Melanoma Essentials

A Concise Guide

Edition 2.0

Melanoma Institute Australia

Melanoma Institute Australia

MELANOMA ESSENTIALS

A Concise Guide

Edition 2.0

Senior Editor

Jonathan R. Stretch

Editors

Alexander H.R. Varey

Joel Paul Smith

Annette H. Chakera

Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the editors, nor the publisher, nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete. Readers are encouraged to confirm the information contained herein with other sources. For example, and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this book is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

First edition published 2015; Second edition published 2018

Proof reading acknowledgment: Elizabeth Walton and Jim McBride

Reproduction and communication for educational purposes

Published in Australia by:

Melanoma Institute Australia
Poche Centre
40 Rocklands Road
Wollstonecraft
NSW 2065

National library of Australia Cataloguing-in-Publication data:

Melanoma Institute Australia
Melanoma Essentials - A Concise Guide
Edition 2.0
ISBN: 978-0-9924548-0-7

Table of Contents

Melanoma Institute Australia

Tap an entry to jump to it's corresponding chapter and section.

Please help us with your Feedback

Using This Book

The nature of the multitouch book format provides several interactive features that we hope will make this book more useful than traditional volumes.

The following pages demonstrate the unique interactive features, called widgets, that you will encounter.

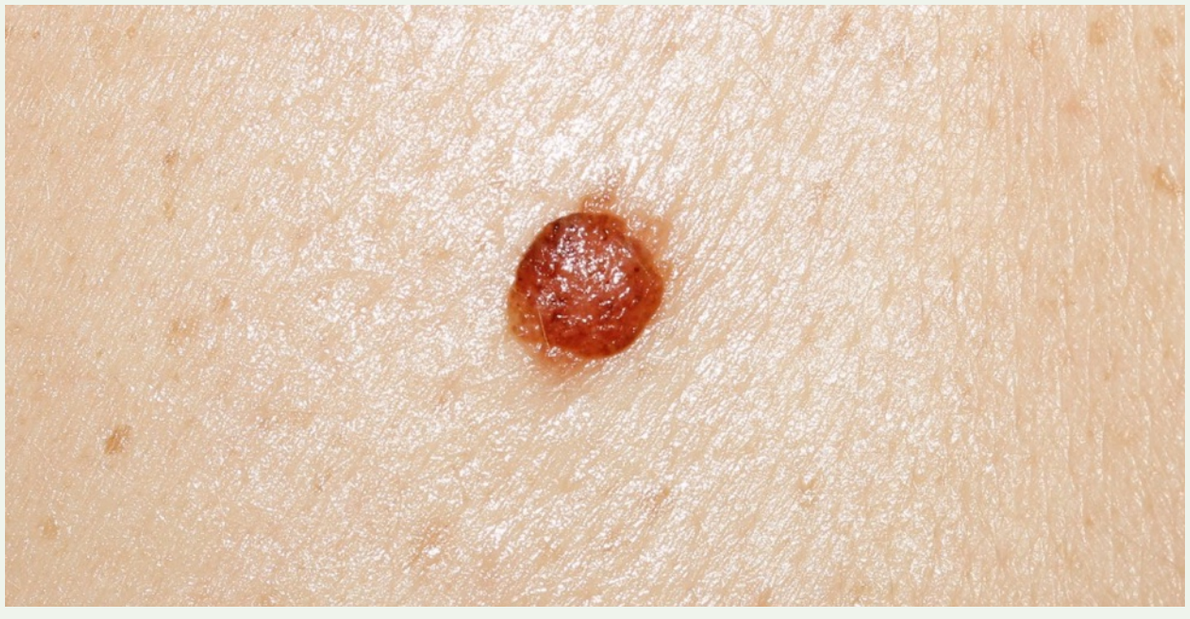
How does it work?

- Swipe your finger horizontally across the image to browse to the next image in the sequence.
- Pinch (spread two fingers apart) to scale gallery to fullscreen.
- Pinch again in the opposite direction (squeeze two fingers together) to leave fullscreen view.

Melanoma Institute Australia

Image Galleries

GALLERY EXAMPLE: CASE STUDY EXAMPLE

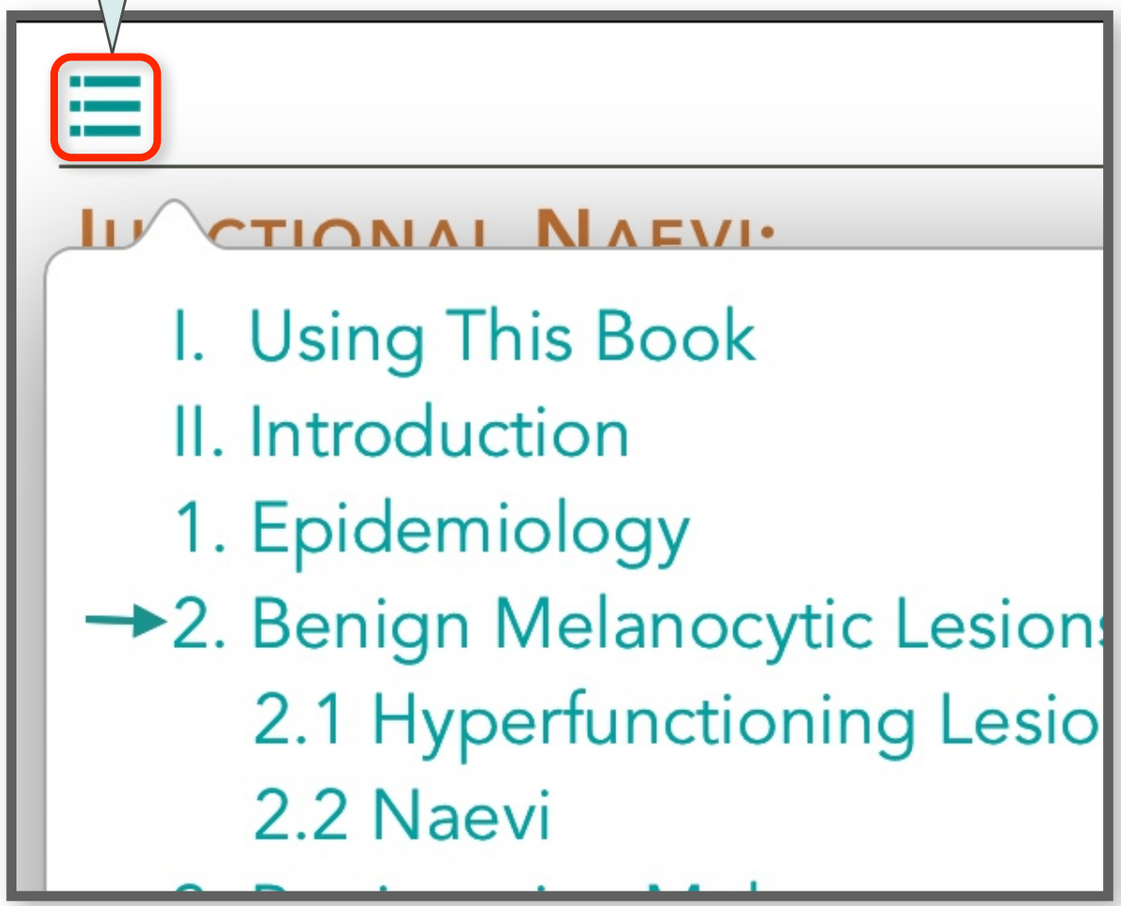


Benign dermal naevus

Navigation

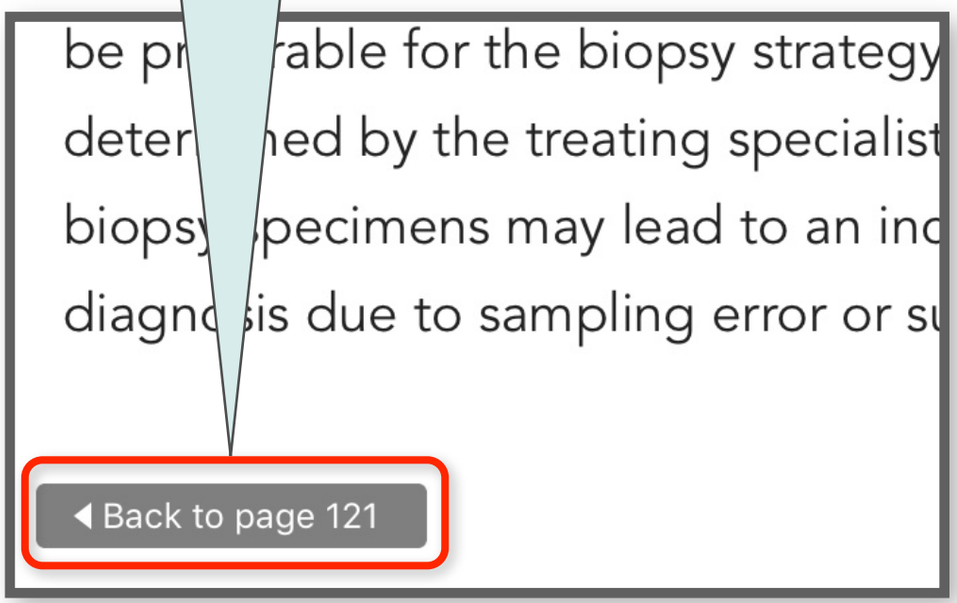
Table of Contents

- Tap on the icon in the upper left corner.
- Tap on the Chapter or Section you want.
- Arrow indicates current chapter.



Following a hyperlink

- Tap on the hyperlink.
- Return to your last location via the *Back to* overlay in the lower left.
- The *Back to* overlay appears for a few seconds after following a link.
- Tap anywhere once to recall the overlay after it disappears.

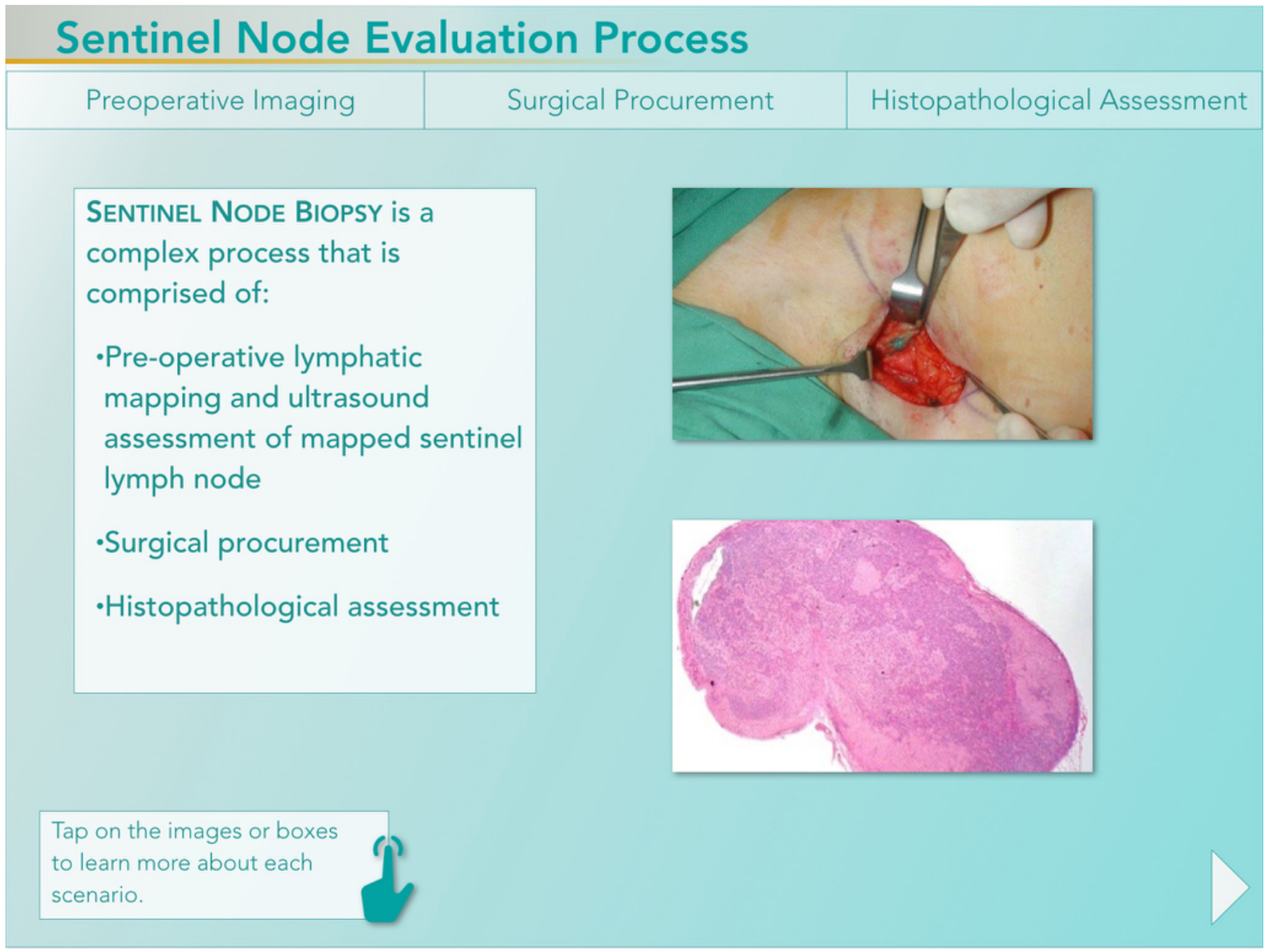


Interactive Presentations

Interactive presentations use the multimedia and interactive potential of the multitouch book format to create detailed ways to understand complex topics. They are used for providing academic understanding and as hands-on tools to help improve patient care.

How does it work?

- Tap a presentation to scale it to fullscreen.
- Tap buttons to navigate the presentation.
- Pinch again in the opposite direction (squeeze two fingers together) to leave fullscreen view.



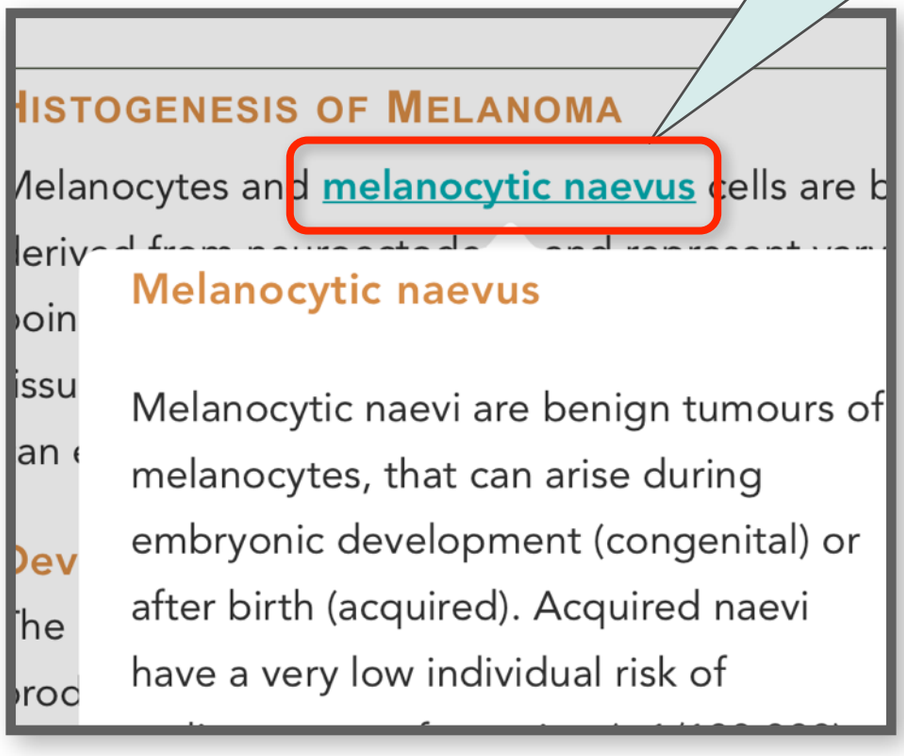
Glossary

The multitouch book format has a built-in glossary feature. This is a great tool for a medical book like Melanoma Essentials that lets the unfamiliar reader understand melanoma jargon quickly with only a short detour to reading.

The Glossary also has the ability to show related terms and articulate definitions visually where necessary.

How does it work?

- Tap on items with in the glossary term style.
- Scroll down the pop-up window to see all of the entry.
- Tap outside the pop-up window to dismiss.
- Example: Melanoma

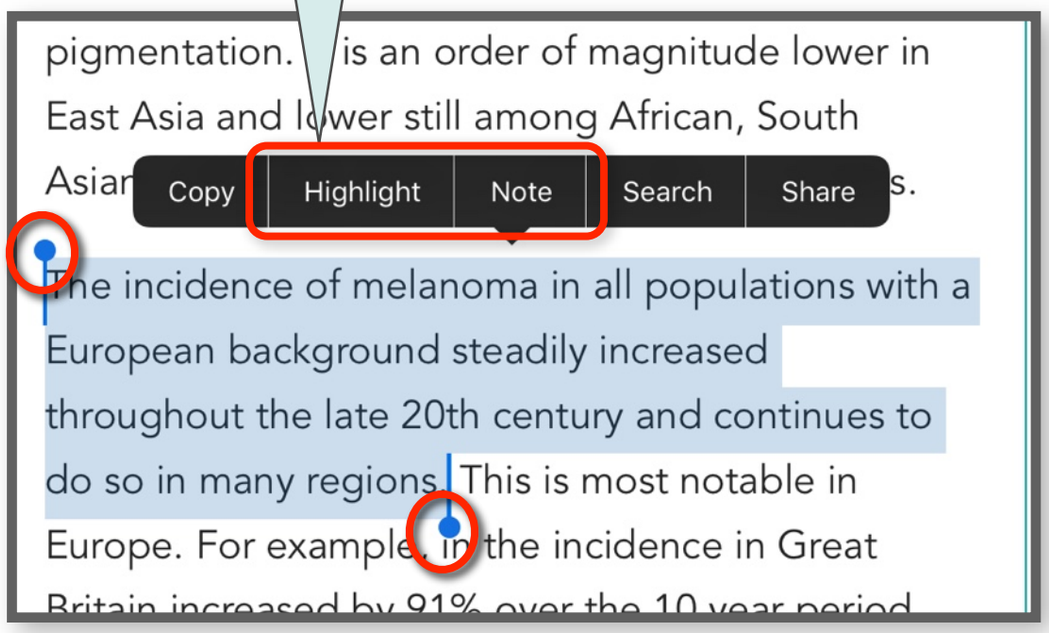


Highlighting & Notes

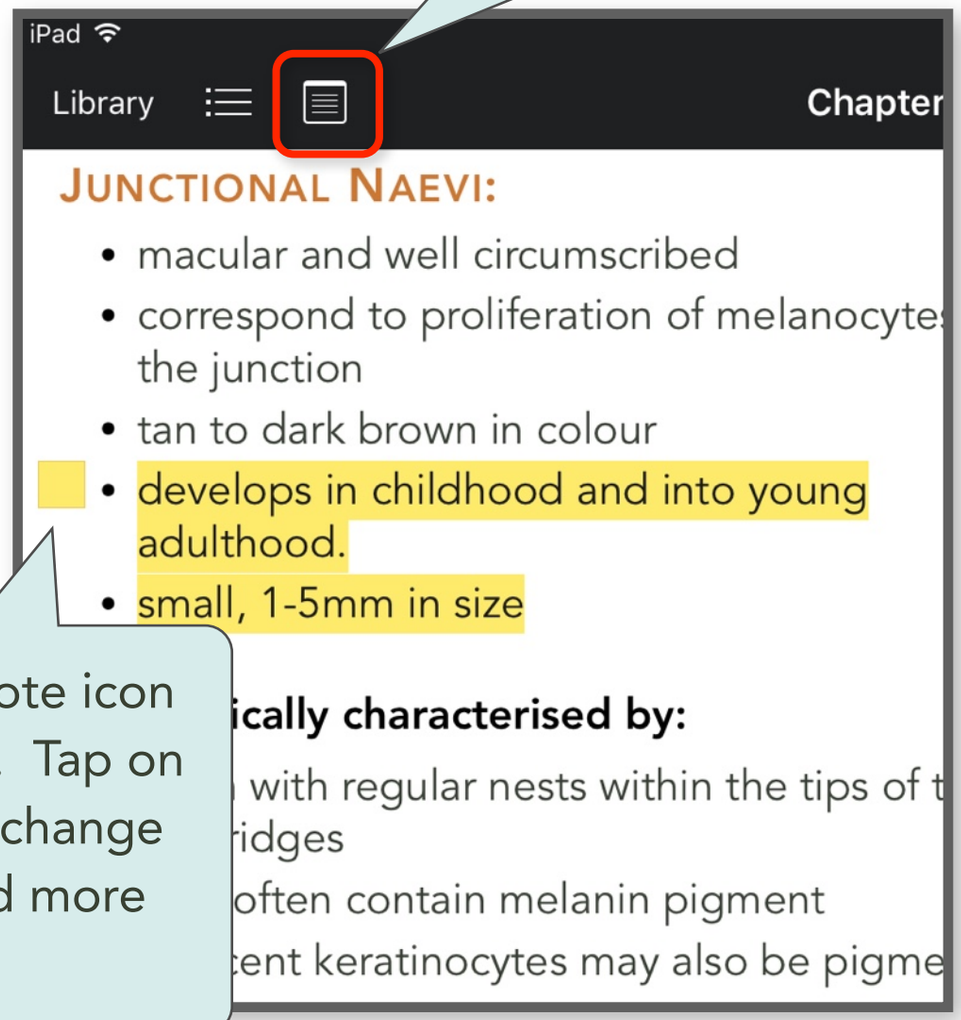
Highlights and Notes are the best way to make Melanoma Essentials a tool you can reference quickly. You can highlight relevant points in several colours with accompanying notes that are accessible in one collected index for quick reference.

How does it work?

- Double tap a word to select it.
- Drag blue selection handle around text.
- Tap Highlight or Note.



Tap here to see an index of all highlights and notes.



Tap on the note icon to read note. Tap on highlight to change colour or add more text.

Introduction

Melanoma is one of the commonest cancers of Caucasians; 4th overall in Australia, 5th overall in the UK and 6th overall in the USA. Furthermore, it is the commonest cancer of younger adults in these countries and consequently has a huge impact on young families and productive members of society. Accordingly, the disability adjusted life years attributable to melanoma in Australia in 2012 were 22,800, of which 17,200 were due to premature death.

This book aims to provide non-specialists with a concise and practical resource for the assessment and management of patients with suspected or confirmed melanoma. Therefore, the book has been designed to be easily readable by those not familiar with melanoma and its terminology, utilising illustrations and videos to provide clear explanations of key concepts. An additional, substantially more encompassing text, Melanoma; Principles & Practice, containing comprehensive detail across the entire spectrum of melanoma practice, will be published October 2016, also on the iBooks Store.

The Melanoma Institute Australia (MIA) clinicians practice under the evidence based Clinical Practice Guidelines published by the NH&MRC. The content presented here seeks to expand on that knowledge base and provide further practical information that will assist clinicians, trainees and associated personnel in understanding and confidently dealing with melanoma. This book will enable readers to gain a better understanding of the clinical management practiced at MIA, the largest melanoma treatment centre in the world.

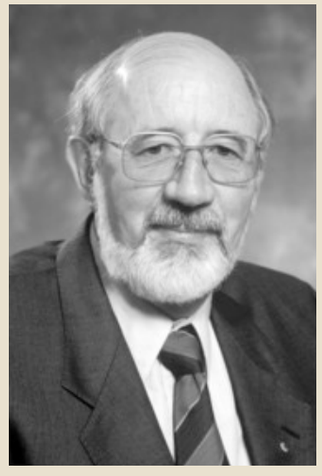
Melanoma Institute Australia

Melanoma Institute Australia (MIA) was established in 2008 to provide a world leading multidisciplinary cancer centre dedicated to **patient care, research and education**. The generous benefaction of Mr Greg Poche enabled this evolution of the **Sydney Melanoma Unit,** which was formed in the early 1960s by Dr Gerald Milton at Sydney Hospital and subsequently relocated to Royal Prince Alfred Hospital in 1982.

MIA is primarily located at the purpose built Poche Centre on the Mater Hospital campus in North Sydney, with additional activity at Royal Prince Alfred, Westmead and Royal North Shore hospitals. With over 50 years of leadership in the melanoma field, MIA remains the largest melanoma treatment centre in the world, treating over 1500 new melanoma patients per year. This unparalleled experience has been painstakingly documented in a prospectively maintained database of over 40,000 patients. This provides a unique research resource to underpin much of MIA's activity, which is strongly coupled to the University of Sydney and Macquarie University.

GERALD MILTON

FOUNDER & DIRECTOR
1962 - 1990



BILL MCCARTHY

DIRECTOR
1990 - 1996

JOHN THOMPSON

DIRECTOR
1996 - ONGOING

This book was produced by the Clinicians, Fellows and Associates of Melanoma Institute Australia.

