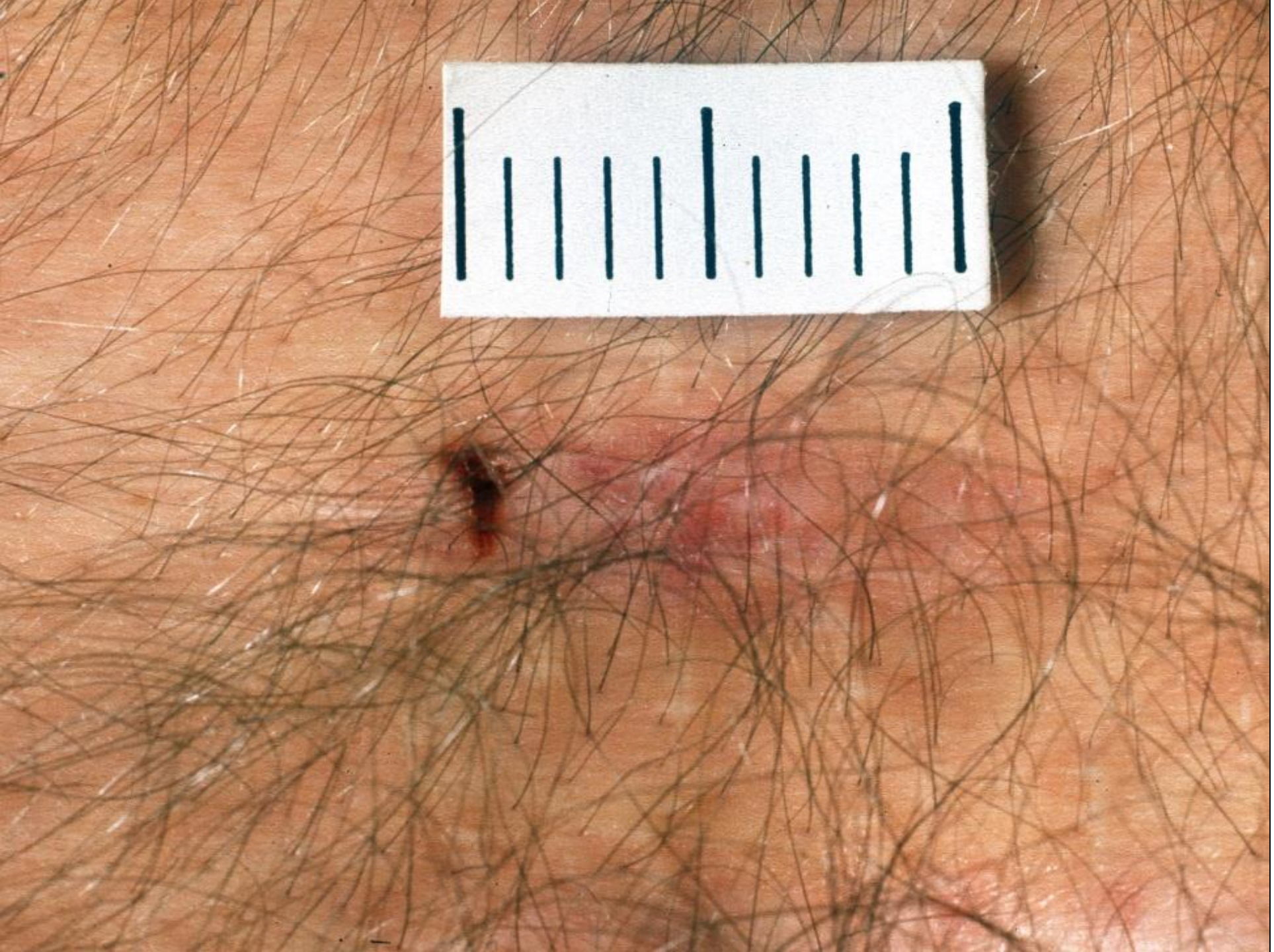
Assessment of the architecture also helps to identify the borders of melanoma. One of the most important criteria is a relatively sudden drop in the number of melanocytes that can be assessed readily in traverse sections.