Surgeons

John F Thompson AO MB BS MD FRACS FACS

Jonathan Stretch AM MB BS D.Phil (Oxon) FRACS

Robyn Saw MB BS MS FRACS

Andrew Spillane MB BS MD FRACS

Kerwin Shannon MB BS FRACS

Ken Lee MB BS FRACS

Michael Quinn MB BS FRACS

Brian McCaughan MB BS FRACS

Brindha Shivalingam MB BS FRACS

Michael Crawford MB BS M.Med FRACS

Sydney Ch'ng MB BS PhD FRACS

Omgo E Nieweg MD PhD FRACS

Medical Oncologists

Rick Kefford AM MB BS PhD FRACP

Georgina Long BSc PhD MB BS FRACP

Alex Guminski MB BS PhD FRACP

Peter Hersey MB BS FRACP D Phil

Alexander Menzies MB BS FRACP

Fran Boyle AM MB BS FRACP PhD

Matthew Carlino BMedSc MB BS FRACP

Radiologists

Louise Emmett BHB MB ChB MD FRACP

Roger Uren MD FRACP DDU

Dermatologists & Skin Diagnosticians

Pascale Guitera MD PhD FACD

Diona Damian MB BS PhD FACD

Scott Menzies MB BS PhD

Radiation Oncologists

Angela Hong MB BS MMed PhD FRANZCR

Gerald Fogarty BSc MB BS FRANZCR

Tim Wang MB BS(Hons) BSc MPH FRANZCR

Pathologists

Richard Scolyer BMedSci MB BS MD FRCPA FRCPath(UK)

Stan McCarthy AO MB BS FRCPA FFOP

Geoff Watson MB BS FRCPA

Translational Research

Graham Mann MB BS FRACP PhD

Nicholas Hayward PhD

Helen Rizos BSc(Hons) PhD

Lymphoedema Therapists

Teresa Lee PhD BAppSci(Physio)(Hons)

Carol Morris M.Phty BSc Dip Sports Therapy

Ocular Melanoma

Michael Giblin MB BS(Hons) FRACO FRACS

Fellows

The following recent **Fellows** have made a significant contribution to this book:

Annette Chakera MHealthSci MMed PhD (Denmark)

Alexander Varey MB ChB FRCS(Plast) PhD (United Kingdom)

Ricardo Vilain MB BS(Hons) BSc(Hons) PhD FRCPA (Australia)

Rebecca Read BSc(Hons) MB BS DPhil FRACS (Australia)

Lilian Rocha MD (Brazil)

Helena Collgros MD (Spain)

Deborah Bourke MB BS MRCS(Eng) MD
(United Kingdom)

Philip Brackley BSc BMedSci PhD BM BS
FRCS(Plast)
(United Kingdom)

Jonathan Duncan BSc MB ChB MRCS(Ed) MD
(United Kingdom)

Alastair MacKenzie Ross BChir MB MA MD
FRCS(Plast)
(United Kingdom)

Jong Kim MB ChB PhD MSc(Psych) FRCS(Plast)
(United Kingdom)

Kieran Power MB BCh BAO BMedSci MScSurgSci
FRCS(Plast)
(Ireland)

Hidde Kroon MD PhD
(Netherlands)

Megan Lyle MB BS FRACP
(Australia)

Melanoma Institute Australia

Multidisciplinary Care, Research and Education

The Institute's weekly Multidisciplinary Meeting

The Institute's clinicians and researchers have met almost every Friday morning since the early 1960's when the original group was formed by Gerry Milton as the Sydney Melanoma Clinic.

The meeting has now evolved to comprise a range of specific agendas including:

- research
- morbidity & mortality
- clinical activity
- trial enrolment
- biospecimen acrual
- journal club

Patient Management is always at the forefront of these activities.

Melanoma Institute Australia (MIA) is an entirely independent entity, which is registered as a *not for profit* company, that is lead by its senior clinicians and research members. Guidance is provided by a board of directors that is predominantly drawn from the community.

MIA provides the fundamental infrastructure to support the management of the patient caseload. This includes informatics and database services, clinical trials unit, biospecimen banking, laboratory support and a broad range of educational programs for clinicians, researchers and the general public.

Direct patient care is provided by the Institute's affiliated clinicians within their own individual practices. These are located in the Poche Centre and at other sites within metropolitan Sydney, including Royal Prince Alfred, Westmead and Royal North Shore hospitals.

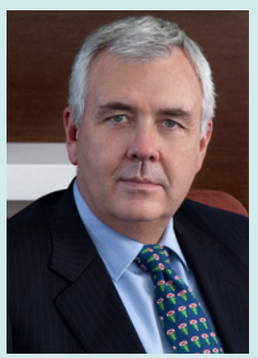
The Board

Reg Richardson AM
Chairman

Garry Sladden
BBus, CPA, FINSA

Jennifer Elliott
Chair, Finance Committee

John Thompson AO
Executive Director



Jonathan Stretch AM
Deputy Director

GREG POCHE AO is a philanthropist, who has with extraordinary generosity, supported Melanoma Institute Australia. Understanding the substantial impact of melanoma on Australian society, Greg Poche personally committed $40M to fund the construction of a comprehensive facility for melanoma research and patient care. Following his initial donation he has continued to generously support the Institute.

His further intent, is to promote giving by others and thereby benefit society generally. Greg Poche's commitment to Melanoma Institute Australia represents the greatest gift by an Australian to a single cause in our nation's history.

He has separately developed initiatives to promote the health of Indigenous Australians. Throughout these projects, Greg Poche has been supported by his wife Kay and guided by his great friend Reg Richardson AM.

1

Epidemiology

REBECCA L. READ GRAHAM MANN

Key Points

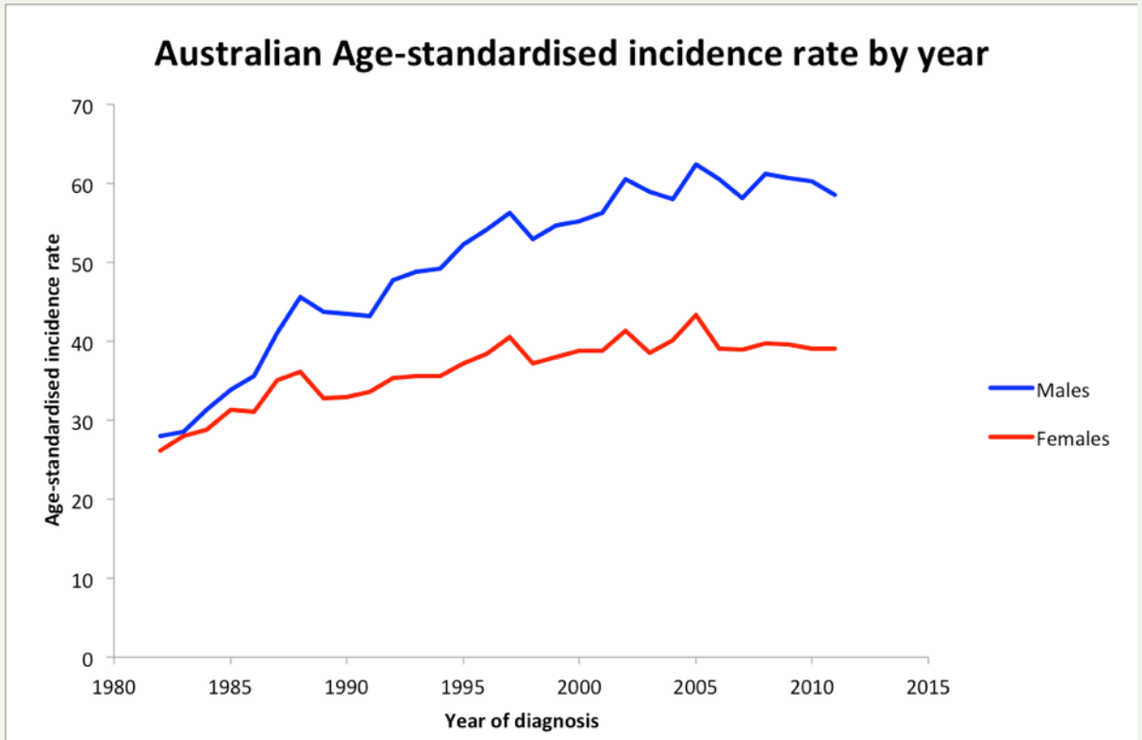
- The incidence of melanoma exhibits extreme global variation.
- Genetic and environmental factors interplay - especially skin type and UV exposure.
- Melanoma most prevalent in Caucasian populations with high UV exposure eg, Australia/New Zealand.
- Sunburn and sunbed use, especially during childhood/young. adulthood, increase melanoma risk substantially.

Incidence and Mortality

On the global stage, melanoma is relatively uncommon with approximately 200,000 new cases reported each year, accounting for 49,100 deaths in 2010. Australia and New Zealand experience the highest rates of melanoma in the world, where lifetime risks to age 85 are currently 4.3% for women and 7.0% for men. Melanoma incidence falls by a factor of 4 to 5 from North-Western to South-Eastern Europe, due largely to ethnic differences in pigmentation. It is an order of magnitude lower in East Asia and lower still among African, South Asians and other heavily pigmented populations.

The incidence of melanoma in all populations with a European background steadily increased throughout the late 20th century and continues to do so in many regions. This is most notable in Europe. For example, in the incidence in Great Britain increased by 91% over the 10 year period between 1998 and 2007 (Figure 1.1). In contrast, it is encouraging to see that the melanoma rates are stabilising in Australia, New Zealand, North America and Norway, suggesting that strategies for

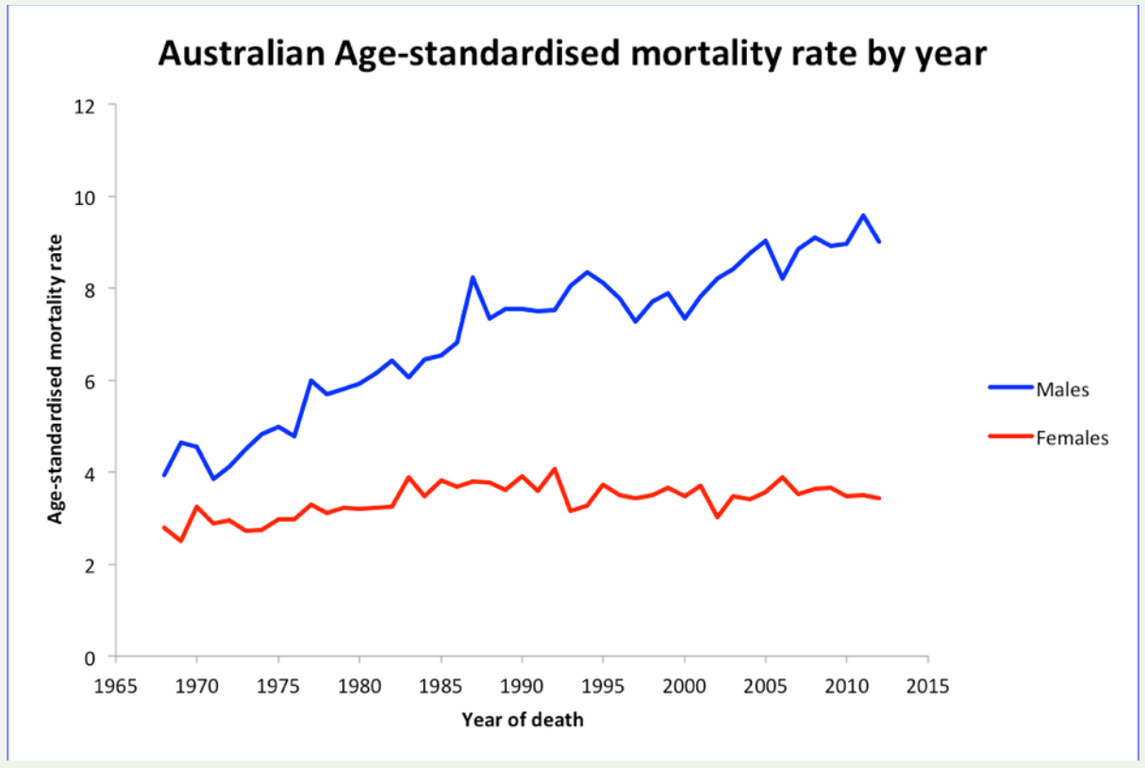
Figure 1.1 Melanoma Incidence Rates



Australian melanoma incidence can be seen to be reaching a plateau amongst both men and women. However, the incidence is still 1.5 fold higher in men than women.

improved primary prevention may be having a beneficial effect. In addition, the continued increase in incidence in many regions in part represents an increase in the diagnosis of thin melanomas with better prognosis. Melanoma specific mortality has also increased over recent decades, with a global rise of 58.4% between 1990 and 2010. However, the rises in incidence and mortality have diverged, as is clearly demonstrated in both Australian and UK/ British data (Figure 1.2) and is indicative of improved survival. This may be attributed to the early detection and timely treatment of thinner melanomas (secondary prevention) though direct evidence for this is lacking.

FIGURE 1.2 MELANOMA SPECIFIC MORTALITY RATES



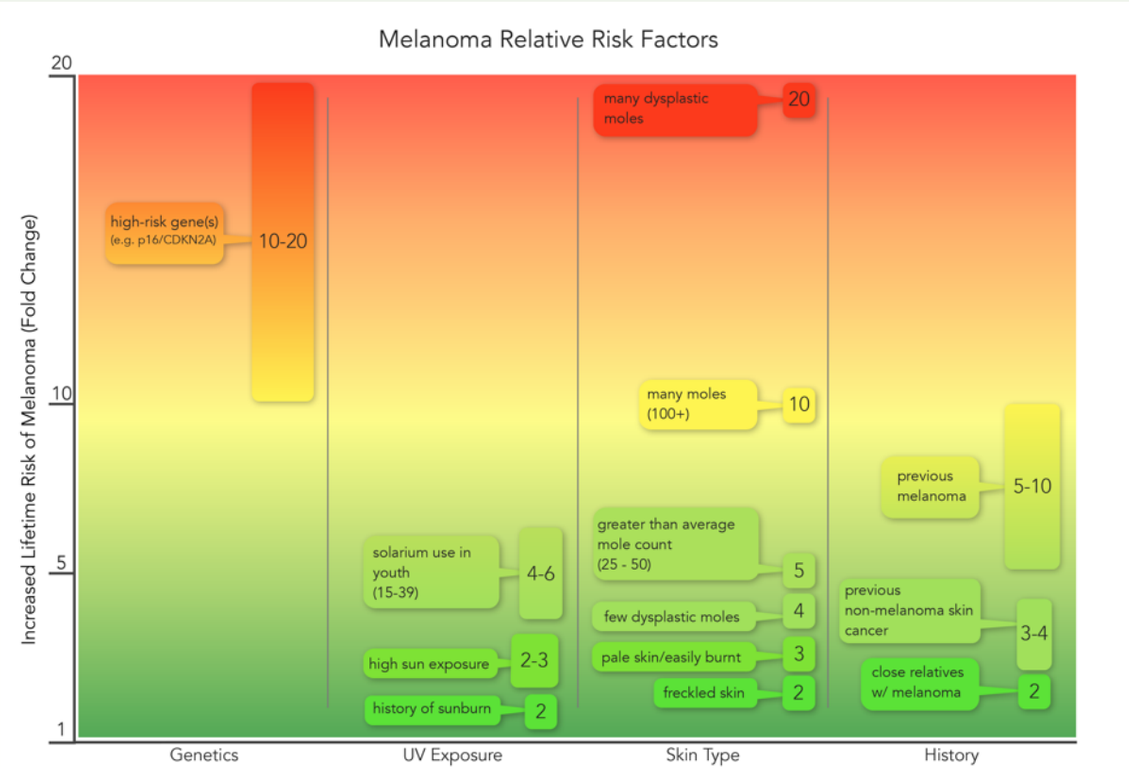
Female melanoma mortality rates in Australia have been stable for several decades, despite a rise in incidence. However, male mortality rates have been steadily rising, although this trend is possibly slightly slowing in recent years.

RISK FACTORS

A person's risk of developing melanoma is based on factors that are non-modifiable (such as age, gender and genetic predisposition) and those that can be altered by changes in behaviour (such as UV exposure). Population-based studies have defined the major risk factors for melanoma (Figure 1.3), which were well summarised by Gandini and colleagues in 2005. These authors performed

systematic meta-analyses of the effect on melanoma risk of the following variables: common and atypical naevi, sun exposure and family history, actinic damage and other skin phenotypes.

FIGURE 1.3 RISK FACTORS FOR MELANOMA



The chart depicts the relative risk associated with each of the various factors that are known to increase the risk of developing a melanoma.

AGE AND SEX

Although the incidence of melanoma increases with age, melanoma affects many young patients in the midst of their working lives. Melanoma in 2011 was the third highest cancer risk for Australian men and women, the fourth most common cancer overall, and the most common cancer among men aged 15-49, and women aged 15-29. The burden of melanoma and its social impact, particularly that of premature death, is best captured by years of potential life lost (YPLL). Recent US data demonstrated the overall YPLL from melanoma to be 20.4 years (males 19.0 years, females 21.4 years). This compared to 16.6 years for all cancers, 15.3 years for colorectal cancer, 16.7 years for lung and bronchial cancers, 9.9 years for prostate cancer and 20.3 years for female breast cancer.

On a global scale melanoma affects men and women relatively equally but interesting differences

are seen across continents. In Australia melanoma is 1.5 times more common in men than women (Figure 1.1). In contrast, in many European populations melanoma is more common in women. Sex also influences clinical outcome. Men are known to present with less favourable primary tumour characteristics and being a man remains an additional independent predictor of poor outcome. The reason for this imbalance is yet to be fully established.

Having had a previous skin cancer is an under-appreciated risk factor for melanoma, with an increased risk of up to ten-fold in the first few years after diagnosis of a first melanoma. Previous non-melanoma skin cancer (SCC or BCC) increases melanoma risk four-fold.

Genetic Factors

These are the primary genetic risk factors contributing to a melanoma risk profile.

Pigmentation

The variation in the incidence of melanoma between ethnic groups is largely accounted for by variation in skin type, which is genetically determined. Patients with red/blond hair and fair skin that always burns and never tans (Fitzpatrick Type I) are the most likely to develop melanoma, given the same sun exposure. Red hair and fair skin are largely caused by natural variants of the melanocortin 1 receptor (MC1R). In most people, activation of the MC1R receptor stimulates melanocyte production of the brown/black pigment eumelanin. In contrast, people with red hair have variants of the receptor that lead to the production of red-yellow phaeomelanin, which has weaker UV-absorbing properties.

Naevi

The total number of common naevi on the body is an important risk factor for the development of melanoma. People with more than 100 common naevi have a 7-fold increased risk of developing melanoma when compared to patients with <15 common naevi. The presence of atypical (or dysplastic) naevi is also an independent risk factor for melanoma. Patients with ≥5 atypical naevi have a 6-fold increased risk of developing melanoma. Both total naevus count and the number of atypical naevi are under genetic influence, which is amplified by sun exposure.

Familial

All these risk factors can lead to clustering of melanoma in families. A history of melanoma in a first-degree relative approximately doubles a person's lifetime risk and about 10% of people with melanoma will have at least one affected first degree relative. Genome-wide studies are elucidating the common genetic variants responsible for melanoma across the population. Many of these variants increase the risk of melanoma through their effects on pigmentation, naevus number and sun-sensitivity, but not all.

A few family clusters are associated with an inherited, high-penetrance mutation in the CDKN2A gene, or much more rarely CDK4. Such mutations are more likely if more relatives are affected, if more of them have had multiple primaries, or if pancreatic cancer or neural tumours are also present. CDKN2A encodes two proteins, p16INK4A and p14ARF, that regulate the G1-S transition in the cell cycle via Cyclin (CDKs 2,4,6) inhibition. Carriers of these mutations do not have a distinctive phenotype, but are more likely to have multiple naevi than non-carriers do.

Environmental Factors

These are the primary environmental factors contributing to a melanoma risk profile.

Pattern of UV exposure

Solar and artificial sources of UV radiation (including UVA, UVB and UVC) are known to be carcinogenic to humans and are the principal causes of melanoma. There is strong evidence for a link between sunburn (RR 1.6) and intermittent (or recreational) sun exposure and the development of melanoma. While childhood and adolescence is the most important period, total exposure throughout life affects risk. In contrast to actinic sun damage and squamous cell carcinoma, chronic and occupational exposures are only weakly associated with melanoma, if at all.

Geography

The east coast of Australia exemplifies the way in which geographic location influences ambient UV exposure and consequently the incidence of melanoma. Melanoma rates in men in Queensland, New South Wales and Victoria were 55.8, 38.5 and 27.3 per 100,000 respectively (1998-2002), demonstrating an increase in melanoma incidence with decreasing latitude. However, the highest rate of melanoma is found in the coastal corner of southeast Queensland indicating that lifestyle also contributes to melanoma risk.

Sunbeds

The use of artificial sources of UV radiation for tanning is associated with a significant increase in the risk of developing melanoma. The risk of melanoma increases with the number of sun bed sessions and their use at earlier ages. People using sun beds before 35 years of age have an average 1.9-fold increased risk of developing melanoma,

with an even greater risk in the early decades of life. In Australia, sunbed use before 30yrs age was estimated to increase melanoma incidence five–fold. It was estimated that 75% of melanomas diagnosed before age 30 in this group of patients were attributable to the sunbed exposure. These findings have led to bans on the commercial use of tanning devices in several countries including Australia, Brazil and some US states.

Immunosuppresion

Immune suppression, such as in the setting of solid organ transplant or human immunodeficiency virus (HIV), results in an increased risk of cutaneous malignancy, and squamous cell carcinomas are particularly common. Australia-wide data from all classes of transplant recipients show a 2-4-fold increased risk of melanoma, as well as poorer survival.

Citations and Further Reading

1. Boniol M, Autlier P, Boyle P, Gandini S. Cutaneous melanoma attributable to sunbed use: systemic review and meta-analysis. 2012. BMJ, 345:e4757.

2. Buettner PG, MacLennan R. Geographical variation of melanoma in Queensland. Aust JRural Health 2008; 16(5): 269-77.

3. Erdmann F, Lortet-Tieulent J, Schüz J, Zeeb H, Greinert R, Breitbart EW, Bray F. International trends in the incidence of malignant melanoma 1953-2008--are recent generations at higher or lower risk? 2013. Int J Cancer. 132(2):385-400.

4. Familial Atypical Multiple Mole Melanoma Syndrome Cancer Syndromes [Internet]. Riegert-Johnson DL, Boardman LA, Hefferon T, et al., editors. Bethesda (MD): National Center for Biotechnology Information (US); 2009-. Dara Eckerle Mize, MD, Michele Bishop, MD, MMSc, Erin Resse, MD, and Jason Sluzevich, MD.

5. Ekwueme DU, Guy GP, Li C, Rim SH, Parelkar P, Chen SC. The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity – United States, 2000-2006. 2011. J Am Acad Derm. 65, s113. e1-12.

6. El Ghissassi F, Baan R, Straif K, et al. A review of human carcinogens—part D: radiation. Lancet Oncol 2009;10:751–2.

7. Gandini S, Sera F, Cattaruzza M, et al. Metaanalysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer 2005;41:28–44.

8. Gandini S, Sera F, Cattaruzza M, et al. Metaanalysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005;41:45–60.

9. Gandini S, Sera F, Cattaruzza M, et al. Metaanalysis of risk factors for cutaneous

2

Hyperfunctioning Lesions

Naevi

Benign Melanocytic Lesions

PASCALE GUITERA HELENA COLLGROS
SHU WANG RICHARD A. SCOLYER

Melanoma Institute Australia

Key Points

- Naevi can transform into melanoma but it is very rare.
- Over 60% of melanomas are unassociated with naevi.
- Widespread prophylactic excision of naevi is not useful.
- Increased numbers of naevi, particularly dysplastic naevi, increases risk of melanoma.
- Numerous non-melanocytic lesions can enter in the differential diagnosis of melanoma.
- Dermoscopy is an essential adjunct to diagnosis.

Benign melanocytic lesions can be considered in two broad groups based on whether they represent increased melanin production by a normal number of hyperfunctioning melanocytes or due to increased numbers of melanocytes. The increase in number may be due to either melanocytic hyperplasia or a clonal neoplastic process. Benign neoplastic melanocytic lesions are commonly termed 'naevi'.

The sections of this chapter catalogue the various types of benign melanocytic lesions commonly encountered in the clinic with photos and dermoscopic images of each for comparison.

SECTION 1

Hyperfunctioning Lesions

INTRODUCTION

This section focuses on those lesions that feature an increased concentration of pigment particles within keratinocytes, produced by an approximately normal number of melanocytes. These lesions represent a hyperfunctioning of melanocytes. Common examples include:

- ephelides (freckle)
- lentigo simplex
- solar (actinic) lentigo
- café-au-lait macule

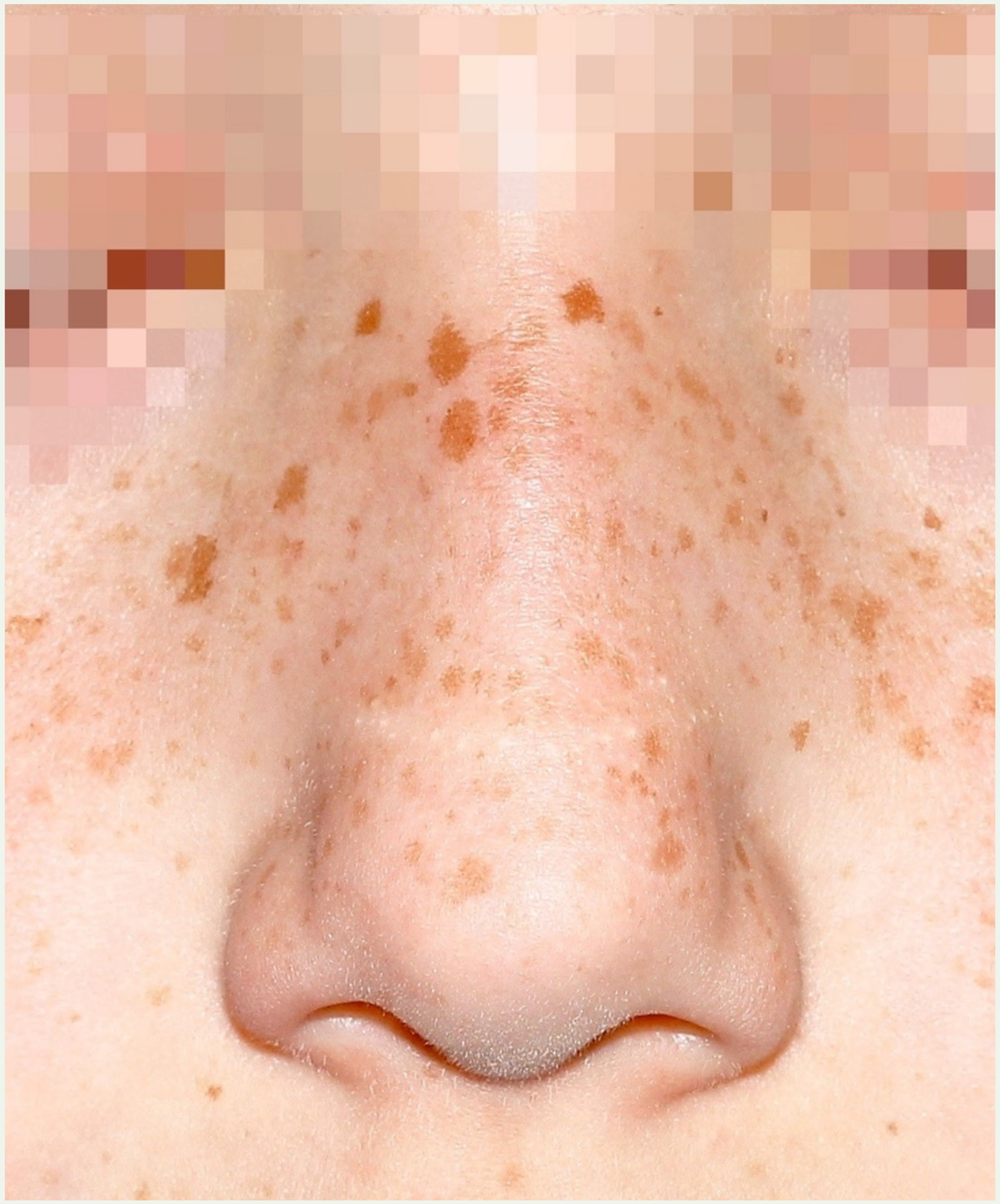
Ephelides (freckle):

- common, particularly in phototype I
- uniform brown colour
- associated with sunlight exposure/sun damage
- typically occur in sun damaged skin
- fade in absence of sun exposure
- become less clinically obvious with age (though visible under Wood's lamp)
- most common site head and neck region, arms, back
- typically ~2mm in size

Histologically characterised by:

- an increase of pigmented keratinocytes at the dermoepidermal junction
- there is no increase in melanocytes

Figure 2.1 Ephelides



Ephiledes on the nose and cheeks of a child.

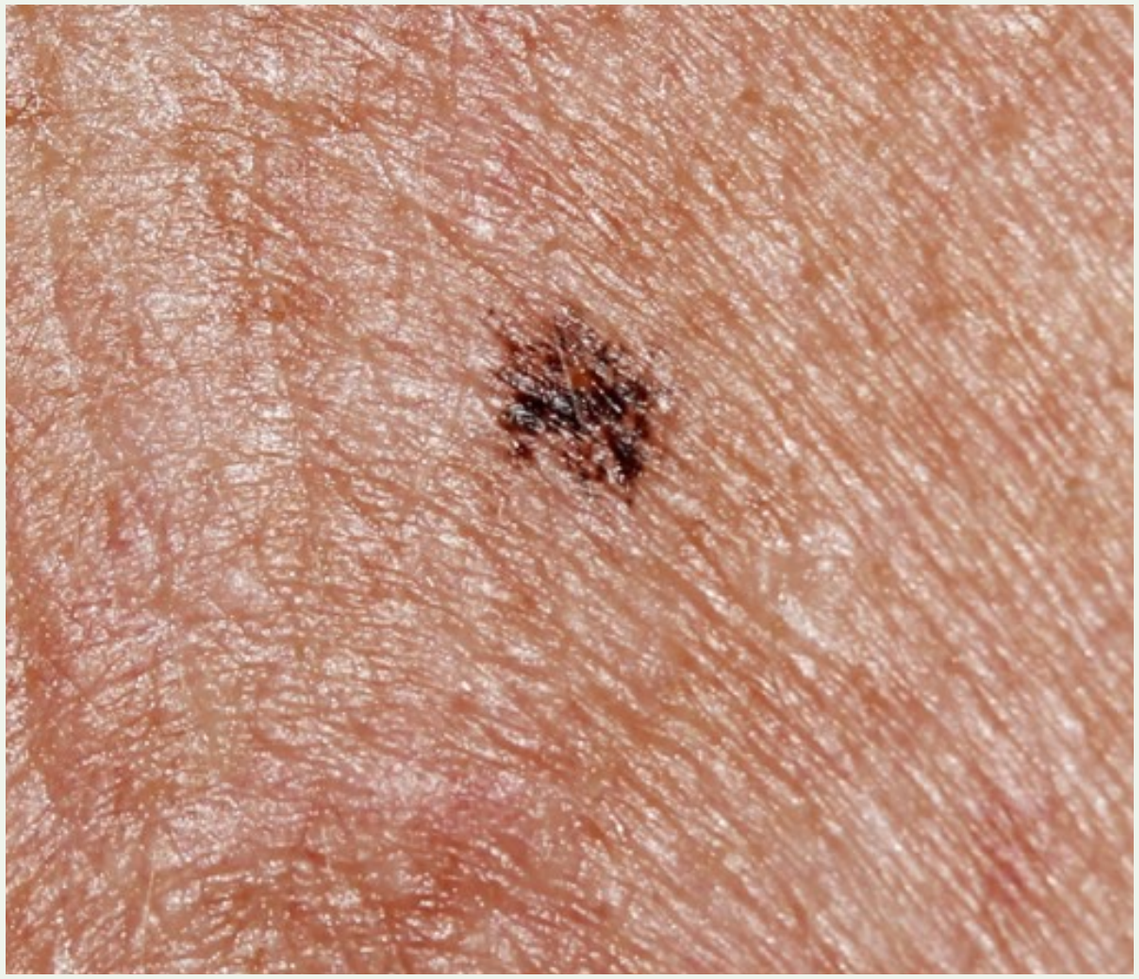
Lentigo Simplex (Melanotic Macule):

- clinical features very similar to the clinical description of ephelides
- appears as a well-demarcated, small (<6mm), uniform brown macule
- in contrast to ephelides, not caused by sun exposure
- can occur at any site on the tegument including mucosal sites

Histologically characterised by:

- elongated rete ridges
- increased basal keratinocyte pigmentation
- slight increase in non-atypical melanocytes
- so-called labial and genital melanotic macules have a similar histological appearance
- considered the earliest stage in the development of a melanocytic naevus

Figure 2.2 Lentigo Simplex



Clinical example of lentigo simplex.

(Image 1 of 2)

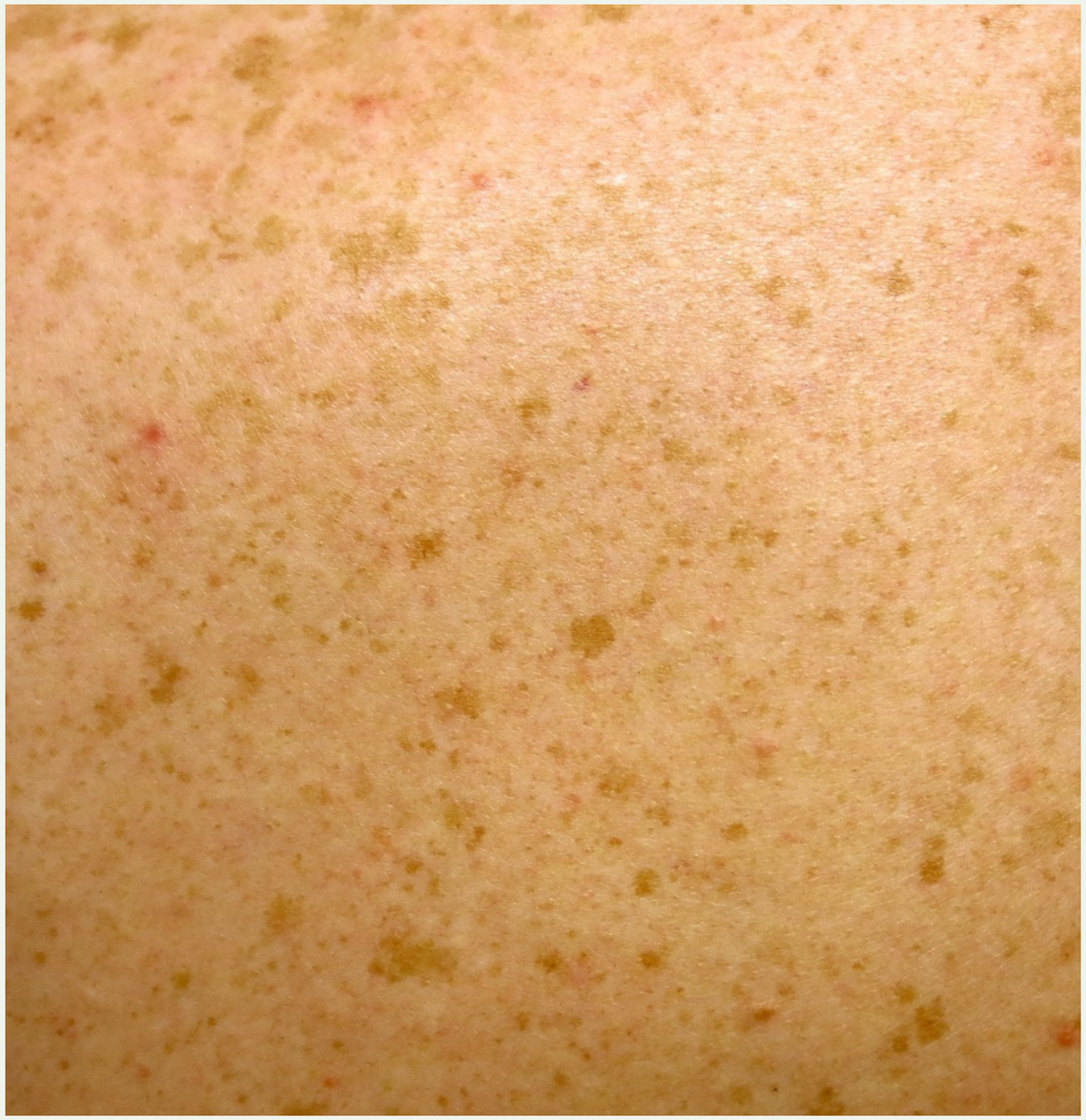
Solar (Actinic) Lentigo:

- more irregular in size and shape than ephelides and lentigo simplex
- still macular with uniform pale brown colour
- caused by sun-damage occurring later in life than ephelides
- affect ~90% of caucasians over the age of 60 years
- typically 2-10mm in size

Histologically characterised by:

- rete ridges typically elongated with "club-like" shape (may be effaced particularly in lesions on the face)
- increased keratinocyte pigmentation, particularly at the tips of rete ridges
- may have a mild increase of non-atypical melanocytes
- an accompanying inflammatory cell infiltrate is sometimes present in the underlying superficial dermis

Figure 2.3 Solar Lentigo



Clinically diffuse solar lentigo

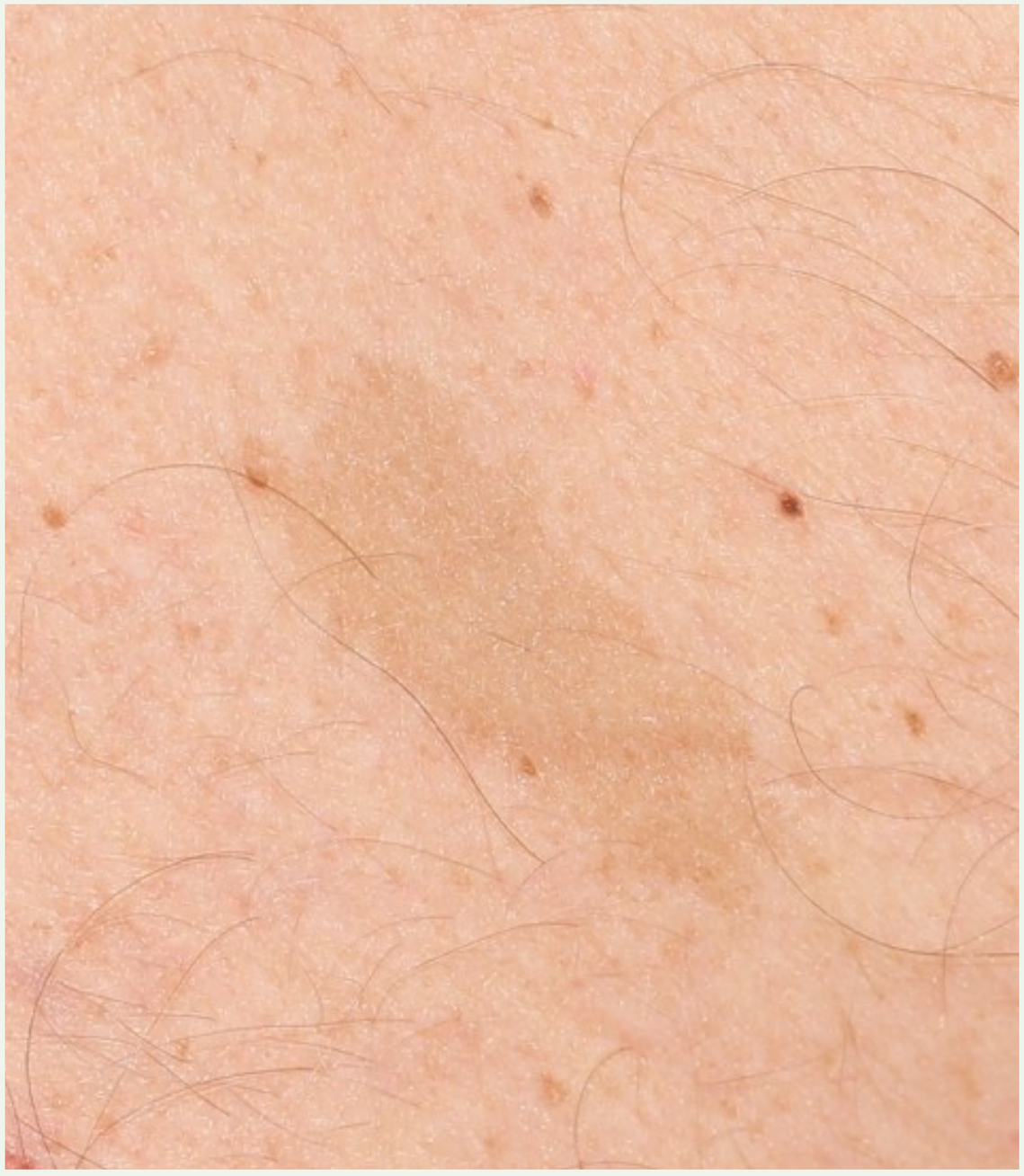
Café-au-lait Macule:

- occur singly in about 10% of the population
- appears at birth or childhood
- multiple lesions can be associated with a number of syndromes, including neurofibromatosis types 1 and 2
- appear as homogenous, pale brown ("coffee and milk")
- often ovoid in shape
- can vary from a few millimeters up to several centimeters in size
- diagnosis is usually made clinically

Histologically characterised by:

- somewhat similar to ephelides
- increased basal epidermal pigmentation
- normal to slightly increased numbers of normal-appearing melanocytes

Figure 2.4 Café-au-lait macule



Café-au-lait Macule

Section 2

Naevi

Melanocytic Lesions

This section focuses on naevi, the benign variety of melanocyte proliferation. Although the term "naevus" (Latin for birthmark) can refer to a number of non-melanocytic hamartomatous tumours, it is commonly associated specifically with melanocytic naevi.

Melanocytic naevi are benign proliferations of melanocytes, thought to be of neoplastic (clonal) origin. They can be classified according to a number of frameworks, including onset (congenital or acquired), size (notably for congenital naevi), site (glabrous, acral, genital, among others), and micro-anatomical location (junctional, compound, dermal). Often combinations of these frameworks are employed in the naming of various naevi.

Clinical features:

- usually present in childhood and adolescence
- usually disappear by the eighth decade
- maximum number present in the third decade
- particularly common in Caucasians, less in Asians and even less in Afro-Caribbean people
- develop more after sun exposure, in particular intermittent intense exposure during the first two decades of life
- they can develop in skin, mucosa, the nail matrix, conjunctiva and uveal tract

Significance: Naevi can transform into melanoma but it is a very rare occurrence (~1/100,000). More than 60% of melanomas arise de novo and it is well demonstrated that widespread prophylactic excision of naevi is not useful. However an increased number of naevi and in particular dysplastic ones, does give an increased risk of developing melanoma (see below).

Naevi can be broadly considered as either **congenital** or **acquired**.

Congenital Naevi

Congenital naevi are found in around 1% of the population. They are often irregular in pigmentation, with small hyperpigmented papules and sometimes hairy. Most of them are quite deep lesions.

Congenital naevi are by definition present at birth, however may become clinically apparent in infancy ("tardive" congenital naevus). They are arbitrarily subdivided into small (<1.5cm), medium (1.5-20cm), and giant (≥20cm) naevi based on projected adult size.

Although typically larger than common acquired naevi (see following section), small congenital naevi may otherwise be clinically (and sometimes histologically) indistinguishable from acquired naevi. Small congenital naevi appear as ovoid to round, symmetrical, tan to brown, slightly elevated lesions. They are thought to be present in approximately 1% of newborns.

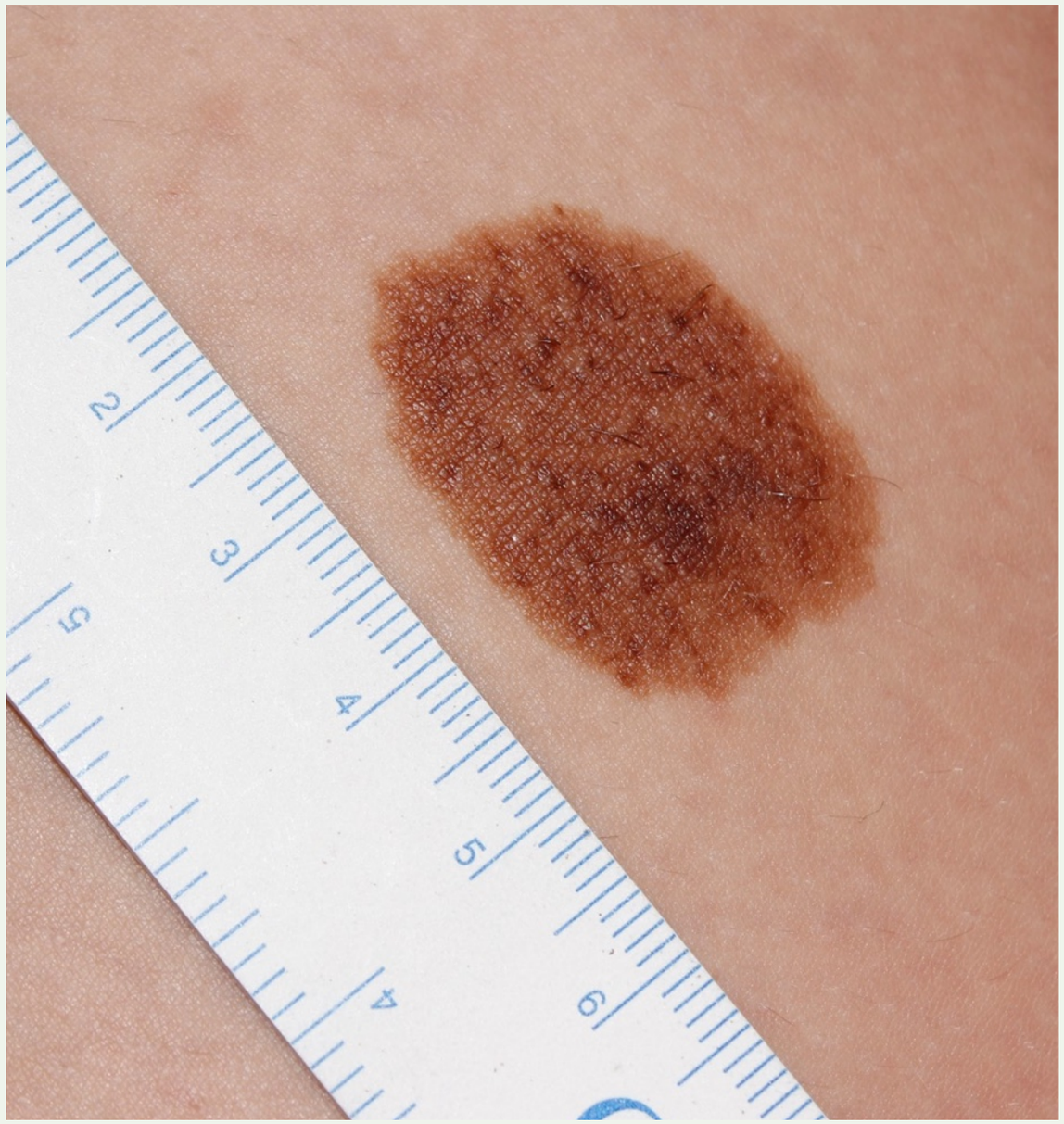
Giant congenital naevi are very rare, with an estimated prevalence of about 0.005% (1:20,000). They often occur in axial locations, described as "garment" or "bathing trunk" like lesions. Clinically there is often hypertrichosis, and the contour and

colour of the naevus may be quite irregular. Satellite lesions may be also be apparent around the main lesion. Giant congenital naevi are associated with neurocutaneous melanocytosis (presence of naevus cells in the central nervous system). Management of congenital naevi is a complex issue that has been comprehensively reviewed by Vourc'h-Jourdain et al., but excision does not fully remove the risk of developing melanoma.

The risk of melanoma arising from a congenital naevus is proportional to size. Small naevi are probably at very low risk, while around 2% of giant congenital naevi may develop melanoma, either during childhood or in later life (mean age 12 years). However, the development of melanoma in infancy is exceptionally rare.

Histologically, superficial small congenital naevi can be indistinguishable from common acquired naevi.

FIGURE 2.5 CONGENITAL NAEVI



Clinical example of a congenital naevus.

(Image 1 of 2)

Some typical features of congenital naevi include extension into the deep reticular dermis (with "splaying" of collagen bundles), as well as into subcutaneous tissue and even fascia in a minority of cases. Naevus cells typically involve (either within or around) adnexal structures such as hair follicles and sweat ducts. Neural differentiation can occasionally be seen in congenital naevi (neurofibroma-like, Schwannian, or Meissnerian areas). In neonates, the junctional component can show pagetoid involvement of the epidermis, simulating melanoma. Giant congenital naevi can develop dermal cellular or proliferative (when mitoses are present) nodules, typically about 5mm in size, composed of epithelioid to spindle shaped cells merging with adjacent background naevus cells. These nodules are more likely to occur in neonates and development later in life can cause clinical concern for melanoma. Other features of dermal nodules that may raise concerns for melanoma include the presence of significant atypia, increased mitoses (greater than 2/mm^2), ulceration, necrosis, or a well-defined border with the adjacent naevus.

Acquired Naevi

There are 3 main types of acquired naevi, classified by the compartments of skin involved:

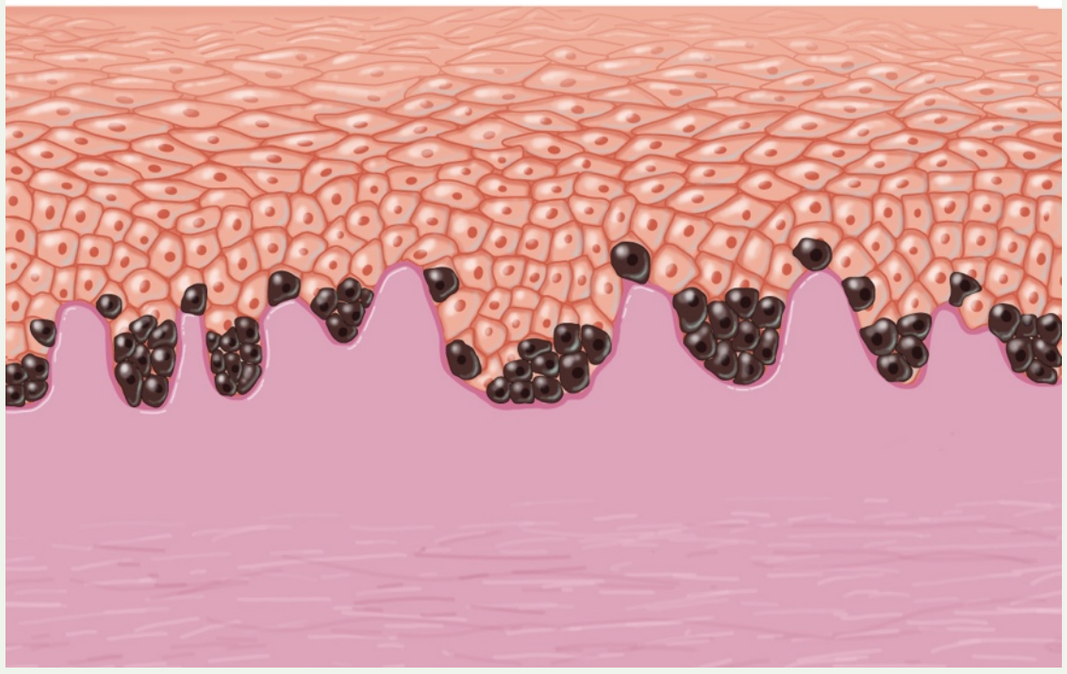
- junctional
- compound
- dermal

Acquired naevi are very common, with most Caucasian young adults having 15-30. Such naevi appear from early childhood through to the third decade, when they peak in number. Their development is related both to genetic factors, as well as to sun exposure, particularly in childhood. They can develop at any site, but are seen more commonly on sun-exposed areas. Although increased numbers of common acquired naevi may be associated with a small increase in melanoma

risk, these lesions individually are considered entirely benign and almost never progress to melanoma.