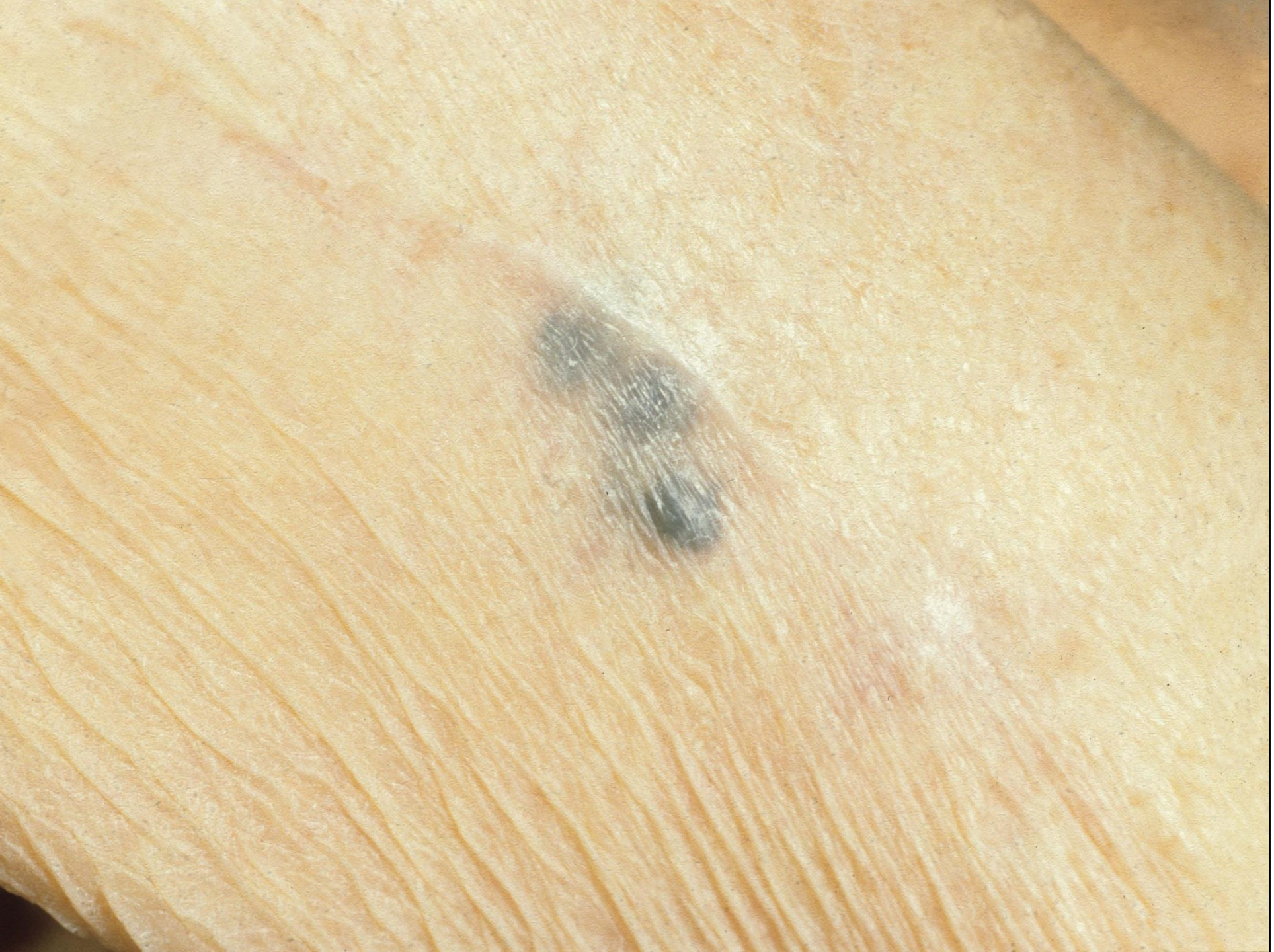
Peripheral sections do not reveal the relationship to the rest of the lesion, and it is much more difficult to decide whether or or not a slight increase in the number of melanocytes is still evidence of melanoma. In short, both methods have advantages and disadvantages, and none of them can guarantee safety, but there is no such thing as absolute safety.



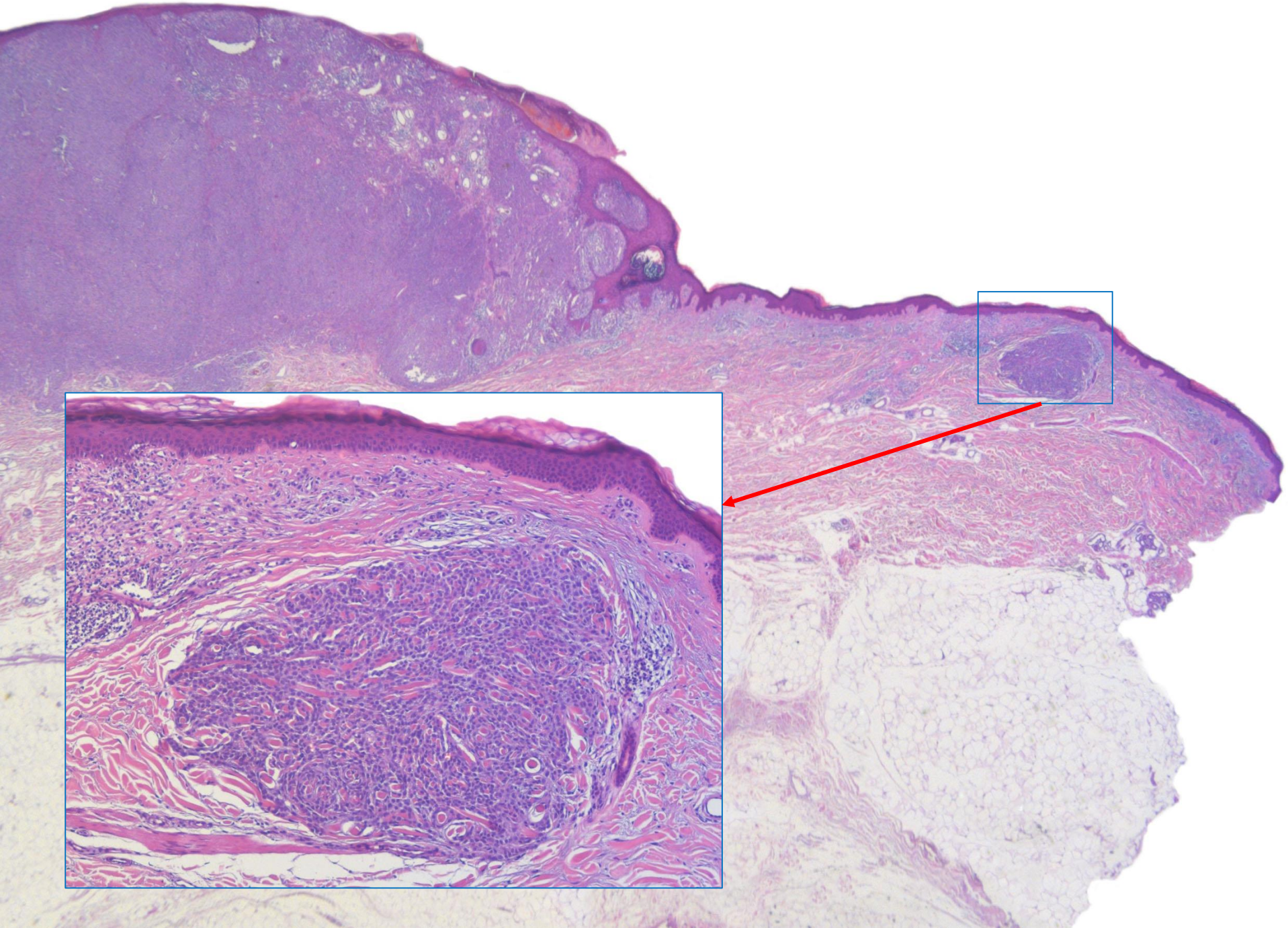
Fortunately, if something goes wrong and remnants of a melanoma persist, they are usually in an early in-situ stage, and when they regrow,