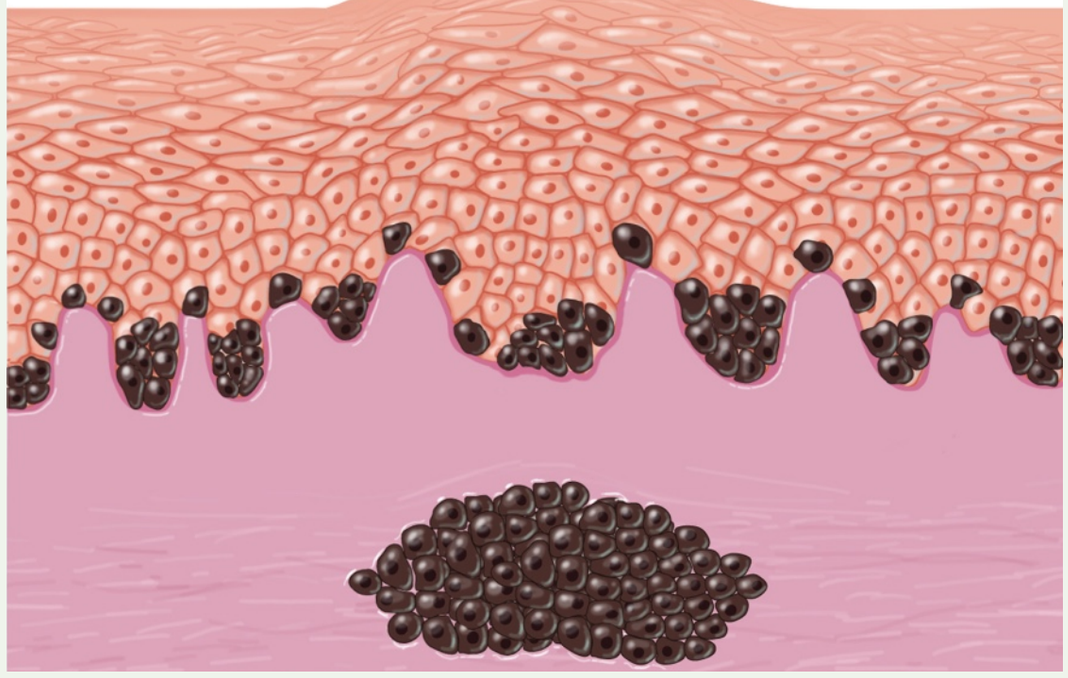
The development of acquired naevi is thought to progress though a number of stages. The first stage consists of increased singly dispersed melanocytes at the dermoepidermal junction (lentigo simplex),

FIGURE 2.6 JUNCTIONAL NAEVUS



Increased density of basal epidermal melanocytes, forming nests predominantly at the tips of the rete ridges. The melanocytes lack their usual dendritic processes (epithelioid).

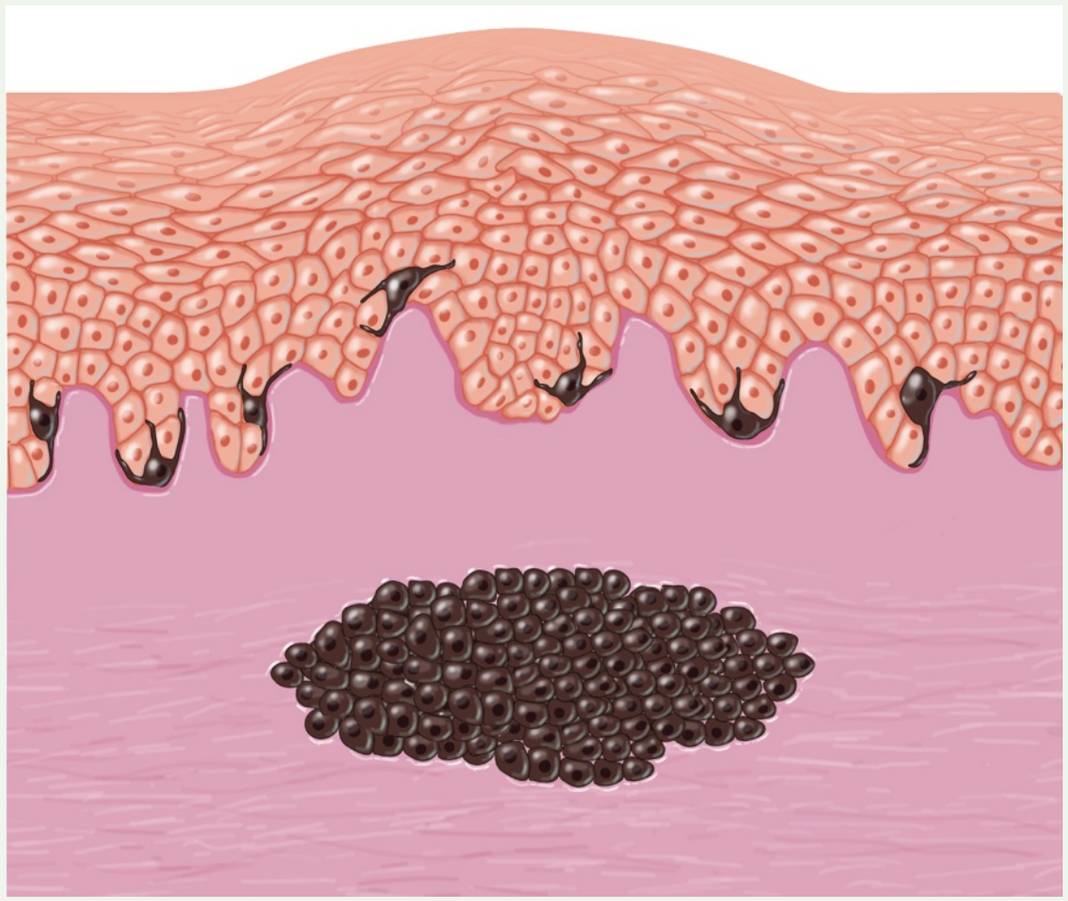
FIGURE 2.7 COMPOUND NAEVUS



Features as seen in a junctional naevus are supplemented with a discrete dermal component beneath, causing the overlying epidermis to distort upwards.

which take on an epithelioid, rather than a normal dendritic histological appearance, and begin to form aggregates termed nests (or theques) (Figure 2.6). This stage is called a junctional naevus. The naevus cells then "drop off" into the underlying dermis, forming a separate dermal component underlying the junctional component, termed a compound naevus (Figure 2.7). Over time, the lesion becomes entirely intradermal (dermal naevus) and slowly involutes, becoming replaced by fibrous and fatty tissue (Figure 2.8). This process could theoretically arrest at an earlier stage, allowing some lentigines simplex, junctional and compound naevi to persist into adulthood.

FIGURE 2.8 DERMAL NAEVUS



The intradermal nest of epithelioid melanocytes distorts the normal overlying epidermis upwards.

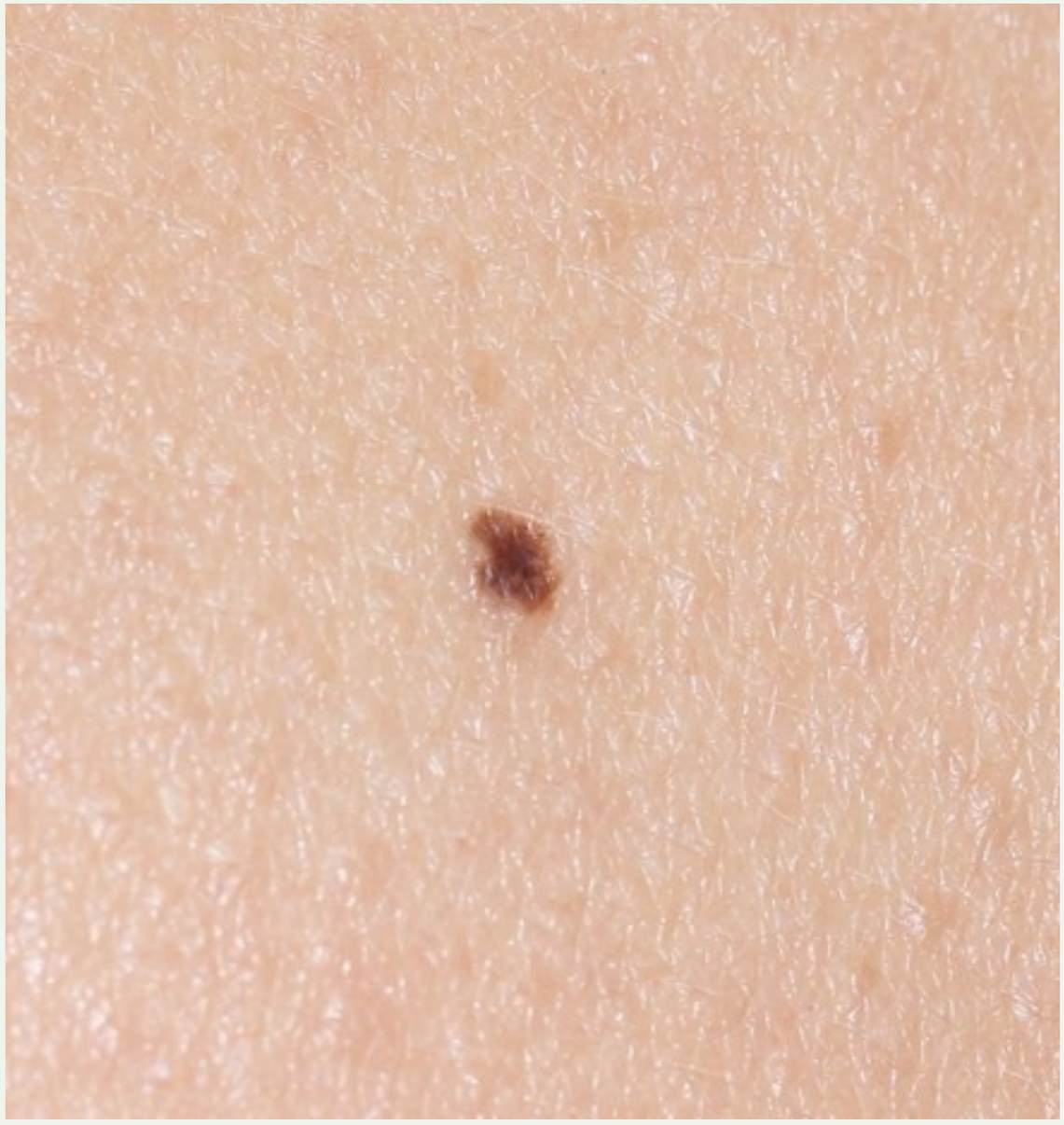
Junctional Naevi:

- macular and well circumscribed
- correspond to proliferation of melanocytes at the junction
- tan to dark brown in colour
- develops in childhood and into young adulthood.
- small, 1-5mm in size

Histologically characterised by:

- often with regular nests within the tips of the rete ridges
- cells often contain melanin pigment
- adjacent keratinocytes may also be pigmented

Figure 2.9 Junctional Naevi



Clinical example of a small junctional naevus.

(Image 1 of 2)

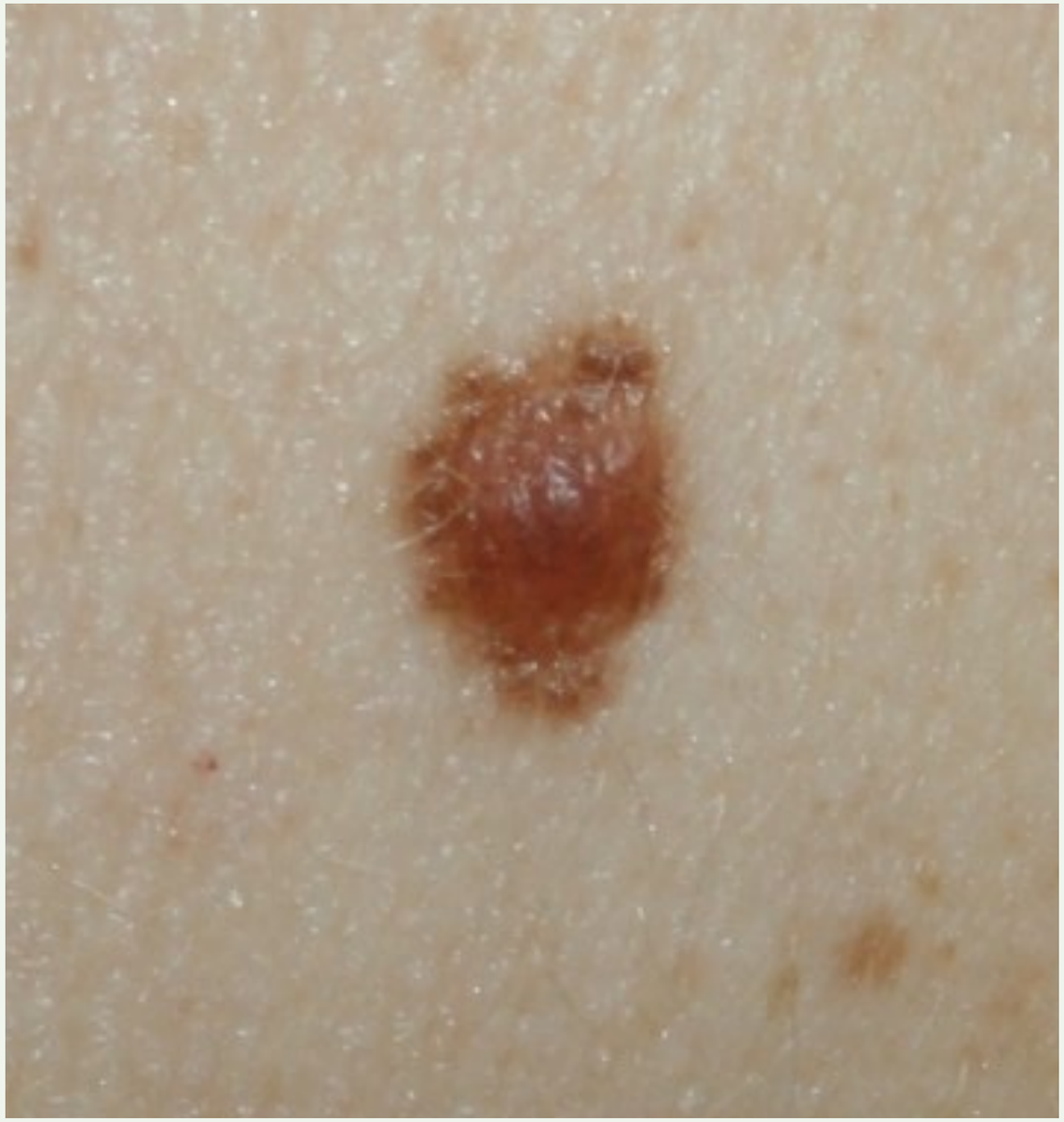
Compound Naevi:

- slightly raised
- circumscribed and symmetrical
- papular and tan to dark brown in colour
- appear in childhood through to young adulthood
- small, about 2-6mm, but can occasionally be up to 10mm in diameter

Histologically characterised by:

- same junctional activity with nests of epithelioid naevus cells
- dermal component consists of some nests and cords of naevus cells, which take on a more lymphocytoid appearance (with smaller nuclei that contain darker, condensed chromatin), and become smaller in size with depth ("maturation")

Figure 2.10 Compound Naevi



Clinical example of a compound naevus.

(Image 1 of 2)

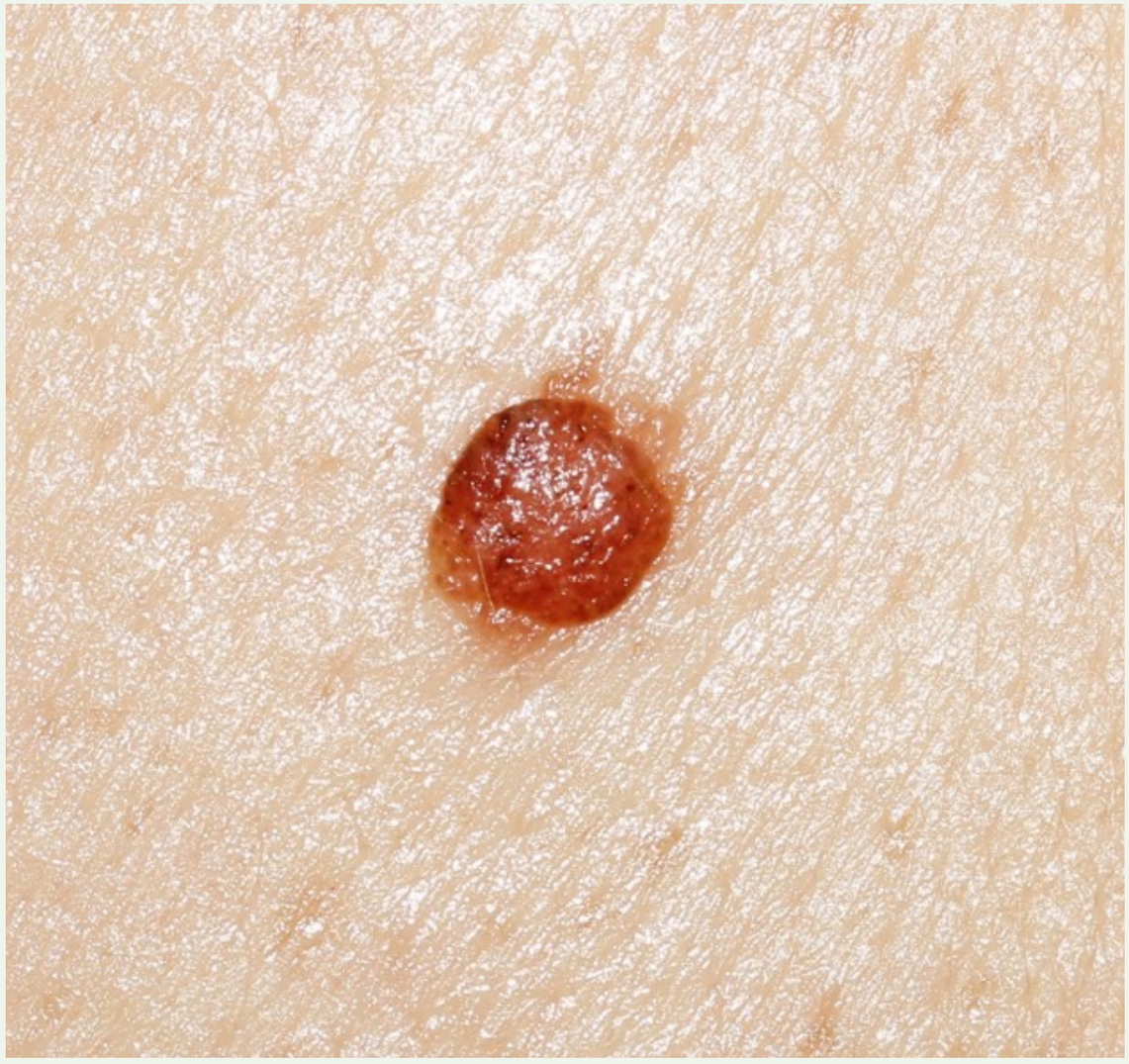
Dermal Naevi:

- papular dome-shaped
- sometimes polypoid or papillomatous in appearance
- circumscribed and symmetrical
- often devoid of pigment due to "maturation" as the dermal melanocytes lose the ability to synthesise pigment
- range from 2-6mm up to 10mm in diameter
- more commonly seen in adults

Histologically characterised by:

- entirely intradermal, nests are mostly in the dermis
- often expanding superficial dermis and effacing rete ridges
- naevus cells are arranged in nests and cords, sometimes showing a spindled/fusiform (Schwannian) morphology towards the deep aspect of the lesion

Figure 2.11 Dermal Naevi



Clinical example of a dermal naevus.

(Image 1 of 2)

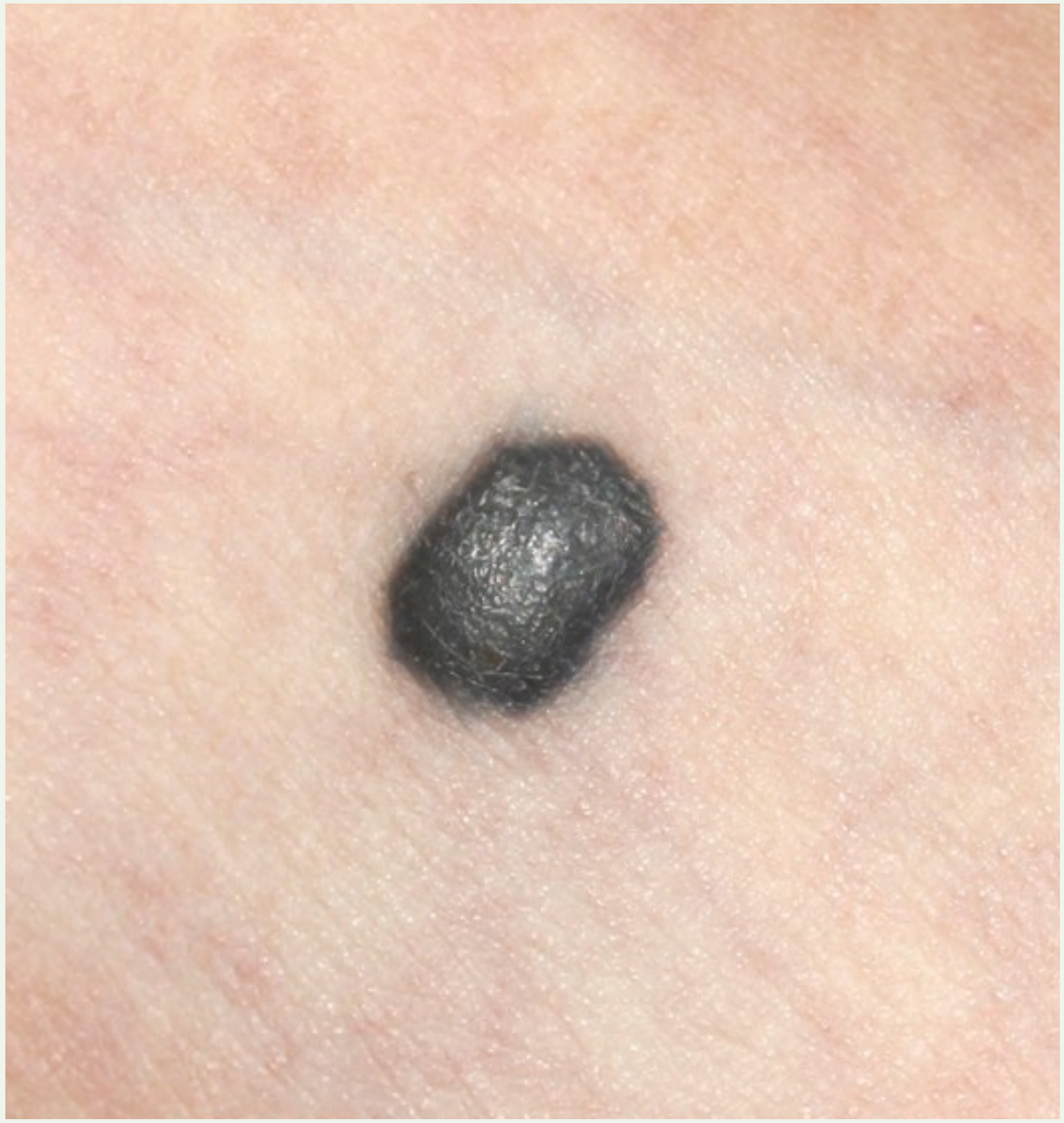
Blue Naevi:

- a variant of dermal naevi
- appear bluish clinically due to pigment in the reticular dermis and the Tyndall effect
- well-circumscribed, dome-shaped
- usually <10mm in diameter, but can be larger, or even plaque-like
- appear during childhood to young adulthood on hands, feet, face, scalp and buttocks.
- this variant can rarely transform into melanomas, and atypical cellular blue naevi are also recognised

Histologically characterised by:

- characterised by dendritic, spindle-shaped melanocytes
- associated fibrosis and melanophages are present
- no "maturation" with depth
- no junctional component

Figure 2.12 Blue Naevi



Clinical example of a blue naevus.

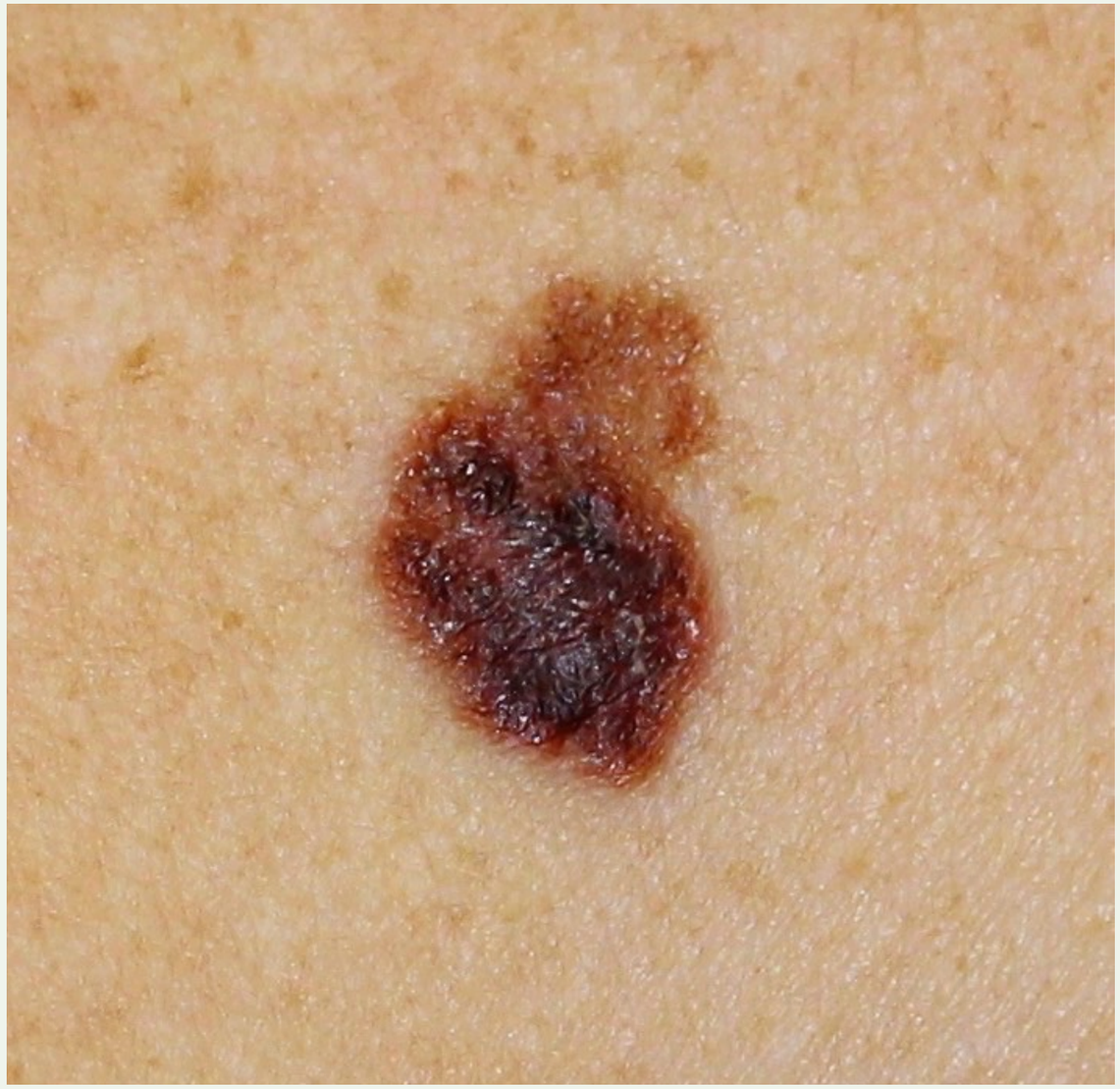
(Image 1 of 2)

Dysplastic Naevi

The concept of dysplastic naevi has been the subject of much controversy over many decades. Naevi that appear dysplastic/atypical clinically may or may not show dysplastic-type features histologically, and vice versa. The term itself remains controversial, and it has been argued that the use of the word "dysplastic" is inappropriate because these lesions are rarely premalignant. Nevertheless it is well accepted that people having multiple dysplastic naevi are more at risk of melanoma.

The definition of a dysplastic naevus is ill-defined; clinically it may be asymmetrical, with multiple colours and have atypical dermoscopy features that overlap with melanoma, but not enough features to qualify as a melanoma. The greater the number and severity of these features, the more likely the lesion is to be a melanoma. Despite a very vague clinical

Figure 2.13 Dysplastic Naevi



Clinical example of a dysplastic naevus.

(Image 1 of 2)

definition, it is important to recognise patients with Dysplastic Naevus Syndrome (DNS). Total body photography is regularly utilised to assist with clinical follow up of DNS patients.

Whether a dysplastic naevus is a direct precursor to melanoma is unclear. Few dysplastic naevi will evolve to melanomas, but 36% of melanomas have adjacent features of dysplastic naevi. However, as dysplastic naevi are significantly more common than melanoma, the risk of any one dysplastic naevus developing into melanoma is likely to be very small (around 1:3000) and does not justify the removal of such lesions unless there is clinical suspicion of melanoma.

Some pathologists provide an indication of the subjective degree of dysplasia (mild, moderate, or severe). This may be particularly relevant at the severe end of the spectrum, when the distinction from melanoma in situ can be difficult.

Table 2.1 MIA Definition of Dysplastic Naevus Syndrome

- All three of the following criteria are required:
  - >100 naevi
  - >6 dysplastic naevi
  - one naevus >8mm diameter

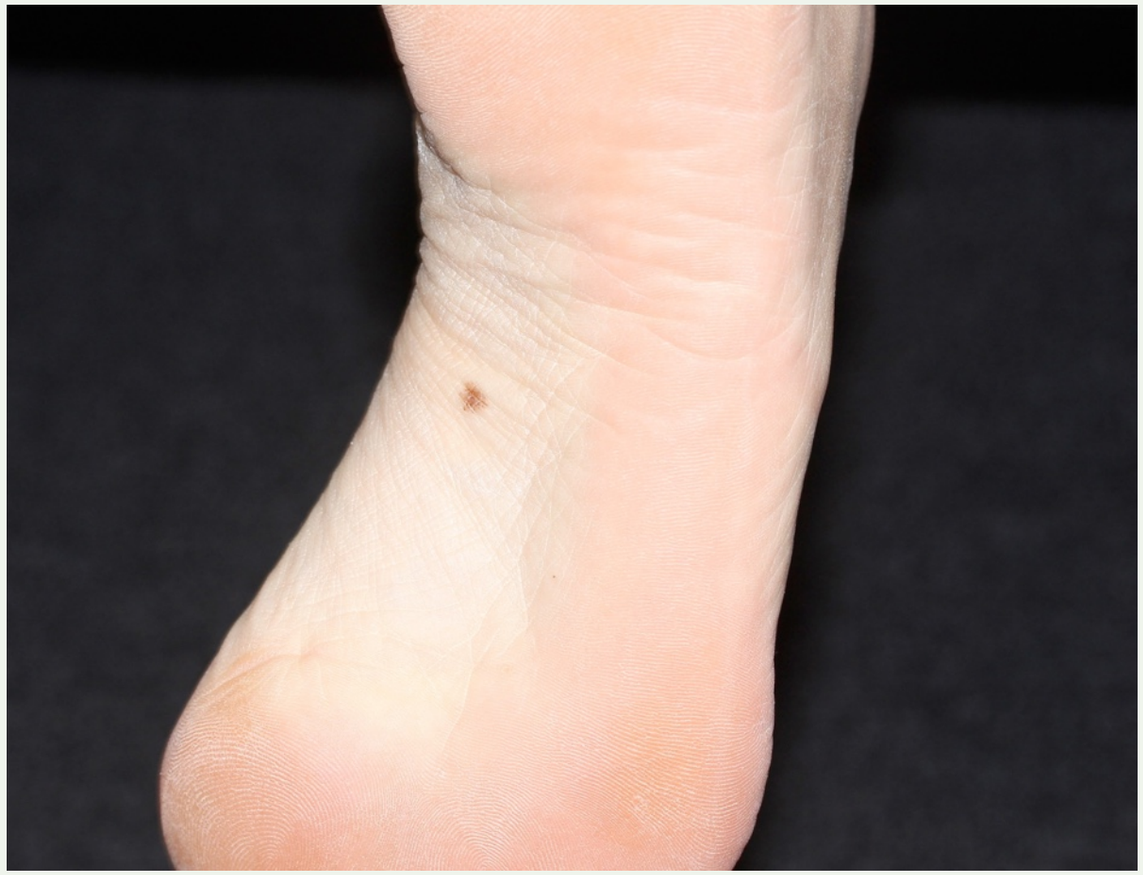
Naevi of Special Sites

Naevi occurring on several so-called "special sites" can have a broader spectrum of appearances, including atypical features, which do not necessarily connote dysplastic naevus or increased melanoma risk. The best known are genital and acral naevi, but flexures, breast, and head and neck are also considered special sites.

Genital naevi are most common on the vulva of premenopausal women. Atypical features include cell enlargement superficially, large or variably-sized, coalescent junctional nests and dermal fibroplasia. Similar features can also be seen in naevi involving breast, head and neck, and flexural sites.

Acral naevi are more common in Asian and black populations. They have a junctional component with or without a dermal component. Acral naevi have a propensity for lentinginous growth and pagetoid spread into the epidermis, however this remains orderly and lacks significant cytological atypia.

Figure 2.14 Naevi of Special Sites



Clinical image of a benign acral naevus on the sole of the right foot.

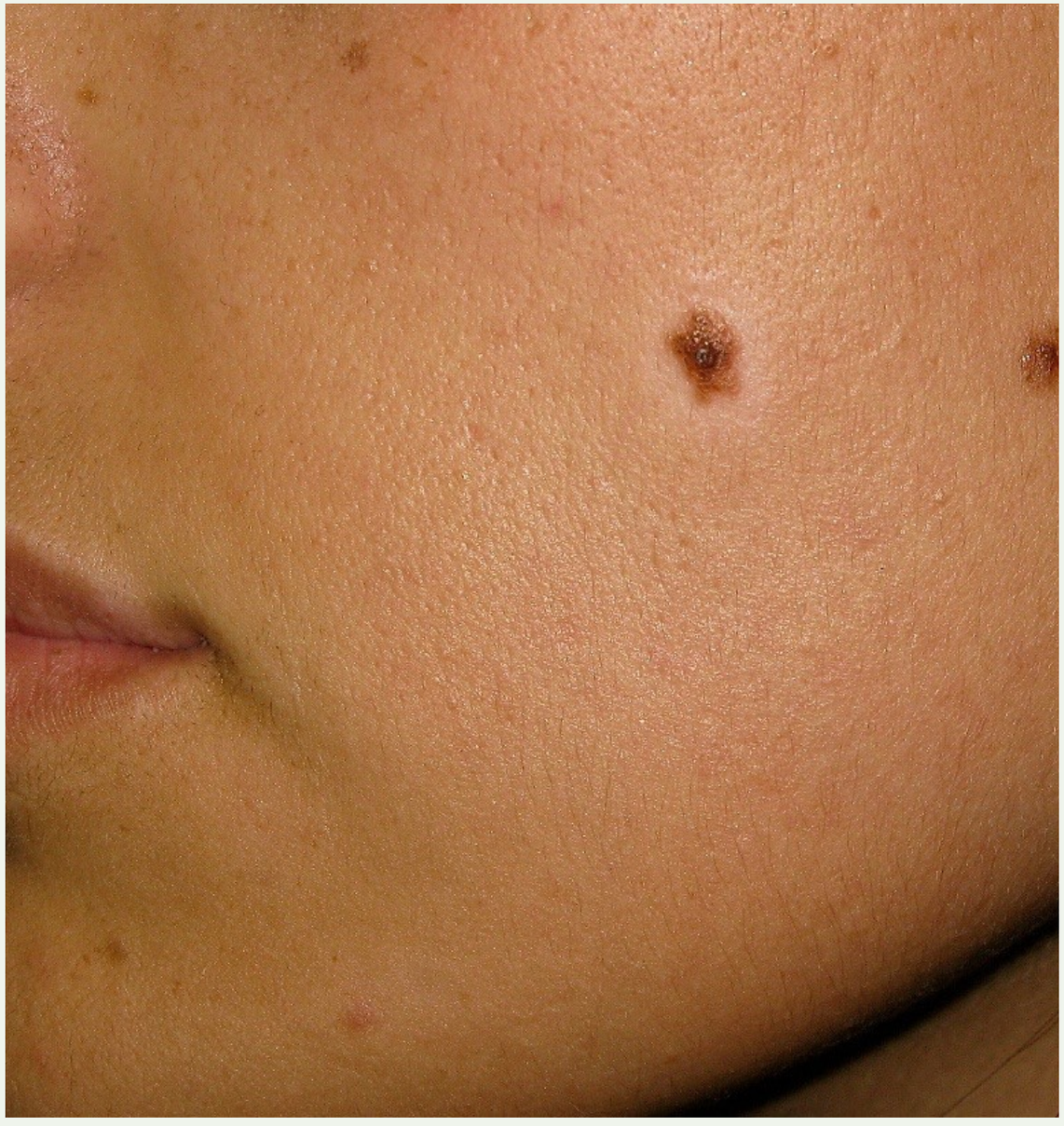
(image 1 of 2)

Halo Naevi

As the name suggests, a halo naevus appears as a depigmented "halo" around an otherwise ordinary acquired (usually compound) naevus. The halo can be several millimeters across and is symmetrical. They occur mainly in adolescents. Over time, the central naevus regresses and the depigmented area can repigment to appear as normal skin. The halo phenomenon can also arise around a melanoma, but the halo will often be asymmetric. There is an increased incidence of vitiligo in these patients.

Histologically, there is a dense lymphocytic infiltrate within which residual naevus cells are present otherwise showing features of a common acquired naevus, including symmetry and maturation. If biopsied later, the naevus may have completely disappeared, leaving essentially normal skin with only a lymphocytic infiltrate, or possibly an occasional area of fibrovascular proliferation.

Figure 2.15 Halo Naevi



Clinical example of a classic halo naevus.

(Image 1 of 3)

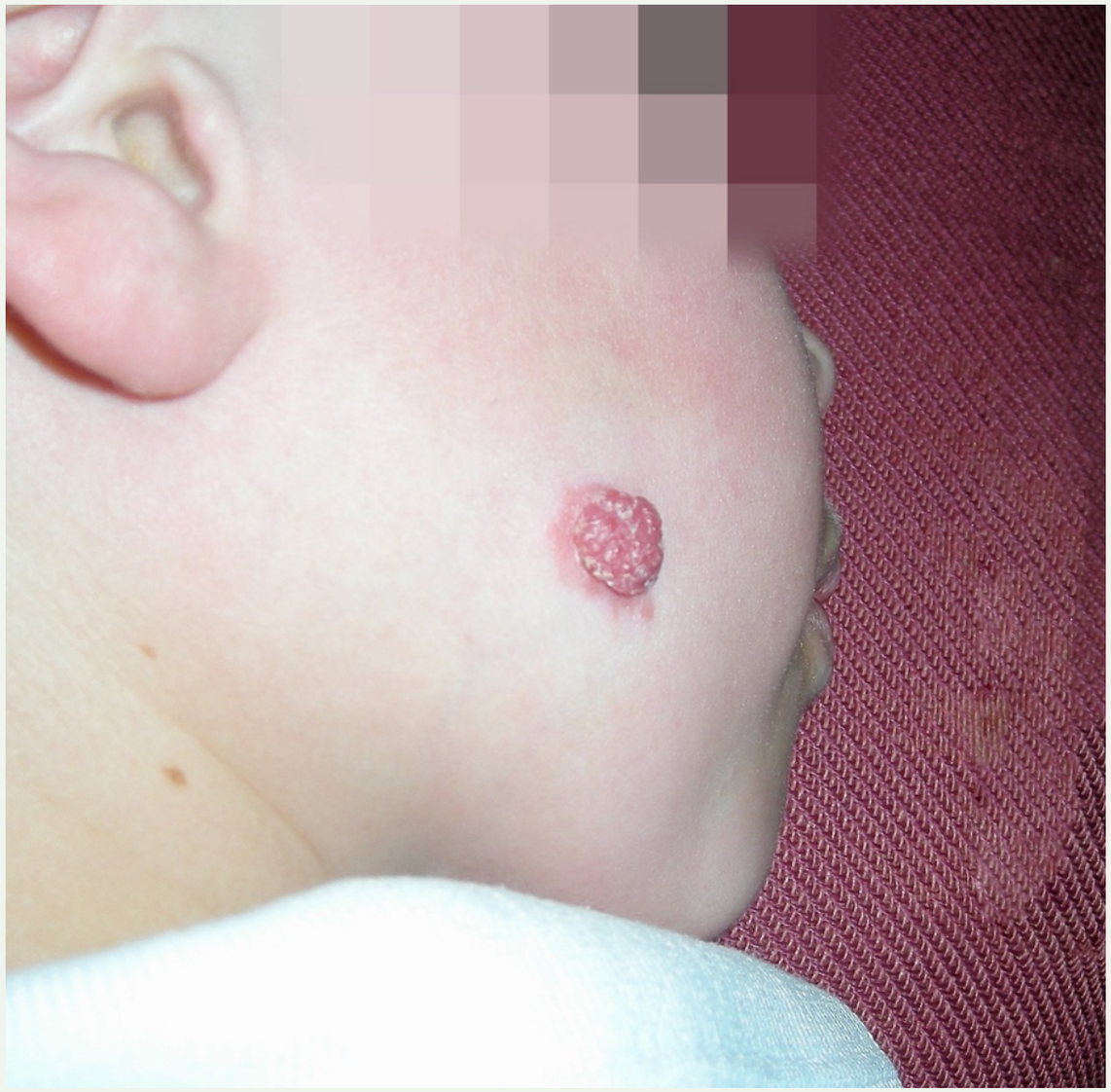
Spitz Naevi

Spitz naevi are benign lesions that are histologically distinct from common acquired naevi. They have a preponderance in children, and can be histologically confused with melanoma. However, Spitz naevi can also occur in adults, though the likelihood of "spitzoid" melanoma becomes far greater with increasing patient age. They can occur on any site, but the face of children and legs of young women are the better known locations.

Clinically they usually appear as circumscribed papular lesions, pink to tan or brown in colour. Spitz naevi are generally less than 10mm in diameter but can be larger. Initially they may grow rapidly, but then stabilise in size. Occasionally they can be multiple.

The main histological feature is of large spindled and/or epithelioid melanocytes. Spitz naevi, like common acquired naevi, can be junctional,

Figure 2.16 Spitz Naevi



Clinical example of a spitz naevus.

compound, or dermal, and an evolutionary process is also thought to occur.

Deviation from the standard Spitz naevus pathological description, for instance the presence of a greater number or deep mitoses, prominent pagetoid spread, asymmetry, and incomplete maturation, amongst others, leads to the designation of “atypical Spitz tumour” (of uncertain or indeterminate biological potential) or even “spitzoid” melanoma, depending on the degree and number of atypical findings, as well as clinical factors such as age of the patient and lesion size. The histological diagnosis of these borderline cases is often best approached in consultation with an expert dermatopathologist.

Other naevi, such as dysplastic naevi, can also show some features of Spitz naevus, in which case the descriptor “spitzoid” can also be used.

Citations and Further Reading

1. Vourc'h-Jourdain M, Martin L, Barbarot S. Large congenital melanocytic naevi: therapeutic management and melanoma risk: a systematic review. J Am Acad Dermatol. 2013 Mar;68(3):493-8

2. Rhodes AR, Harrist TJ, Day CL, Mihm MC Jr, Fitzpatrick TB, Sober AJ. Dysplastic melanocytic naevi in histologic association with 234 primary cutaneous melanomas. J Am Acad Dermatol. 1983 Oct;9(4):563-74.

3. McCarthy SW, Scolyer RA. Melanocytic lesions of the face: diagnostic pitfalls. Ann Acad Med Singapore. 2004 Jul;33(4 Suppl):3-14. Review. PubMed PMID: 15389301.

4. Barnhill RL, Argenyi ZB, From L, Glass LF, Maize JC, Mihm MC Jr, Rabkin MS, Ronan SG, White WL, Piepkorn M. Atypical Spitz nevi/tumors: lack of consensus for diagnosis, discrimination from melanoma, and prediction of outcome. Hum Pathol. 1999 May;30(5):513-20. PubMed PMID: 10333219.

Acknowledgements

Michelle Avramidis BSc

Photography

Roula Drossis MSc BSc

Illustrations

3

Pre-Invasive Melanoma

ANNETTE CHAKERA

Key Points

- Melanoma in situ (MIS) poses no risk of metastasis if adequately treated
- The rate of conversion to invasive melanoma is unknown.
- MIS increases the risk of developing another primary melanoma.
- Lentigo maligna (LM) is usually regarded a variant of MIS on chronically sun-damaged skin.
- LM is commonly located on the head and neck, where significant functional and cosmetic considerations exist.
- LM are often large with indistinct margins.

Introduction

Melanoma in situ (MIS) refers to a non-invasive melanocytic lesion in which the melanoma cells are confined to the epidermis and have not breached the basement membrane. MIS may arise in any site and may be of the superficial spreading (SSM), acral (AM) or lentigo maligna (LM) subtypes. LM is classically regarded as a variant of MIS arising in chronically sun-damaged skin. However, some authorities regard LM as a premalignant condition and distinguish it from MIS.

The two principal concerns regarding MIS are firstly that it may become invasive melanoma if left untreated, although this risk is not quantified. Secondly, that it identifies the patient as being at a several fold greater risk of further melanomas (invasive or in situ) than the background population risk for the same age and sex.

- Some specialists regard LM as a spectrum of lesions ranging from atypical melanocytic lesions with relatively low risk of progression to melanoma, to lesions that are clear-cut in situ melanomas. The term "melanoma in situ, lentigo maligna type" has been suggested to distinguish them from classical MIS of the SSM type. First described by Sir John Hutchinson, LM is also referred to as Hutchinson's Melanotic Freckle and Precancerous Melanosis of Dubreuilh. The invasive form of LM is referred to as lentigo maligna melanoma (LMM), one of the histological subtypes of melanoma.

Epidemiology

The peak age of diagnosis of LM is between 60 and 80 years, whereas MIS of the SSM type generally occurs at a younger age (peaking around 60). The incidence of both MIS overall and the two main histological subtypes, SSM and LM, is increasing among both sexes. This is thought to be due to an

increasing awareness of skin cancer and more frequent prophylactic excision of suspicious early lesions – and for LM in particular to an increasing ageing population worldwide. The conversion rate to invasive melanoma is unknown. One study reported the lifetime risk of developing LMM within a LM to be as low as 2.2% when diagnosed in 65 year olds and 4.7% when diagnosed in 45 year olds. However, other studies have reported conversion rates as high as 50%, with transition times varying from a few months to several decades. However, the generally accepted lifetime risk is estimated to be around 20%.

Aetiology

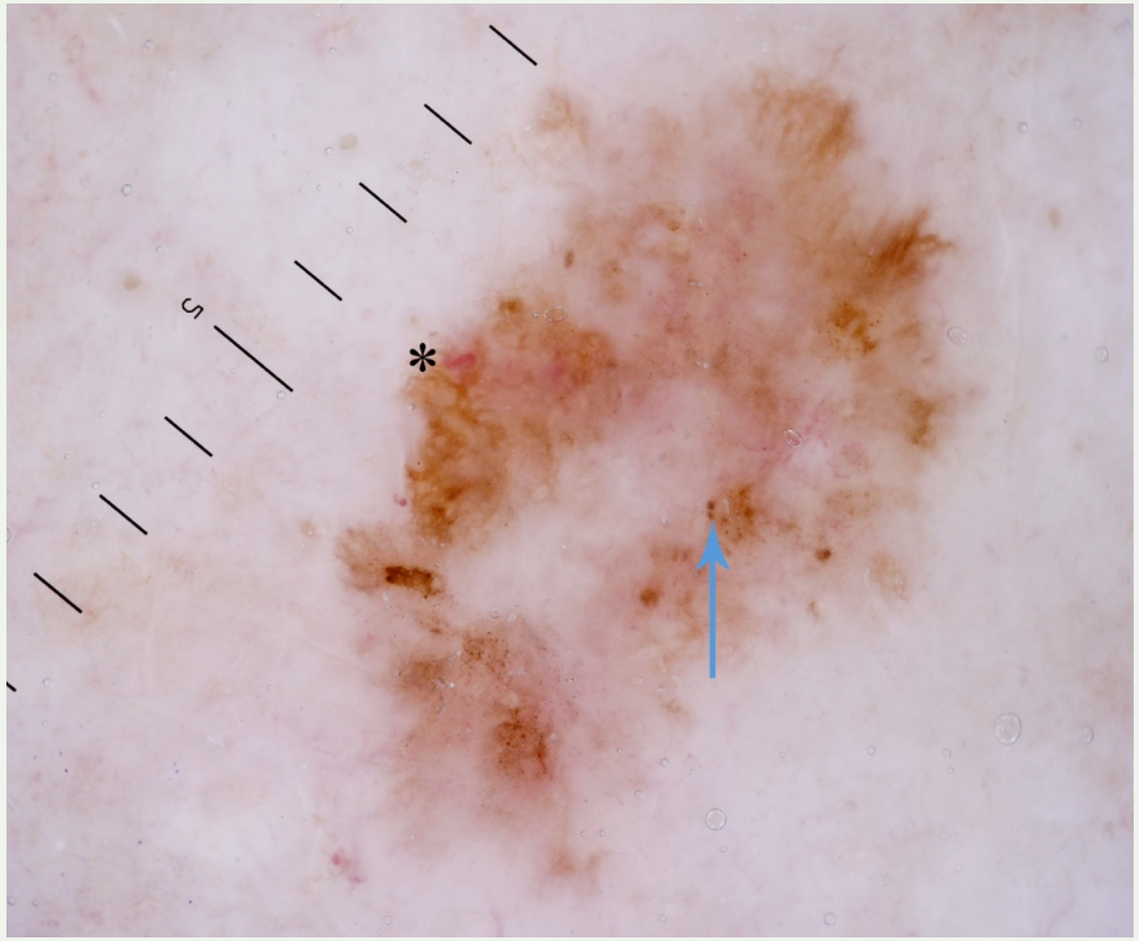
Risk factors for MIS (and invasive melanoma) are the presence of multiple naevi on the extremities, a family history of melanoma, a history of severe sunburns, and sunburn susceptibility (red or blond hair colour and Fitzpatrick skin types I, II and III). LM risk is linked to chronic (occupational) sun exposure, whereas MIS of the SSM type is linked to intermittent sun exposure.

Clinical Diagnosis

MIS of the SSM type are often located on trunk and extremities and although sometimes subtle, they are often well circumscribed (Figure 3.1). They can be difficult to distinguish from dysplastic nevi and early SSM. Invasive tumours are often surrounded by an in situ component, and if the diagnosis of MIS is made on a partial biopsy, then clinicopathological correlation is vital to exclude concomitant invasion.

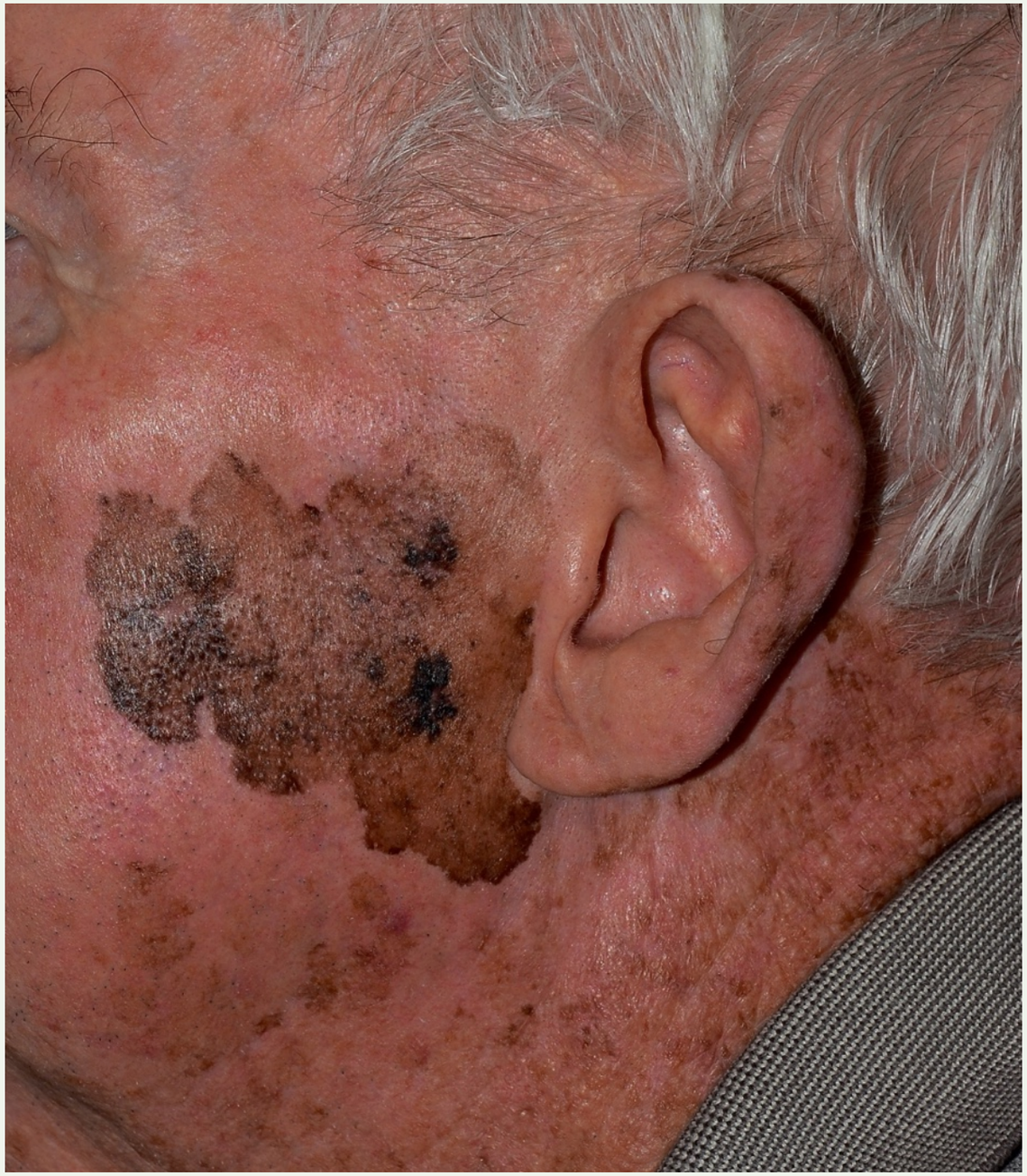
LM present diagnostic, treatment and follow up challenges because of clinically indistinct margins in cosmetically and functionally sensitive areas of the head and neck, often in a background of extensive chronic sun damage, as well as a propensity to recur locally. LM usually presents as a slowly growing or changing discoloured macule. Initially these lesions

Figure 3.1 Dermoscopic examples of Melanoma In Situ



Dermoscopy demonstrating peripheral pigmented network (melanocytic lesion), multiple asymmetric dots (arrow), irregular linear vessels (star), 3 colours (red, light brown and dark brown).