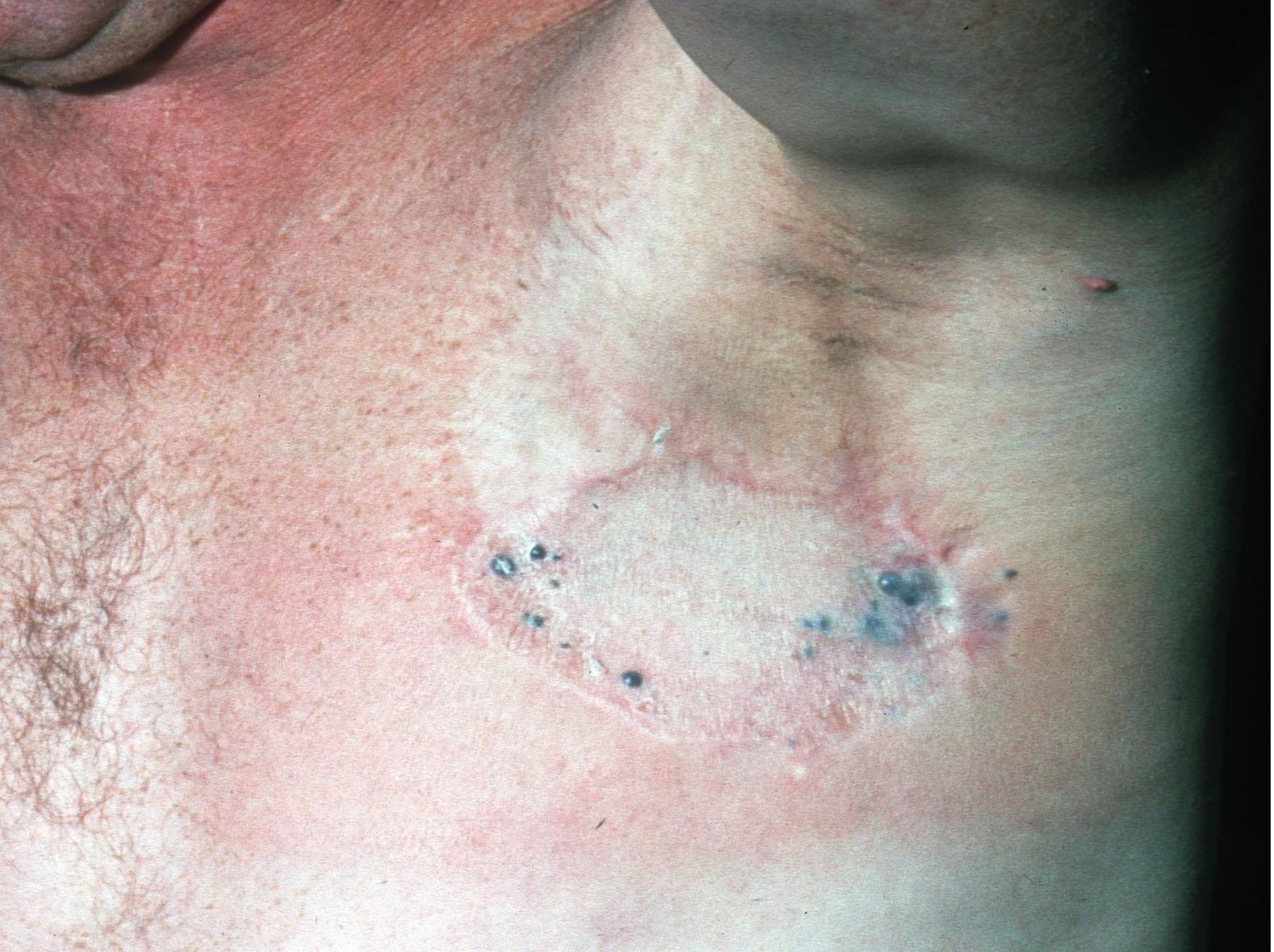
they usually call attention to themselves early-on through production of pigment. When recognized and excised at that stage, persistence of the lesion at the local site has no impact on prognosis.
In sum, in regard to local recurrence of melanoma, a distinction must be made between persistence of the primary tumor



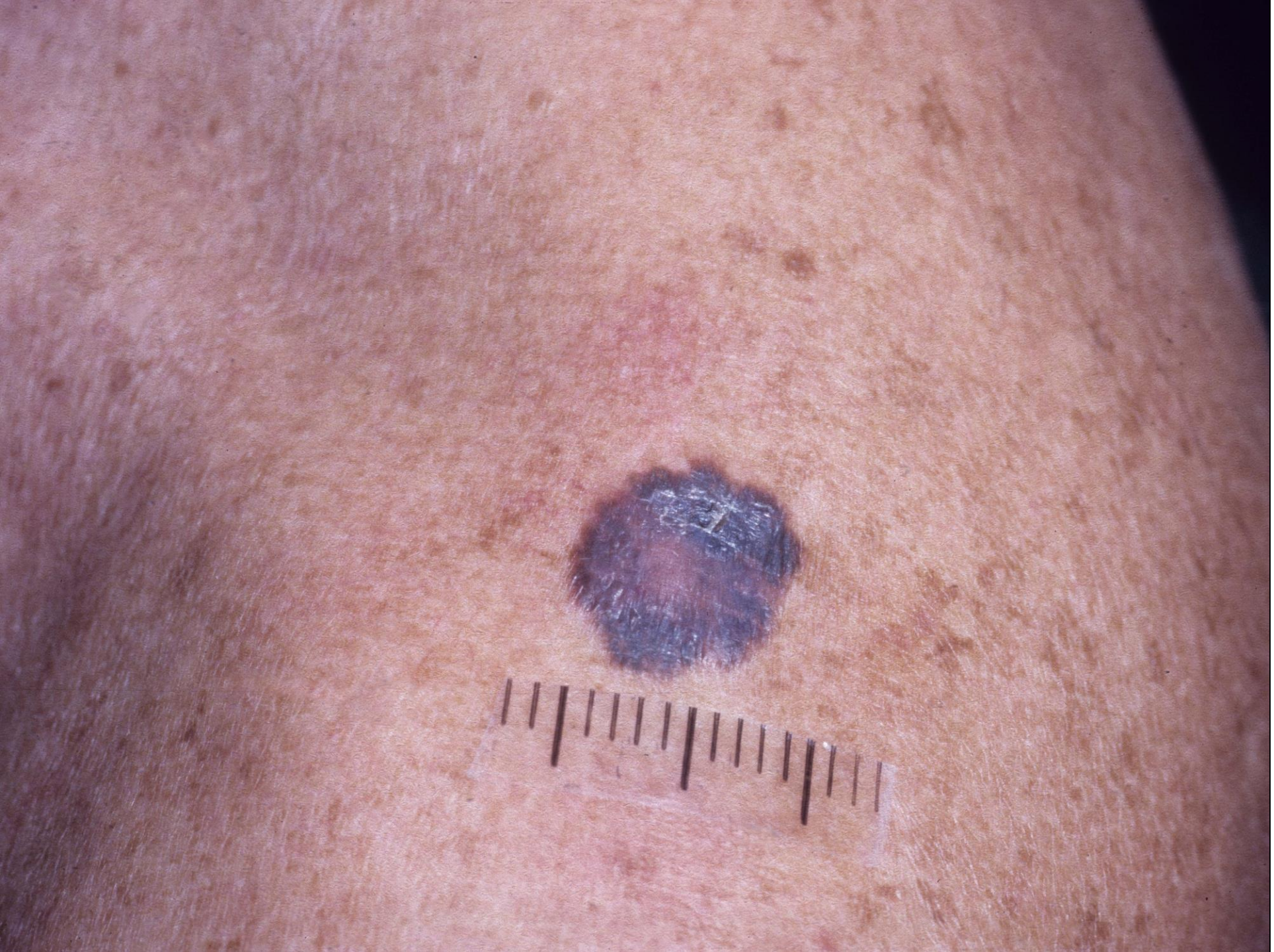
and satellite metastases.
This is not always easy,
neither clinically



nor histopathologically, if there are subtle signs of regression between the primary tumor and what seems to be a satellite metastasis. If there are metastases, they should be treated, but because they are rare and one does not know whether or where they may arise, it makes no sense to strive for removing occult metastases.



Even large exsicions do not prevent the development of further metastases, and survival is not determined by cutaneous metastases but by metastases in internal organs.



Excision of melanoma, therefore, can only aim at complete removal of the primary tumor. Tumor thickness is irrelevant for the margin of excision; the latter must be wide and deep enough to remove the tumor completely.