Figure 3.2 Clinical examples of Lentigo Maligna (facial)



Lentigo maligna left cheek

may resemble simple freckles or brown marks (lentigines), but subsequently over several years or even decades can enlarge to several centimetres in diameter. There may be differing shades of brown, black or red/pink throughout, but LM is commonly partially amelanotic, especially towards the edges. This correlates clinically with an often irregular shape and poorly defined margins. As LM often presents on severely sun damaged skin, it is frequently found on a background of other pigmented lesions eg, seborrhoeic keratoses, lentigo senilis, lentigines, and actinic keratoses, which may further obstruct clinical diagnosis. The presence of papules and nodules may signify areas of invasion to LMM.

Delineating the extent of the disease is clearly crucial for successful treatment. Atypical cells can extend far beyond visible margins and incomplete pathological margins after excision following clinical assessment alone are not uncommon (field change).

Dermoscopy improves the diagnostic accuracy. However, dermoscopic features of melanocytic lesions on the face differ from elsewhere on the body; a pigment network is rarely detected as it results from epidermal melanin along elongated rete ridges. In chronically sun damaged facial skin these appear flattened. Instead, melanocytes along this flattened dermo-epidermal junction appear as structureless diffuse brown pigmentation interrupted by hypopigmented “holes”, which correspond to hair follicles and sweat gland openings (“pseudonetwork”). Other pigmented lesions, such as pigmented actinic keratoses and lentigines, may also reveal these diagnostic criteria.

The identification of the four following additional dermoscopic features is strongly suggestive of LM:

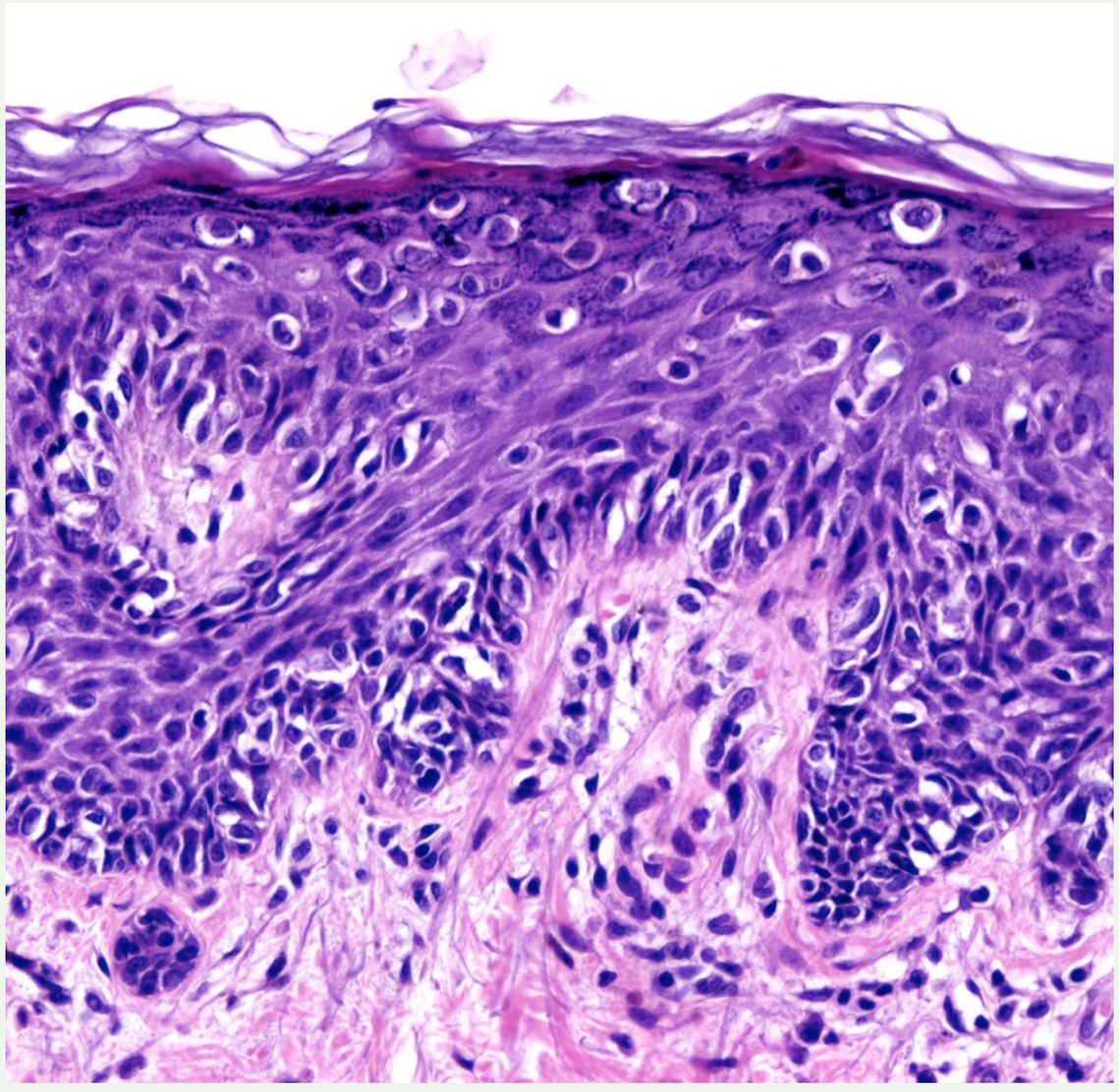
- asymmetric pigmented follicular openings
- dark rhomboidal structures
- slate-gray globules
- dots

When there is clinical suspicion of MIS or LM a biopsy should be performed. Wherever possible, excisional biopsy is advocated; however, due to the size and location of many LMs, one or more incisional or punch biopsies should be performed from the most atypical parts of the lesion, usually guided by dermoscopy.

Histopathology

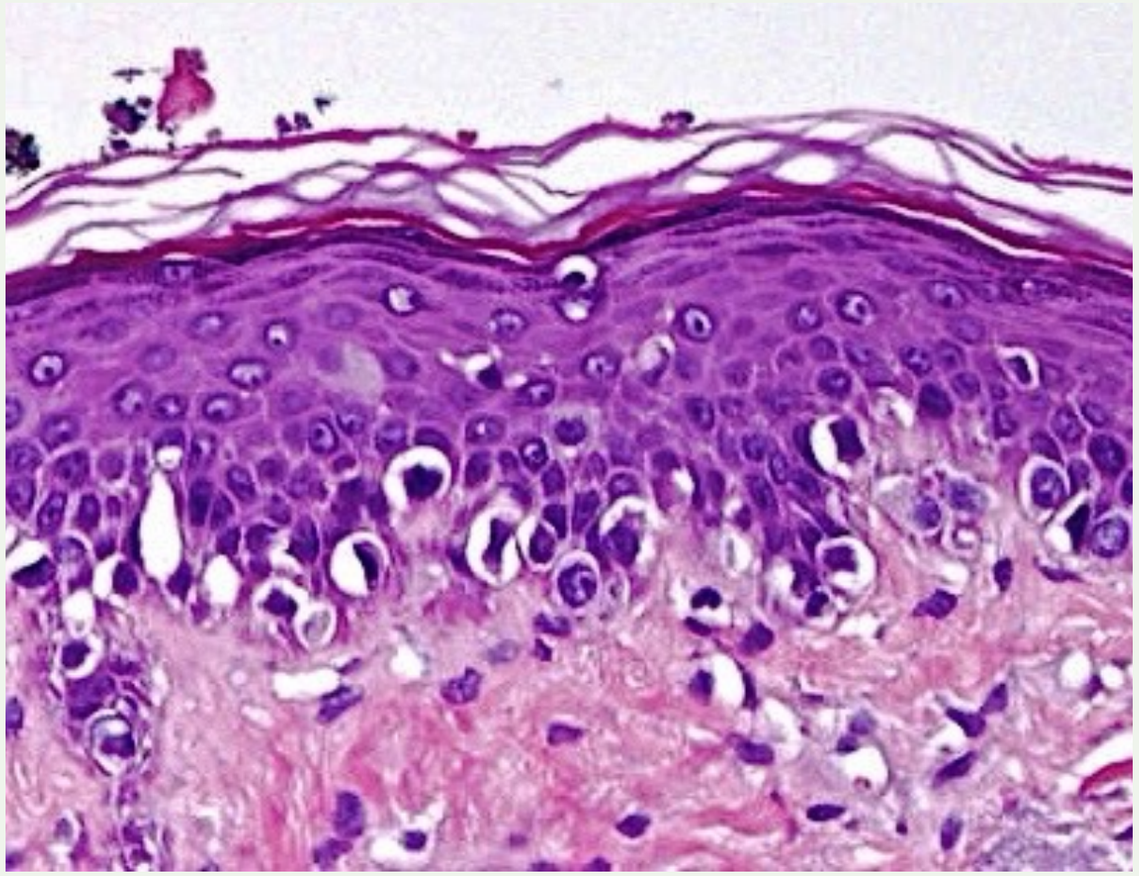
The melanocytes are increased in number and, as in solar lentigines, often disposed as confluent single cells along the dermo-epidermal junction. With tumour progression there is frequent involvement of adnexal structures and sometimes pagetoid spread,

Figure 3.3 Histological Features of Melanoma in situ



Widespread proliferation of melanocytes along the basal epidermal layer, typical of in situ melanoma.

FIGURE 3.4 HISTOLOGICAL FEATURES OF LENTIGO MALIGNA



A close up image of skin populated by atypical melanocytes forming an almost continuous population along the base of the epidermis. The dark crescent shaped melanocyte nuclei are characteristic of the atypia seen in this melanoma subtype.

which is uncommon in early stages. The melanocytes are often hyperchromatic and small but nuclear atypia may be subtle. It is characterised by atypical melanocytes at different epidermal layers (Figure 3.3, Figure 3.4).

TREATMENT

Surgery is regarded the standard treatment of MIS, including LM. This usually consists of wide local excision (WLE) with a 5mm clinical margin. However, LM often presents therapeutic challenges because of large size, location in functionally and cosmetically sensitive areas with limited local tissue availability for flap reconstruction, as well as indistinct clinical and pathological margins. Consequently, a skin graft is often required. In addition, LM often occurs in elderly patients with significant co-morbidities that can further restrict therapeutic options.

LM has a propensity to recur locally, with reported rates after conventional WLE using a 5 mm clinical margin ranging between 8 and 50%. The high recurrence rate has been attributed to a failure to treat subclinical peripheral disease, consisting of atypical junctional melanocytes in the deep adnexal structures. Larger excision margins result in greater clearance rates but also increase morbidity. Alternative surgical and non-surgical options have been suggested for LM to overcome the mentioned challenges:

Surgical

- wide local excision
- staged surgical excision

Non-surgical

- radiotherapy
- imiquimod
- cryotherapy
- 5-fluorouracil
- electrocautery

Staged surgical excision (SSE) consists of preoperative delineation of the lesion, classically using a Wood's lamp and thereafter excision of a marginal band surrounding the tumour at a 5-10mm margin, which is sent for permanent histology. Once adequate histological margins have been achieved, the defect is repaired. The advantages of this technique are that the surgical margins are assessed with permanent histological sections whilst the procedure is being undertaken. A notable disadvantage is that these procedures can be prolonged, expensive and tedious for the patient.

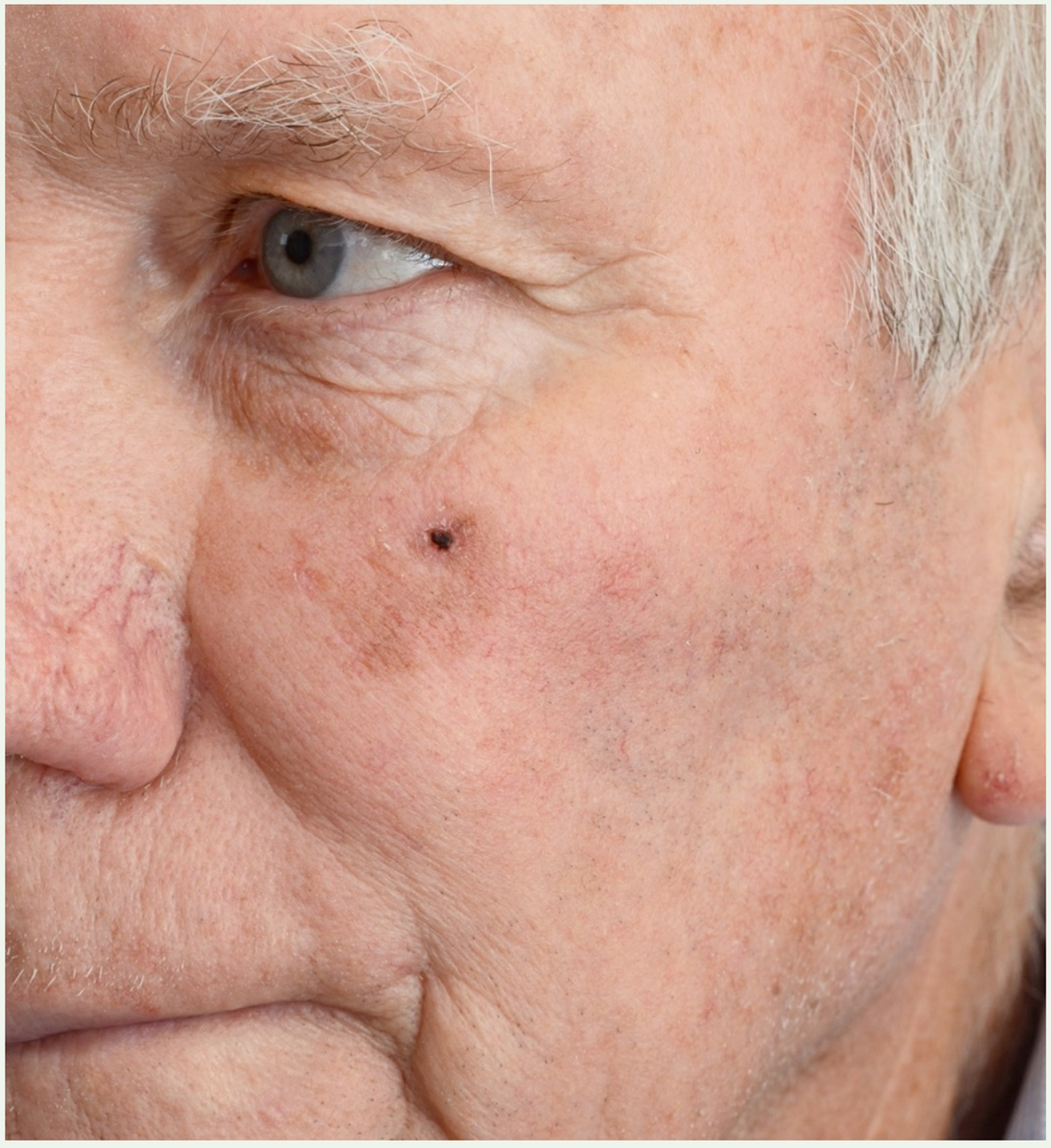
An alternative approach to SSE is to use reflectance confocal microscopy (RCM) to pre-operatively determine the extent of the lentigo maligna. The high diagnostic accuracy of RCM in determining the extent of the lesion beyond that which is visible, facilitates confident resection and immediate reconstruction. As RCM availability has increased, so

this has become a preferred approach in some centres.

Non-surgical therapies are increasingly used with varying success for patients with large LM, significant co-morbidities, or in patients preferring a more conservative approach. The main disadvantages include the absence of a surgical specimen for confirmation of clearance margins and the failure to treat deep peri-appendageal melanocytes.

Radiotherapy (RT) is an option for treatment of LM when surgical margins are inadequate (Figure 3.5), where surgery is not possible or not wanted and for salvage in case of recurrence after surgery or other modalities. Advantages of RT are that it can be given to a large area with a generous margin and superiority to surgery in conservation of tissue. Late effects of RT are primarily fibrosis with hypopigmentation, telangiectasia, alopecia and

FIGURE 3.5 RADIOTHERAPY TREATMENT FOR LENTIGO MALIGNA



Initial presentation of lentigo maligna left cheek.

decreased skin elasticity, which are determined mainly by total dose and fraction size. Ultra-soft x-ray/Grenz-ray radiation, which only penetrates the epidermis, has often been used for LM. There is, however, no consensus about the optimum RT parameters to be used. A recent review showed a 5% progression to LMM with a median follow up of 3 years in 349 patients treated with RT as the primary modality. Based on this, a depth of 5mm of active treatment was recommended, to include appendages and decrease the risk of missing focally invasive areas. The efficacy for RT has been reported to be up to 88%.

Imiquimod is an immune response modifier that is licensed for the treatment of solar keratosis, superficial basal cell carcinoma and genital and perianal warts. It has been used to treat LM in several studies either as the primary modality or together with surgery. Clearance rates between 66-100% have been reported, however cases of invasive LMM have been reported during or after treatment. Imiquimod induces a number of pro-inflammatory cytokines within the skin, including interferon and tumour necrosis factor, which may potentiate immune responses. It also induces a cytotoxic T-cell mediated immune response in situ, which may account for the destruction of malignant melanocytes in LM. The Imiquimod cream is usually applied several times per week for 3 months and to be effective there needs to be a significant inflammation throughout this period. The main side effects are marked erythema, blisters, pain, influenza like symptoms, pruritus, keratitis and conjunctivitis.

Cryotherapy is not used at MIA, as to be effective it has to penetrate deeply into the skin, leading to wound healing problems. Similarly, LASER therapy is not used, due to high recurrence rates as a result of it's failure to penetrate deeply enough.

An alternative approach in an elderly patient with a large LM is to simply photograph and monitor the lesion carefully. Biopsies should be taken from any areas suspicious of invasive disease, however, transition to invasive melanoma is usually regarded as occurring slowly and being unlikely in these patients.

A Lentigo Maligna Clinic has been established at Melanoma Institute Australia. A multidisciplinary team consisting of plastic surgeons, radiation oncologists and dermatologists sees patients with difficult lesions. Patients typically have their lesion mapped with RCM prior to attending the clinic, where the various treatment modalities are discussed in terms of oncological control, cosmesis and function, as well as logistics; principally surgery, radiotherapy, and topical therapy (imiquimod). A treatment plan is formulated in conjunction with the patient. Many patients also have RCM as part of their follow up, as detection of treatment failure is even more difficult than diagnosis, with frequent subtle non-specific pigmentation.

Citations and Further Reading

1. J. Hutchinson. Senile freckle with deep staining - a superficial epithelioma of the cheek. Archives of Surgery, London, 1892, 3: 159.

2. Ackerman AB, Briggs PL, Bravo F. Differential Diagnosis in Dermopathology III. Philadelphia: Lea&Febiger 1993, 166–9.

3. Tannous ZS, Lerner LH, Duncan LM, et al. Progression to invasive melanoma from malignant melanoma in situ, lentigo maligna type. Hum Pathol 2000; 31: 705–8.

4. Flotte TJ, Mihm MCJ. Lentigo maligna and malignant melanoma in situ, lentigo maligna type. Hum Pathol 1999; 30: 533-6.

5. McKenna JK, Florell SR, Goldman GD et al. Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. Dermatol Surg 2006; 32: 493–504.

6. Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. Br J Dermatol 1987; 116:303–10.

7. Stevenson O, Ahmed I. "Lentigo maligna : prognosis and treatment options". Am J Clin Dermatol 2005; 6: 151–64.

8. Klauder JV, Beerman H. Melanotic freckle (Hutchinson), me´lanose circonscrite pre´cance´reuse (Dubreuilh). AMA Arch Derm 1955; 71: 2–10.

9. Dalton SR, Gardner TL, Libow LF et al. Contiguous lesions in lentigo maligna. J Am Acad Dermatol 2005; 52: 859–62.

10. Robinson JK. Use of digital epiluminescence microscopy to help define the edge

Acknowledgements

Michelle Avramidis BSc Photography

4

Primary Melanoma Subtypes

ANNETTE CHAKERA
ALEXANDER H.R. VAREY MEI HUI

Melanoma Institute Australia

Key Points

- Subtypes not well correlated with prognosis, but patterns of distinct genomic mutations are beginning to emerge.
- Superficial spreading melanoma is the most common subtype.
- Nodular melanomas represent the majority of thick melanomas.
- Resection of acral and subungual melanomas has significant functional implications.
- Diagnosis of subungual melanomas can be difficult.
- Lentigo maligna melanoma is frequently extensive and clinically ill-defined.
- Desmoplastic melanomas have lower risk of lymph node metastases than other subtypes of a similar Breslow thickness.
- Neurotropism can compromise resection margins and may justify use of adjuvant radiotherapy to the primary site.

Background

Traditionally, the classification of melanoma has been based on clinical and pathological features and recognised superficial spreading (SSM), nodular (NM), acral lentiginous (ALM) and lentigo maligna (LMM) melanoma. This classification was based on work published in the 1960's and 1970's suggesting that the major subtypes showed different clinical patterns and prognosis. More recently a number of less common subtypes including subungual, desmoplastic and naevoid melanoma, have been recognised.

The major limitations of the subtype classification system are the lack of prognostic significance of the subtypes and the limited correlation with treatment outcomes. The AJCC staging system does not include tumour subtype and therefore its removal from classification and standard reporting has been suggested. However, recent identification of different patterns of mutations between melanoma subtypes has brought new relevance to the subtype classification system. These mutation patterns also relate to clinical behaviour.

BRAF mutations are most common in SSM, commonly arising in non-glabrous non-chronically sun-damaged skin (non-CSD) and less frequent in LMM and ALM whereas melanomas arising in CSD skin, typically LMM, often harbour NRAS and sometimes KIT mutations. NM has a less characteristic mutation pattern (to date), indicating that this may not represent a true subtype.

SECTION 1

Superficial Spreading Melanoma

Key Points

- Superficial spreading melanoma (SSM) is the commonest melanoma subtype.
- SSM is related to intermittent sun exposure and commonly located on the trunk and extremities.
- Clinically SSM correlates well with the ABCDE rule.
- SSM often harbours a BRAF V600 mutation.

INTRODUCTION

Superficial spreading melanoma (SSM) is the most common melanoma subtype, both generally and among young people, and therefore is responsible for the majority of deaths (46%) from melanoma. SSM is characterised by an initial radial (horizontal) growth phase followed by an invasive vertical growth phase. SSM harbours BRAF V600 mutations more frequently than other subtypes and clinically best correlates with the classical 'ABCDE rule'.