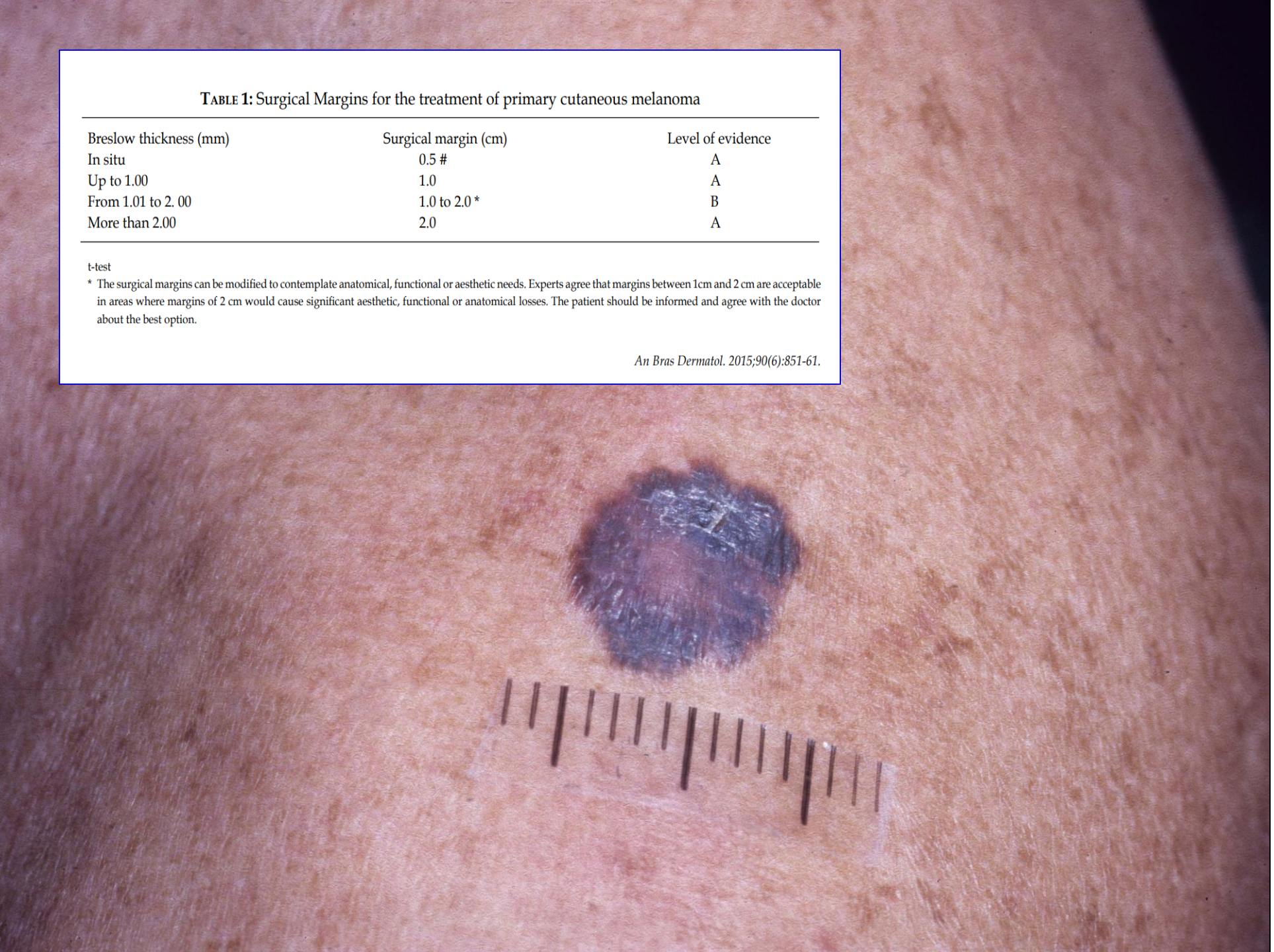
Table 1: Surgical Margins for the treatment of primary cutaneous melanoma

Breslow thickness (mm)	Surgical margin (cm)	Level of evidence
In situ	0.5 #	A
Up to 1.00	1.0	A
From 1.01 to 2. 00	1.0 to 2.0 *	B
More than 2.00	2.0	A

t-test

* The surgical margins can be modified to contemplate anatomical, functional or aesthetic needs. Experts agree that margins between 1cm and 2 cm are acceptable in areas where margins of 2 cm would cause significant aesthetic, functional or anatomical losses. The patient should be informed and agree with the doctor about the best option.

An Bras Dermatol. 2015;90(6):851-61.



The link between thickness and margins of excision is a relic of times passed, just as the concept of clinical safety margins. The latter are relevant only prior to excision of the neoplasm

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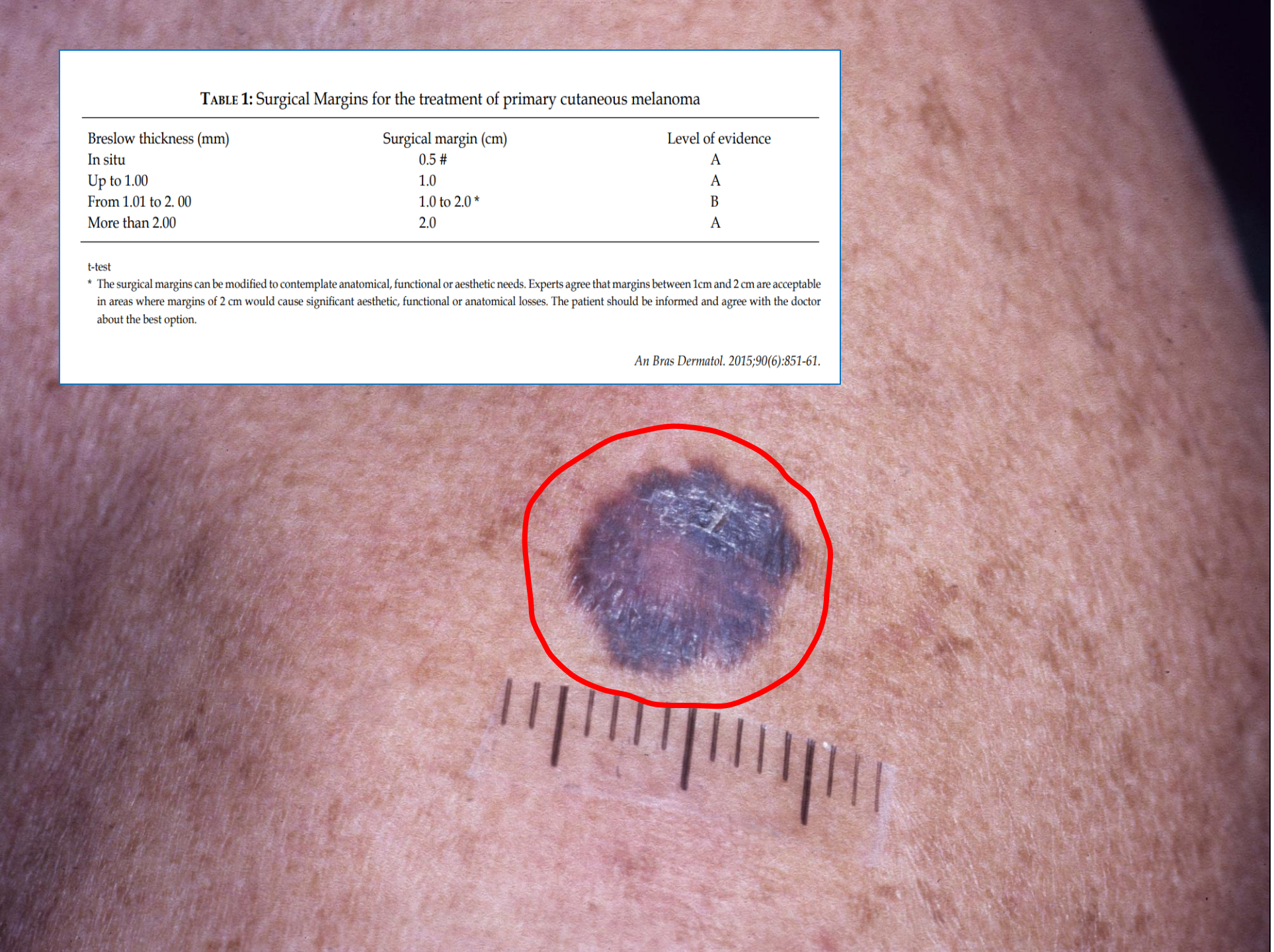

that should be done with a rim of clinically normal skin, but, subsequently, margins of excision must be assessed histopathologically, and in the future possibly by molecular techniques.

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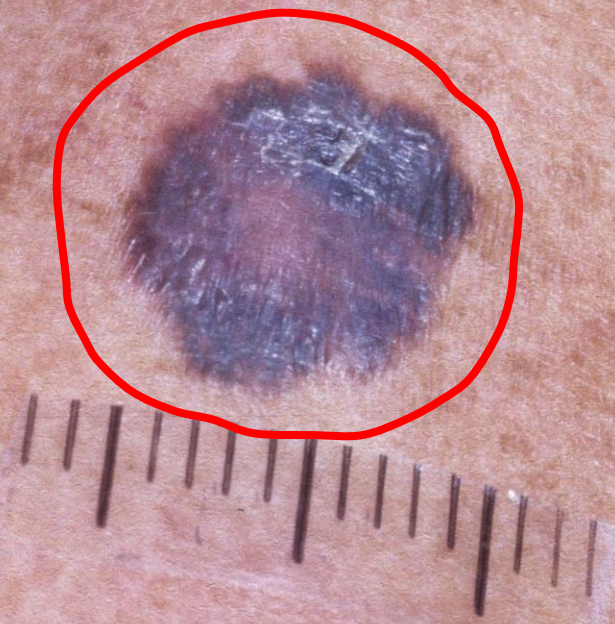

The clinical safety margins of former times were excessive, and for many melanomas this is still the case today, but reduction of them must also come to an end

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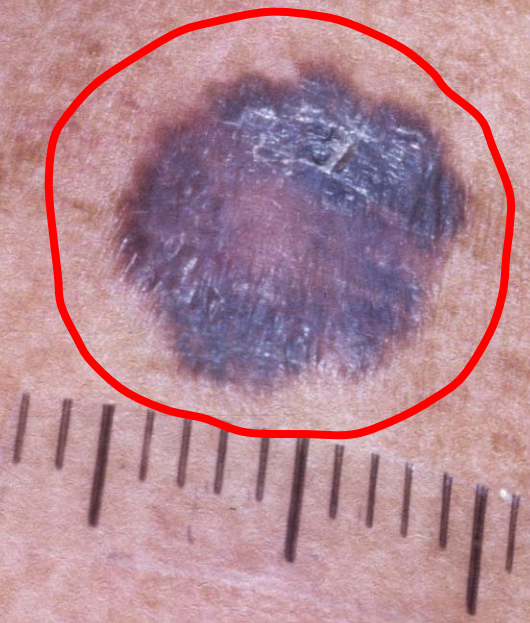

before it gets too tight.
The times of rigid margins of excision must be over; melanoma patients do not need off-the-rack clothes