EPIDEMIOLOGY

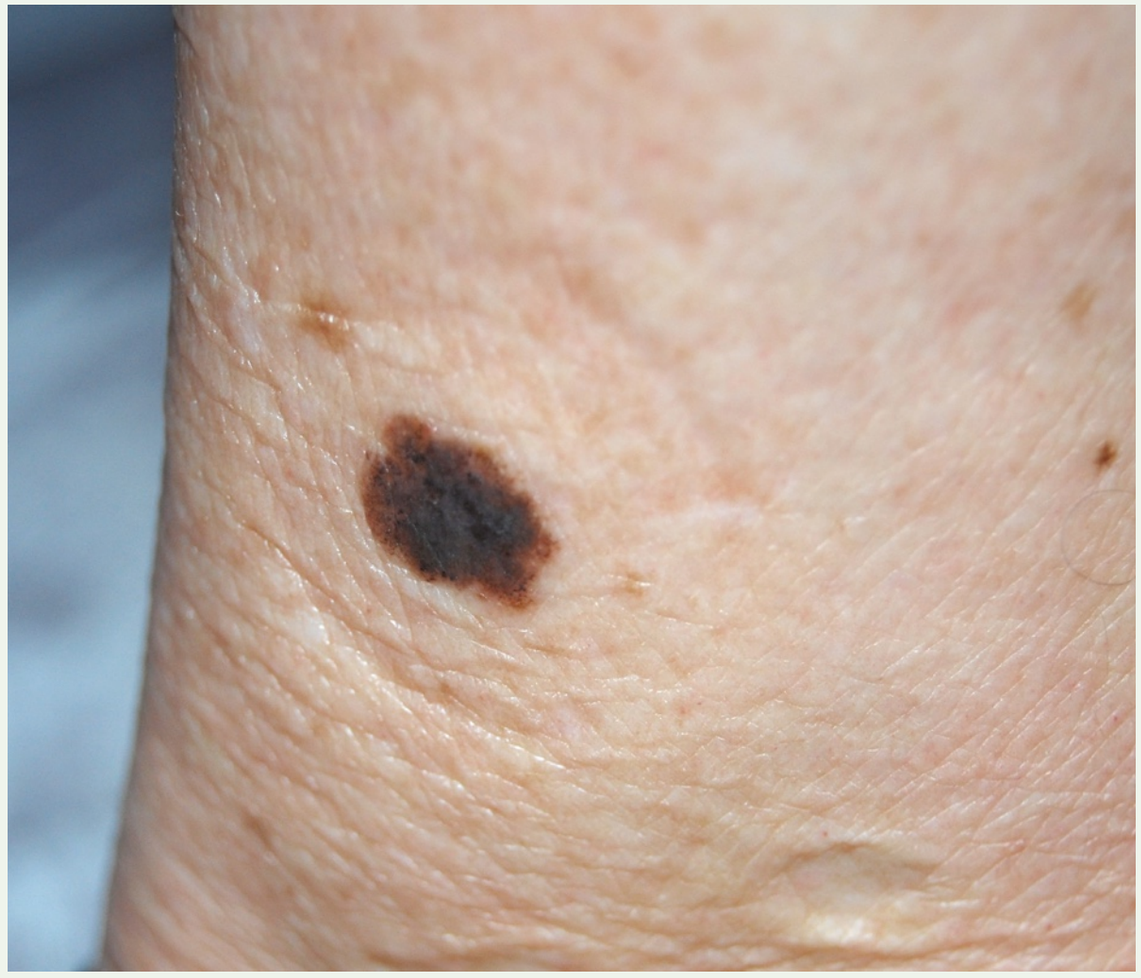
The incidence of SSM has increased by around 50% over the last 30 years. However, the mean tumour thickness has roughly halved, likely due to stage migration and an increase in the incidence of very thin melanomas. In keeping with the reduction in mean Breslow thickness, the mortality incidence has remained stable, therefore reducing within the subtype. SSM accounts for up to 66% of melanomas

and remains the most common histologic subtype, both in general and in young adults. As opposed to NM or LMM, SSM usually occur in younger patients, with median age being the 5th decade.

Aetiology

Risk factors for SSM include sun exposure, family history of melanoma, large numbers of benign naevi and more than a few dysplastic naevi. SSM appear to be more strongly related to intermittent sun exposure and sunburn, especially in childhood, than other melanoma subtypes. Anatomically SSM has a predilection for trunk (males) and extremities (females: esp legs) in fair skinned individuals. BRAF mutations are more common in SSM than other subtypes and are found in approximately 50% of SSM. In general BRAF-mutated melanomas occur in a younger age group on skin without marked solar elastosis, primarily trunk and lower extremities, indicating that BRAF-mutated melanomas arise early

Figure 4.1 Clinical examples of Superficial Spreading Melanomas



Clinical image of a 0.8mm Breslow SSM on the leg.

(Image 1 of 2)

1 of 25

in life at low cumulative UV doses.

Clinical Diagnosis

Clinically SSM usually presents as a flat, slowly growing, irregular lesion with variegated black, brown, tan, blue or reddish pigmentation. It may also have pale areas of regression or nodular areas representing deeper dermal invasion. The lesions typically enlarge in an asymmetric radial manner.

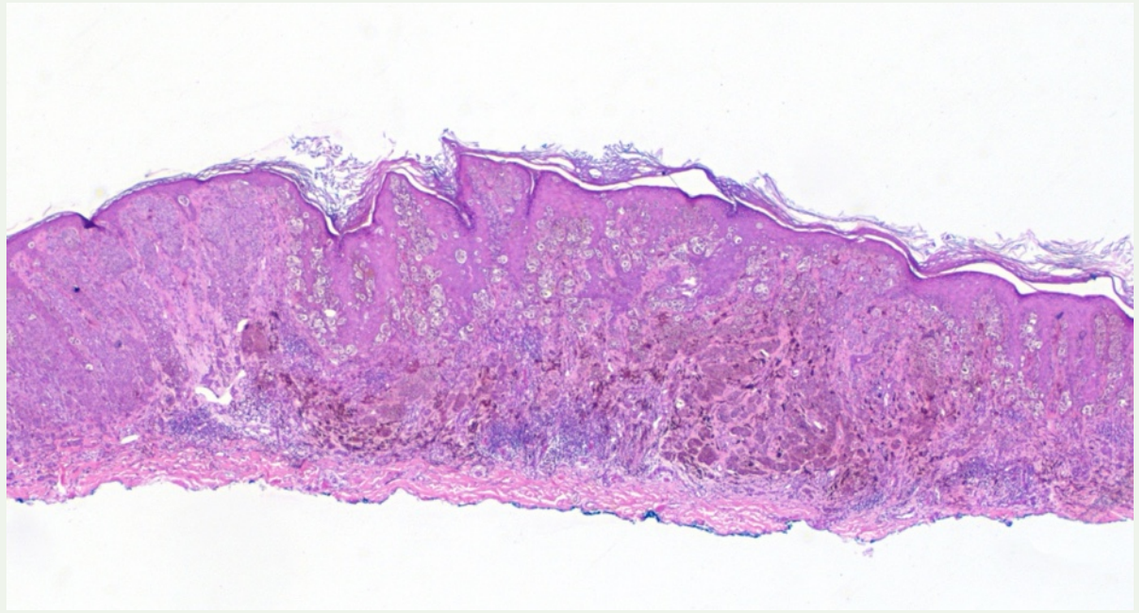
On dermoscopy the clinical multi-component pattern with asymmetry and multiple colours is confirmed. SSM commonly demonstrate an atypical reticular pattern with holes and thick lines, blue-white veil, irregular vessels, central ulceration and irregular distribution of dots.

Histopathology

See Understanding Pathological Assessment *for background explanation of features.*

- SSM is characterised by laterally proliferating melanocytic tumour cells within the epidermis together with poor definition of the lateral extent of this process. This frequently correlates with the clinical observation of indistinct margins of these tumours. The epidermal part of the tumour typically extends beyond the underlying dermal component. Main architectural changes within the epidermis are poor circumscription of melanocytes, single melanocytes predominating over nests, dyscohesive nests, and haphazard, widespread Pagetoid (upward migration above the basal layer) distribution of melanoma cells. Cytologically, epidermal melanoma cells are most commonly large and pleomorphic with abundant eosinophilic cytoplasm, vesicular nuclei and large, eosinophilic nucleoli, which may be multiple. Mitoses are frequently seen.

FIGURE 4.2 HISTOPATHOLOGICAL EXAMPLE OF A SUPERFICIAL SPREADING MELANOMA



In this classical example of superficial spreading melanoma, the epidermis is heavily infiltrated by large round pale melanoma cell, showing upward migration toward the keratin layer (i.e. pagetoid spread). A population of heavily pigmented cells are seen in the subjacent dermis, representing invasive melanoma.

(1 of 3)

- The dermal component of SMM can exhibit increased mitotic activity, brisk and asymmetrical infiltration of inflammatory cells, and occasional regression (fibrosis with neovascularisation). The normal sequence of melanocytic maturation is lacking or unapparent with the cells at the deepest extent of the dermal invasion being cytologically indistinguishable from those within the superficial papillary dermis. The cells are generally of the epithelioid subtype.

TREATMENT

SSM represents the largest subgroup of melanoma and in Australia at least, the typical Breslow tumour thickness is approximately 0.7mm. Fortunately, most of these melanomas are appropriately definitively managed with relatively simple wide local excision after the clinical diagnosis is confirmed with an initial excisional biopsy.

The general principles of primary melanoma management apply to SSM, which in summary are:

- Initial excision biopsy of clinically suspected tumours.
- Consideration of sentinel node biopsy for tumours with Breslow thickness >1mm, or tumours with other adverse features including ulceration, elevated tumour mitotic rate, or lymphovascular invasion, especially in younger patients.
- Definitive wide local re-excision utilising surgical margins of 10 - 20mm.
- Ongoing clinical surveillance to monitor patients for recurrence and further primary skin cancers of all types.

SECTION 2

Nodular Melanoma

Key Points

- Nodular melanoma (NM) accounts for approximately 15% of cutaneous melanoma.
- NM is most common in males and demonstrates a predilection for the trunk.
- At diagnosis NMs are generally thicker, with more adverse features than other melanoma subtypes.
- Up to 1/3 NMs are amelanotic.

Introduction

Nodular melanoma (NM) is most common in male adults and has a predilection for the trunk. When compared with superficial spreading melanomas (SSM), the prognosis is identical when controlled for depth of invasion. However, NM is believed to immediately enter a vertical growth phase, correlating with more rapid growth and a higher rate of metastasis. The genetic mutation profile identified to date is less well defined than for other melanoma subtypes.

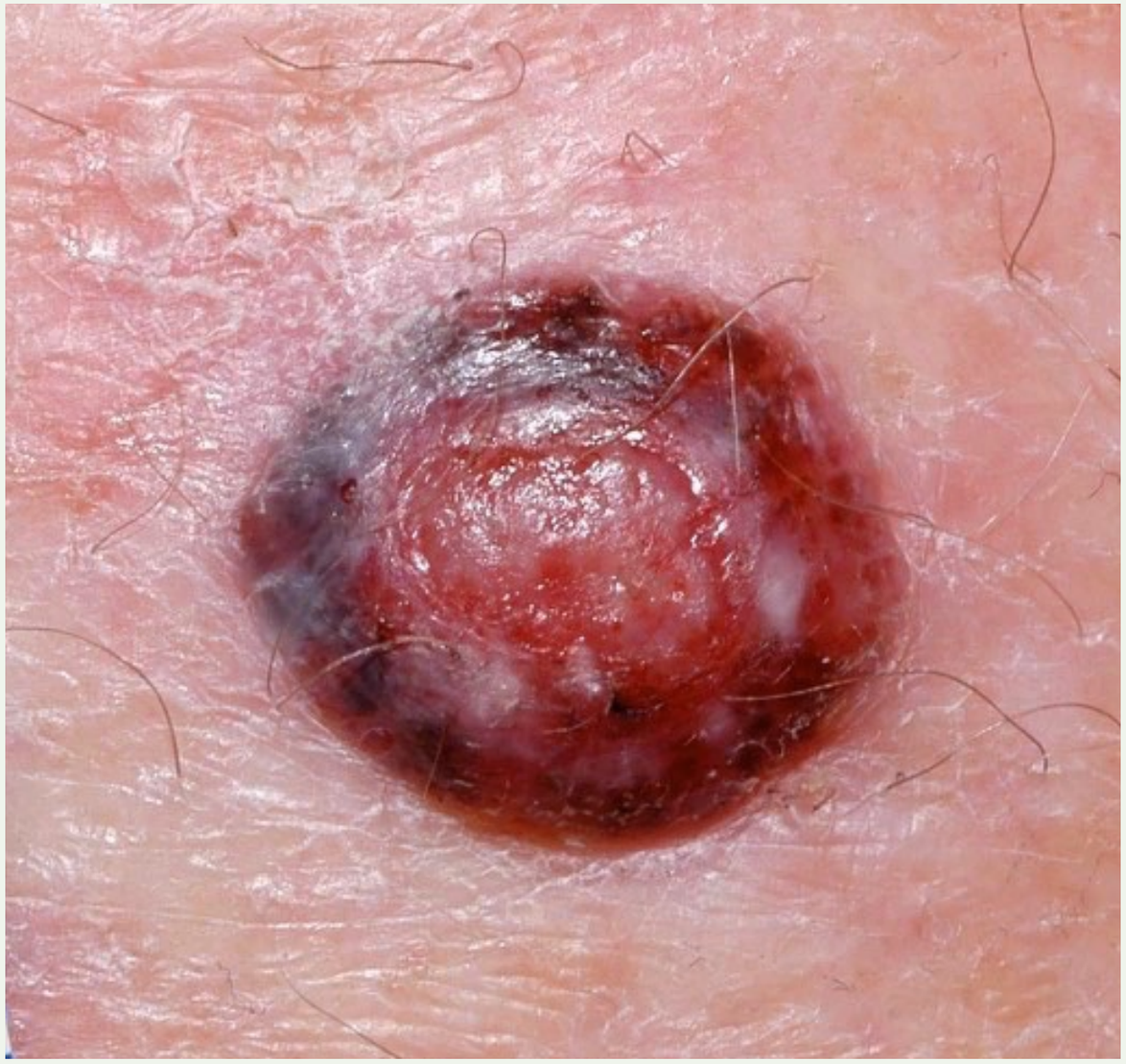
Epidemiology

Nodular melanoma accounts for only about 15% of melanomas, but a similar percentage of melanoma related deaths as the far more common SSM. Amongst thick melanomas, NM is the most common subtype (70% of those with Breslow >3mm) and are generally thicker than other subtypes at diagnosis; in a large study the median thickness was 2.6mm for NM and 0.6mm for SSM. The thickness of SSM tumours has halved in recent years, whereas there has been no change in median thickness, incidence or survival of NM. This lack of reduction in thickness may be due in part to a difficulty in diagnosing NMs, as they are less likely to be recognised with the ABCDE rule, due to their typically regular border and homogenous colour. NM is twice as common in males as females and most patients are over the age of 50 at diagnosis.

Aetiology

NM is less strongly associated with sun exposure than SSM and lentigo maligna melanoma. The patient-reported duration of change in the lesion before diagnosis is shorter for NM than for SSM (5 vs 9 months), correlating with early rapid vertical growth. The evidence of mutations in NM is conflicting and less characteristic than for other subtypes, suggestion that NM may not represent a

FIGURE 4.3 CLINICAL EXAMPLES OF NODULAR MELANOMA



Nodular melanoma. This tumour demonstrates significant symmetry, a smooth outline, and only minimal pigmentation peripherally. The tumour is clinically ulcerated. Breslow thickness: 3.72mm.

true subtype.

CLINICAL DIAGNOSIS

Clinically NM often does not adhere to the 'ABCDE rule' and usually presents as a dark rapidly growing nodule with more regular borders and uniform colour than SSM (Figure 4.3). NM is more frequently amelanotic/hypomelanotic than other melanoma subtypes (up to one third).

On dermoscopy, pigmented NM not infrequently demonstrate a symmetrical shape and pigment pattern with large vessels, and areas of homogeneous blue pigmentation. Blue-white veil, pink colour, black colour, and milky red/pink areas are also common.

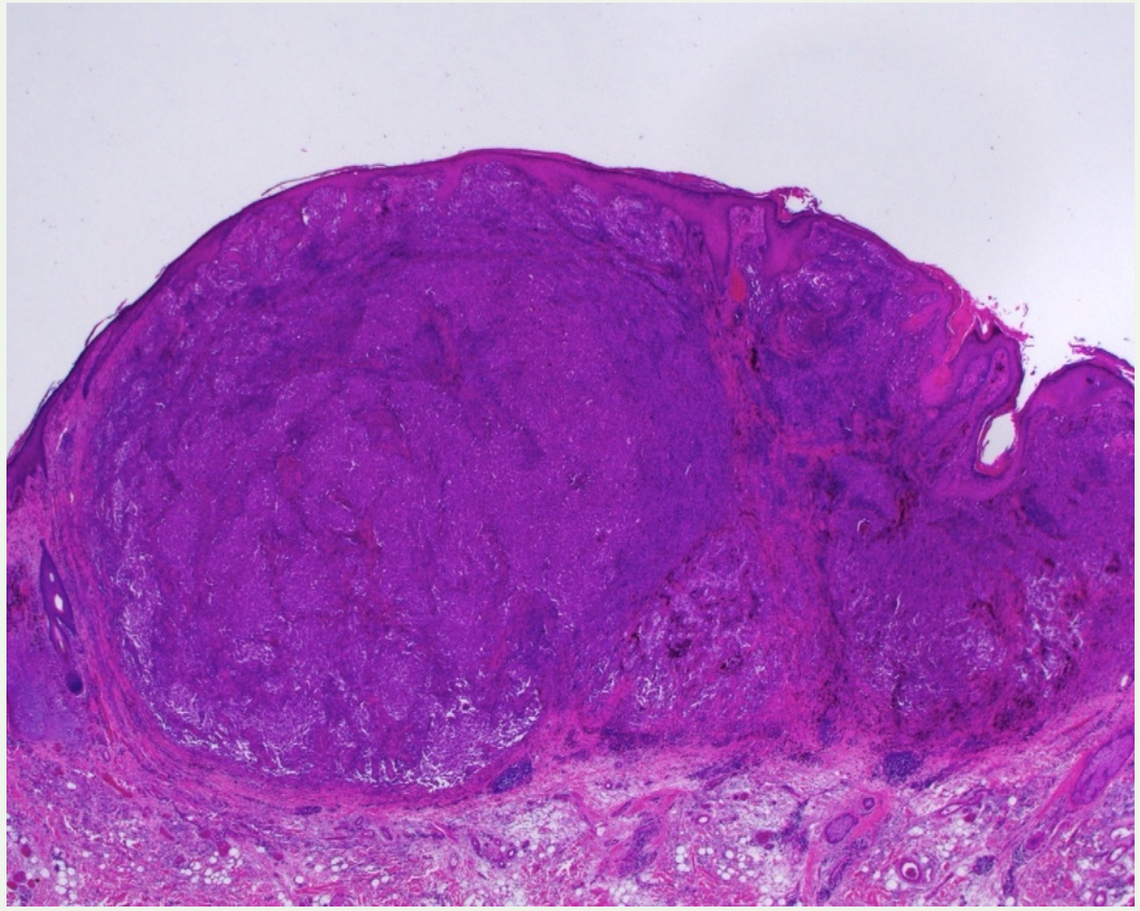
HISTOPATHOLOGY

See Understanding Pathological Assessment for background explanation of features.

NM shares many histological features with SSM, but differs particularly by commonly demonstrating sharp lateral circumscription and an epidermal component that is limited to the underlying dermal extension of the tumour (Figure 4.4). This correlates with the nodular clinical appearance of NM. The epidermal component of NM is characterised by epithelioid melanocytes with abundant cytoplasm, vesicular nuclei and prominent nucleoli. While single cells may predominate over nests, pagetoid spread is less abundant than in SSM. Ulceration is common.

The vertical growth phase usually begins at an early stage in NM. Consequently, the dermal component is often characterised by large nests and sheets of cytologically atypical melanocytes, correlating with the aggressive downward growth. An elevated mitotic rate is common in NM.

FIGURE 4.4 HISTOPATHOLOGICAL EXAMPLE OF A NODULAR MELANOMA



This nodular melanoma shows the characteristically rapidly expansile pattern of growth, which confers the tumour a protuberant appearance and in part explains the use of the term 'nodular'.

Treatment

NM is managed in essentially the same manner as SSM. However, the typical thickness of NMs is greater and other adverse histological features, including ulceration and an elevated mitotic rate, are more common. Excision margins and indications for sentinel node biopsy are based on the same general principles of management as for melanomas in general.

Section 3

Acral Melanoma

Key Points

- Acral melanoma (AM) accounts for approximately 1-3% of cutaneous melanoma in Caucasians, but up to 58% in dark skinned people, however the incidence is identical.
- AM occurs on glabrous skin and is more common on feet than hands.
- Clinical appearance is often atypical and AM is often mistaken for benign conditions, delaying diagnosis; a high index of suspicion is needed for acral lesions.
- AM has a poorer prognosis than melanoma located elsewhere.

Introduction

Acral melanoma (AM) is a rare melanoma subtype occurring on the glabrous (hairless) skin on soles, palms and subungual areas. Subungual melanoma is often considered as a separate subcategory of AM, due to the unique anatomy and histology of the nail unit. The diagnosis of AM is often delayed, because it is mistaken for benign conditions and it bears a poorer prognosis than melanomas located elsewhere.

Epidemiology

AM accounts for 1-3% of all cutaneous melanomas. The incidence across Caucasian and darker skinned populations appears to be similar. However, AM accounts for a much higher proportion of melanoma in darker skinned individuals, due to the rarity of other melanomas: 36% in black, 58% in Asian and 1-3% in fair skinned populations.

AM is more common on the feet than on the hands. The mean age at diagnosis tends to be higher than for other types of melanoma (between 60 and 70 years), with similar incidences in males and females.

Aetiology

The aetiology of AM is not clear. Genetic or environmental factors other than sun exposure are believed to be important, since the incidence is similar across all skin colours. Previous trauma and acral naevi have been identified as potential risk factors in some studies. However, trauma as a potential risk factor has to be interpreted with caution, as there may be recall bias.

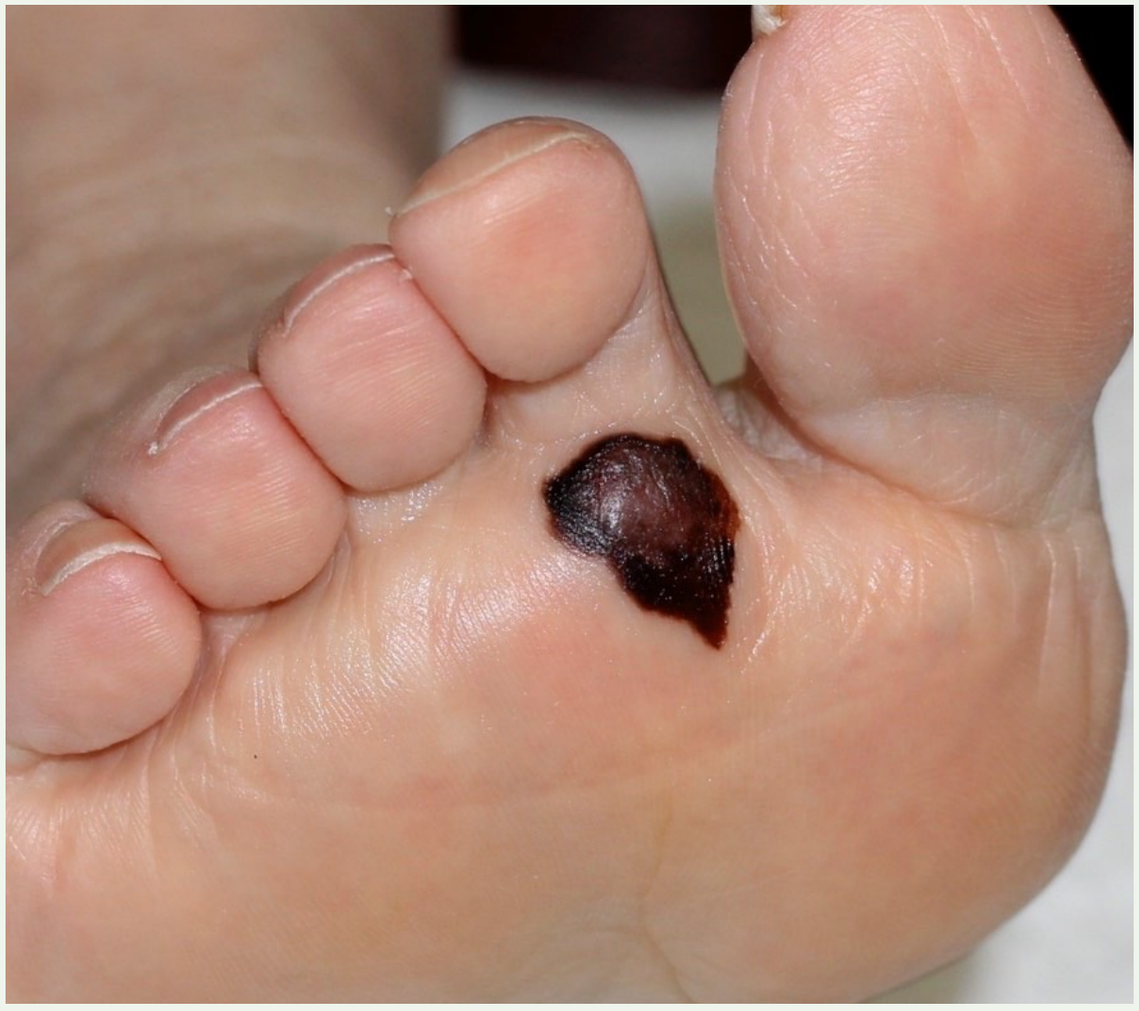
Mutation analysis has shown some unique molecular features of AM. BRAF mutations are less common in AM, whereas KIT mutations are more common than in other melanoma subtypes.

Recent studies have suggested that AM represents a biologically more aggressive form of melanoma than non-acral melanoma, with a poorer survival and a higher rate of local and in-transit recurrence. Molecular tests have shown atypical cells to be present as far as 3mm beyond the histologically detectable boundaries of AM, which could reveal one mechanism of local recurrence.

Clinical Diagnosis

Clinically, AM can present as a classical melanoma (ABCDE rule). However, up to 28% are amelanotic and these pose a particular diagnostic challenge. They are frequently mistaken for benign disease

FIGURE 4.5 CLINICAL EXAMPLES OF ACRAL MELANOMA



Acral Melanoma Breslow thickness 1.90mm TMR: 2/mm²

(Image 1 of 2)

such as warts, benign naevi or fungal infections, resulting in delayed diagnosis. Medical misdiagnosis occurred in 56% cases in one study leading to a median delay of 12 months in the diagnosis of palmoplantar melanomas and 18 months for subungual melanomas. Another reason for delay is patients' failure to appreciate the presence of new and changing lesions, especially on the soles. The Breslow thickness of AM tends to be greater at diagnosis and the stage more advanced with resulting worse survival outcomes. However, in a recent series AM patients were stage matched with patients with non-acral cutaneous melanoma and shown to have a poorer disease specific survival, suggesting that AM is biologically more aggressive.