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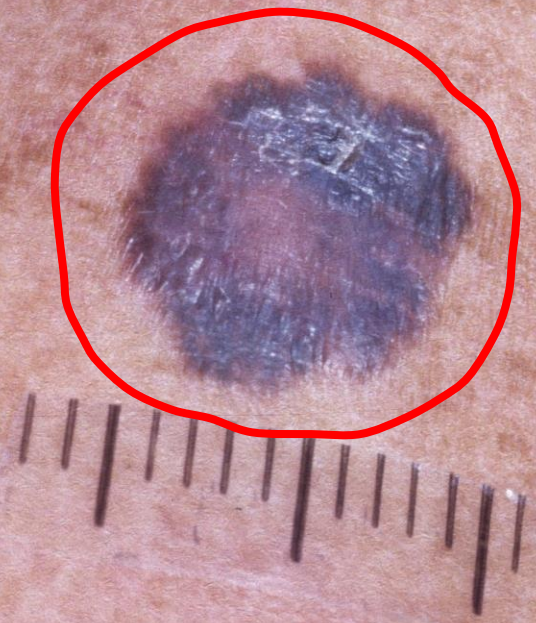

but a suit made-to-measure.

Melanoma treatment is currently a big construction site. New walls are erected at many spots,

Targeted Therapy for Melanoma Skin Cancer

These drugs target parts of melanoma cells that make them different from normal cells. Targeted drugs work differently from standard chemotherapy drugs, which basically attack any quickly dividing cells. Sometimes, targeted drugs work when chemotherapy doesn't. They can also have less severe side effects. Doctors are still learning the best way to use these drugs to treat melanoma.

BRAF inhibitors

Vemurafenib (Zelboraf) and **dabrafenib (Tafinlar)** are drugs attack the BRAF protein directly.

These drugs shrink or slow the growth of tumors in some people whose metastatic melanoma has a *BRAF* gene change. They can also help some patients live longer, although the melanoma typically starts growing again eventually.

MEK inhibitors

The *MEK* gene works together with the *BRAF* gene, so drugs that block MEK proteins can also help treat melanomas with *BRAF* gene changes.

The MEK inhibitors **trametinib (Mekinist)** and **cobimetinib (Cotellic)** have been shown to shrink some melanomas with *BRAF* changes. They are pills taken once a day. Common side effects can include rash, nausea, diarrhea, swelling, and sensitivity to sunlight. Rare but serious side effects can include heart damage, excess bleeding, loss of vision, lung problems, and skin infections.

Drugs that target cells with *C-KIT* gene changes

A small portion of melanomas have changes in the *C-KIT* gene that help them grow. These changes are more common in melanomas that start in certain parts of the body:

- On the palms of the hands, soles of the feet, or under the nails (known as *acral melanomas*)
- Inside the mouth or other mucosal (wet) areas
- In areas that get chronic sun exposure

Some targeted drugs, such as **imatinib (Gleevec)** and **nilotinib (Tasigna)**, can affect cells with changes in *C-KIT*. If you have a melanoma that started in one of these places, your doctor may test your melanoma cells for changes in the *C-KIT* gene, which might mean that one of these drugs could be helpful.

Immune checkpoint inhibitors

These newer drugs have shown a lot of promise in treating advanced melanomas. An important part of the immune system is its ability to keep itself from attacking normal cells in the body. To do this, it uses "checkpoints", which are proteins on immune cells that need to be turned on (or off) to start an immune response. Melanoma cells sometimes use these checkpoints to avoid being attacked by the immune system. But these drugs target the checkpoint proteins, helping to restore the immune response against melanoma cells.

and "targeted therapy" is the concept of the day. Depending on the genetic profile, one can choose between BRAF inhibitors, MEK inhibitors, drugs that target cells with C-KIT gene changes, and immune checkpoint inhibitors. How humiliating for dermatology that, in the era of beginning personalized medicine, nobody asks whether a melanoma is sharply or poorly confined!

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How humiliating that, after all those years, rigid margins of horizontal excision are still demanded and, above all, adjusted to vertical extent of the lesion! If one wants to build high walls, one should not neglect the foundation.