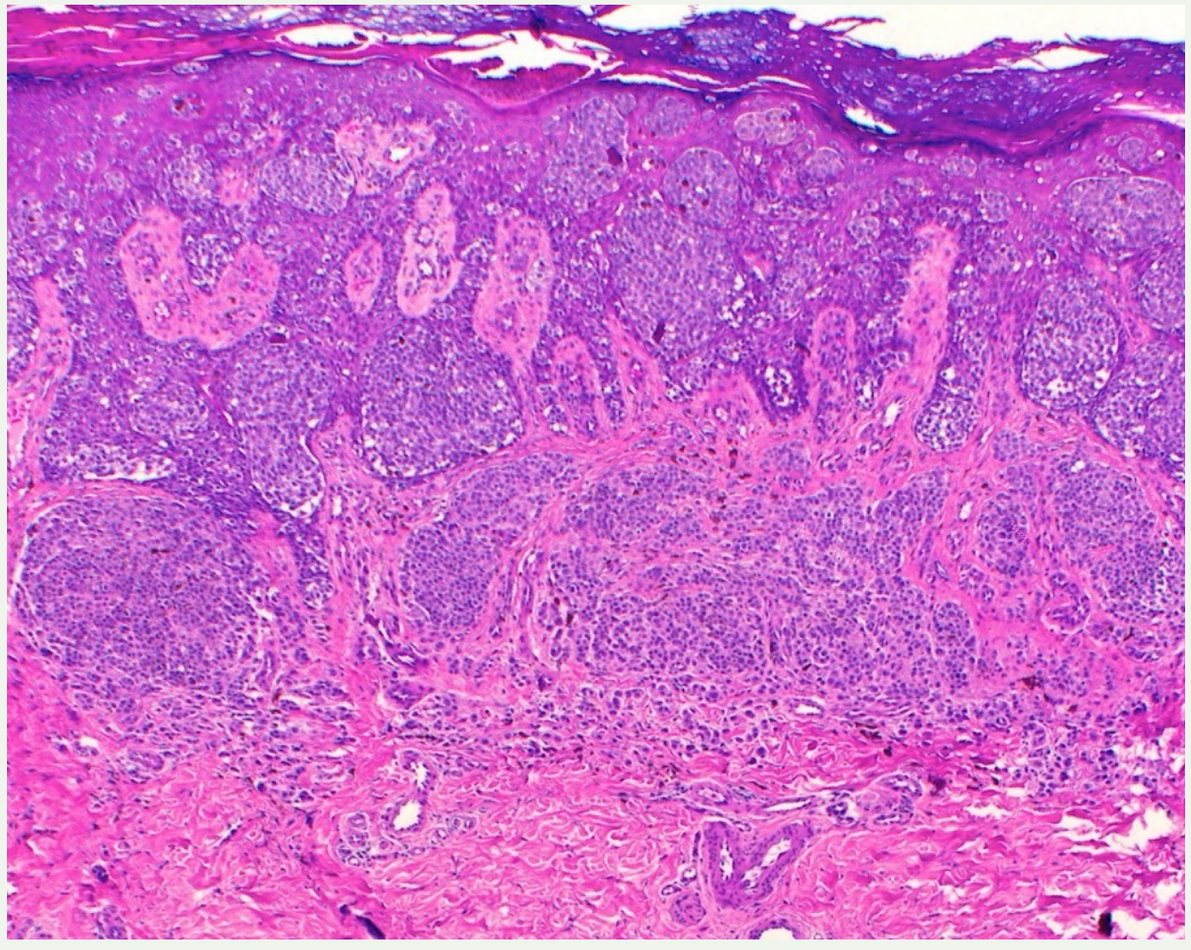
When lesions that were thought to be benign fail to respond to appropriate therapies, biopsy is of critical importance to exclude malignancy. An excision biopsy with 2mm margins is preferred, but can be difficult or inappropriate in the setting of a large acral lesion due to functional impairment. Incisional or punch biopsies can be useful, which should sample both the area of greatest clinical concern and a peripheral, non-necrotic area. Specialist referral before biopsy may be considered.

Dermoscopy can aid in the diagnosis, particularly in differentiating benign acral melanocytic lesions from early melanoma. Specific dermoscopic features are associated with pigmented lesions on glabrous skin; irregular diffuse pigmentation and a parallel ridge pattern with accentuated pigmentation on the ridges is highly suggestive of AM. Dermoscopy has not been validated for amelanotic AM and biopsy should be performed in case of clinical suspicion.

Histopathology

See Understanding Pathological Assessment *for background explanation of features.*

FIGURE 4.6 HISTOPATHOLOGICAL AND CLINICAL EXAMPLE OF ACRAL MELANOMA



This image of acral melanoma shows a markedly disordered epidermis almost completely over run by melanoma spreading as single cells and also forming large nests. The haphazardly distributed population of cells in the dermis signifies invasive melanoma.

(Image 1 of 4)

- The melanocytes in AM are present as nests and single cells along the dermo-epidermal junction. In the epidermis, pagetoid spread is often extensive. Pagetoid spread is also commonly seen in benign acral naevi, but much less widespread. Both epidermal and dermal melanocytes are most commonly hyperchromatic and spindled and nucleoli are often not apparent.

  Dermal invasion is characterised by fascicles, nests and single cells through the dermis. The cells are often tracking down along sweat ducts and blood vessels. There is limited maturation with progressive descent through the dermis. Ulceration is frequently found, whereas mitotic activity is variable.

TREATMENT

The suspected diagnosis of AM should prompt referral to a specialist surgical oncologist. Treatment requires wide excision of the primary site with generous margins, as AM has been shown to

harbour atypical cells far beyond the clinical margins. Adequate surgical resection needs to be combined with suitable reconstruction to optimise the functional outcome of the limb. Most lesions, even in weight bearing areas, can be treated with excision and full thickness or split thickness skin grafting. Over time, grafts tend to partly fill out the contour defect, but are prone to desiccation and cracking. Grafts harvested from the instep of the contralateral foot may overcome some of these problems, but may have higher morbidity initially. Some local flap options are available for smaller defects in weight bearing areas, such as the medial plantar artery flap or the reverse sural flap for heel reconstruction. Thicker, advanced lesions may require amputation. Free flaps are very rarely required.

SECTION 4

Subungual Melanoma

Key Points

- Subungual melanoma (SUM) accounts for approximately 1% of cutaneous melanomas in Caucasians, but a much higher percentage in dark skinned people; however the incidence is identical.
- SUMs most commonly present on the big toe or thumb as a pigmented band or a nodule; ≤50% are amelanotic.
- Clinical and pathological diagnosis can be difficult and is often belated; dermoscopy is valuable for selecting patients for immediate biopsy vs observation.
- SUMs have a poorer prognosis than melanomas located elsewhere.

Introduction

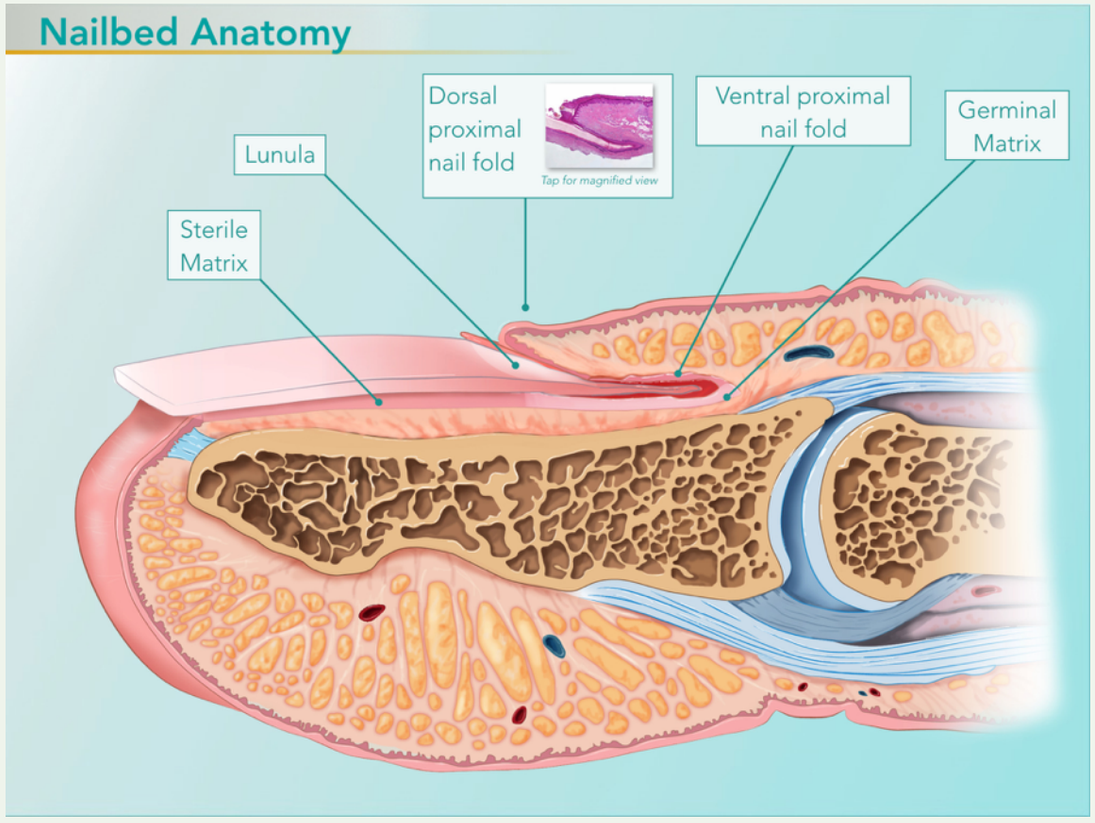
Melanoma of the nail unit is an uncommon form of melanoma that is generally regarded as a subtype of acral melanoma and most frequently arises from the nail matrix (subungual) or from the skin beside the nail plate (periungual). The term "subungual melanoma" (SUM) is usually used to describe both locations.

Diagnosis of SUM may be difficult to diagnose both clinically and pathologically because of the broad range of atypical, often unpigmented, clinical presentations. Diagnostic delay is therefore common with SUMs, which are generally thicker at diagnosis than melanomas located elsewhere. This partly accounts for a higher rate of metastasis at the time of diagnosis. Likewise the survival rate is lower for SUM compared to melanomas located elsewhere. SUM is most often a variant of acral lentiginous melanoma. Other less common subtypes are nodular and desmoplastic melanoma.

Epidemiology

SUM accounts for approximately 1% of melanoma in people of Caucasian heritage, whereas it is a relatively more common melanoma subtype in individuals with darker skin, i.e. 23% of melanoma in

Interactive 4.1 The Nailbed Anatomy



Japanese people. However, the incidence is similar across racial groups and the higher proportion of SUMs in dark-skinned people is due to the rarity of other melanoma subtypes. SUM most commonly affects the great toe (24–43%), followed by the thumb (18–31%). SUMs occur most frequently in the sixth and seventh decade. The distribution between sexes is equal.

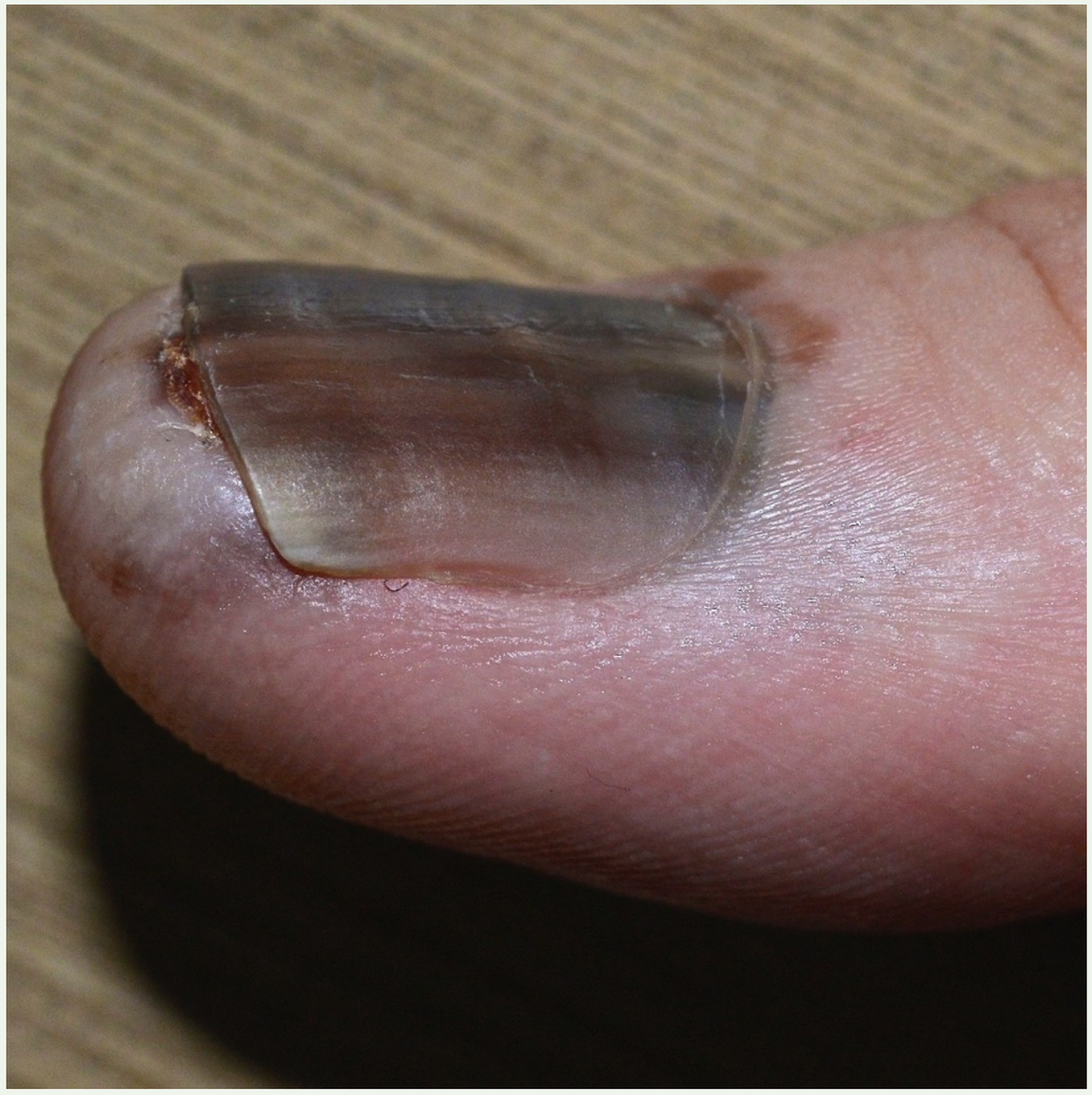
Aetiology

SUM most commonly arises from the germinal matrix, but may involve other components of the nail unit; the proximal nail fold, sterile matrix and hyponychium Interactive -.-. SUM is usually regarded as a form of cutaneous melanoma and is most commonly of the acral subtype. SUM seems not to be associated with sun exposure, as the nail plate acts as a protective barrier against ultraviolet B irradiation. A cause and effect relationship between trauma and SUM has been postulated, as up to 55% of patients present with a history of trauma prior to diagnosis of SUM, especially in the great toe and thumb. However, the high frequency of trauma to these sites means the association is likely to be either coincidental or due to it drawing attention to the tumour. Therefore, the role of trauma in the pathogenesis of the SUM is not conclusively established. Conversely, trauma may also mask an underlying SUM, causing a delay in its diagnosis.

Clinical Diagnosis

SUMs are often difficult to diagnose clinically, with up to half being amelanotic. A common presentation of an SUM is a pigment band along the length of the nail plate (longitudinal melanonychia). Over weeks to months this band may broaden, especially at its proximal end (cuticle) and become increasingly irregularly pigmented. Extension into the adjacent nail fold is called "Hutchinson's sign" and should raise a high suspicion for melanoma.

FIGURE 4.7 CLINICAL EXAMPLES OF SUBUNGUAL MELANOMA



Subungual melanoma right thumb demonstrating Hutchinson's sign and pigmentation of the distal pulp. Breslow 1.20mm, TMR: 0/mm^2 . Image 1 of 3

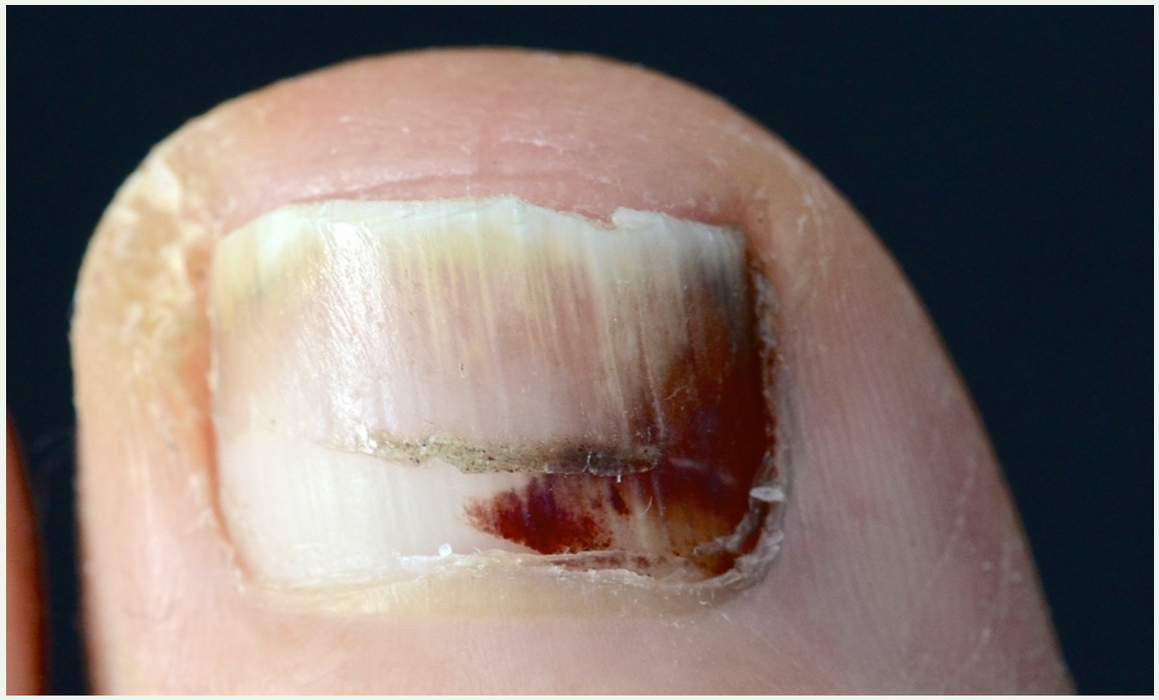
1 of 12

However, longitudinal melanonychia presents in a broad range of conditions (Table 4.1) and is much more frequent in non-Caucasians than in Caucasians. SUM also commonly presents as a nodule with ulceration or bleeding, as well as cracking and distortion of the nail plate (onycholysis). Other features that should cause a raised concern for SUM are; onset at older age, involvement of a single digit, history of rapid growth, or a pigmented band broader than 3 mm and/or triangular in shape.

Subungual haematoma Figure 4.8 is the most common clinical differential diagnosis for SUM, due to the high frequency of this condition. Unlike SUM, haematoma does not conform to a band-like pattern and if suspected, may be observed for a few weeks. If the lesion is a haematoma, it should then be growing out with the nail and normal-appearing nail growing behind it. However, it must be remembered that melanoma may also bleed. Other

differential diagnoses are benign tumours, infectious and inflammatory conditions, as listed in Table 4.1.

FIGURE 4.8 SUBUNGUAL HAEMATOMA; A CRITICAL DIFFERENTIAL DIAGNOSIS



A pigmented lesion affecting the medial half of the left great toe. Note that a narrow band of clear nail is visible behind the lesion centrally. There is no Hutchinson's sign. Provisional diagnosis subungual haematoma. Lesion photographically monitored.

(Image 1 of 2)

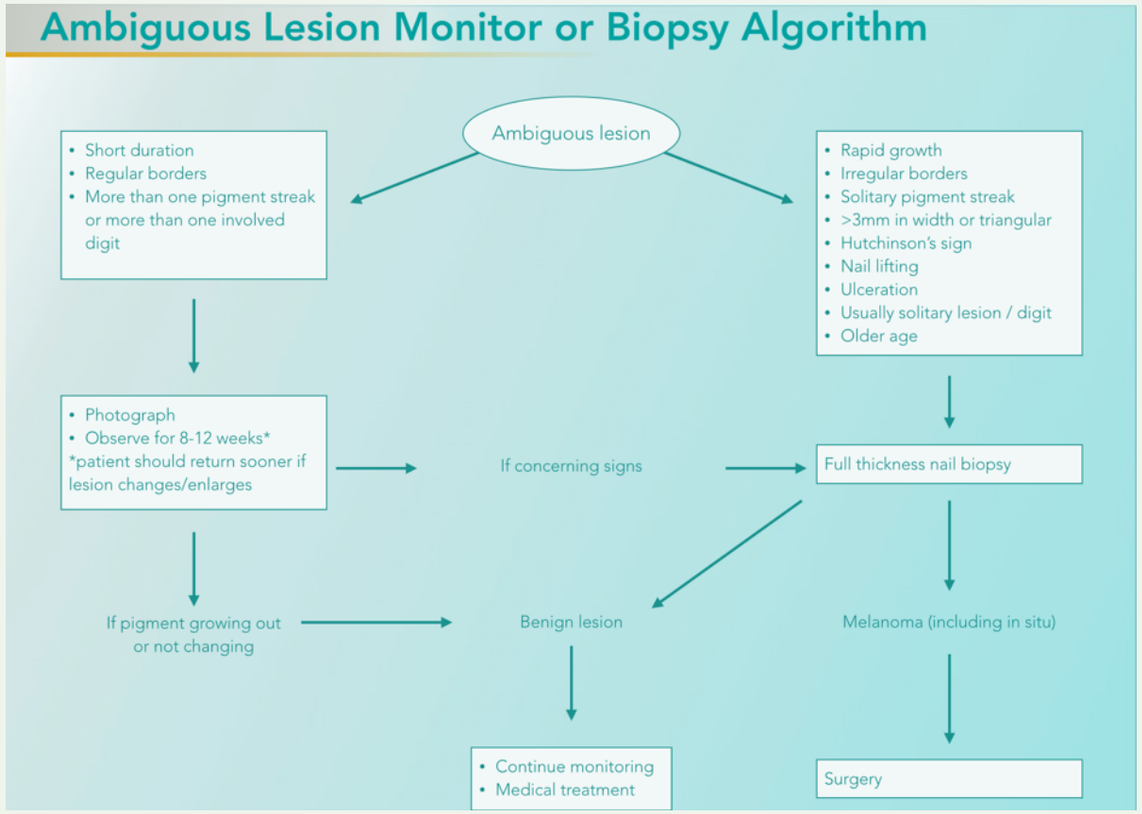
TABLE 4.1 NON-MELANOMA CAUSES OF NAIL PIGMENTATION

Condition	Disease
Malignant and premalignant tumors	• melanoma, melanoma in situ • SCC, Bowen's disease • BCC • Kaposi's Sarcoma • keratoacanthoma
Benign tumors	• naevus • normal hyperpigmentation in skin type IV-VI* • pyogenic granuloma • glomus tumor • epidermal cyst • fibroma • exostosis
Infectious conditions	• fungal infection • bacterial infection (pseudomonas) • warts
Inflammatory conditions	• psoriasis • lichen planus
Systemic conditions and drugs	• addison's disease, Cushing's syndrome* • AZT, antimetabolites, antimalarials, minocycline* • Peutz Jegher syndrome*
Trauma	• haematoma, hemorrhage

** Most commonly seen in multiple digits*

Dermoscopy may be a helpful diagnostic tool to distinguish SUM from other lesions. Haemorrhage is usually characterised by a lack of pigment network and the presence of well-circumscribed dots or blotches with a red to red-black pigmentation. Pigmented lesions of the nail unit, however, often lack the conventional dermoscopic criteria that have been described for other cutaneous sites. SUM may show the following features; Hutchinson's sign, longitudinal irregular bands or lines of varying colour, width and shaping (including triangular), vascular pattern, and ulceration as well as loss of the usually parallel pattern of the ridges along the length of the nail. Dermoscopic diagnosis of amelanotic SUM is particularly challenging, but SUM should be suspected if fragments of melanin granules are seen. Dermoscopes with polarising filters are not recommended for nail bed assessment, due to the optical properties of the nail plate. The convex shape of the nail unit requires an adequate immersion medium, such as ultrasound gel, to fill the cavities and enable proper dermoscopic examination. Although a number of clinical and dermoscopic criteria have been recognised to be at least suggestive of SUM, they are only rarely reliable alone.

FIGURE 4.9 ALGORITHM FOR AMBIGUOUS LESIONS MANAGEMENT



A definitive diagnosis of SUM is made histologically with a biopsy. Ideally, an excisional biopsy is performed with sampling of the entire origin of the pigment in the nail matrix. However, these lesions are often large and punch or incisional biopsies down to periosteum have traditionally been accepted as adequate, to minimise the risk of nail dystrophy. For lesions where there is a high suspicion of melanoma, the goal of a subtotal nail biopsy is to confirm the diagnosis of melanoma and give an indication of the Breslow thickness. The resultant pathology report will guide discussion about final treatment (amputation/wide excision and sentinel node biopsy). Small less suspicious melanocytic lesions up to 2-3mm in diameter can be excised completely, whereas an incisional biopsy is required for larger lesions to establish a diagnosis. A biopsy is performed either through the nail plate or after reflection of the nail fold and careful elevation of the nail plate, to avoid distortion of the specimen or nail matrix. However, even with small biopsies there is a potential for change in the nail bed and nail dystrophy. Nail fold biopsies are similar to biopsies taken elsewhere on the skin, and placing an elevator under the nail fold can protect the nail matrix.

The nail matrix is the most vital part of the nail unit, containing the epithelium that produces the nail plate. The proximal nail fold is continuous with both the nail matrix and the digital acral skin. The extensor tendon inserts approximately 12 mm proximal to the cuticle and therefore is usually not involved in biopsy taking. The use of a digital tourniquet ensures a good view of the operative site and prolongs the action of the digital ring block anaesthetic if plain lidocaine is used, though it is usually safe to use adrenaline.

Histopathology

See Understanding Pathological Assessment *for background explanation of features.*

Subungual melanoma is generally considered a variant of acral melanoma. SUM can be diagnostically challenging for the pathologist, especially in subtotal biopsies or in previously biopsied specimens, which may be associated with worrying cytology and architecture such as mitoses and pagetoid epidermal growth ("pseudo melanomas"). In addition, over-diagnosis of malignancy in melanocytic lesions displaying single cell invasion of the nail matrix epithelium may occur. However, this is a non-specific histopathological finding, particularly at acral sites. Consequently, repeat biopsies may be needed.

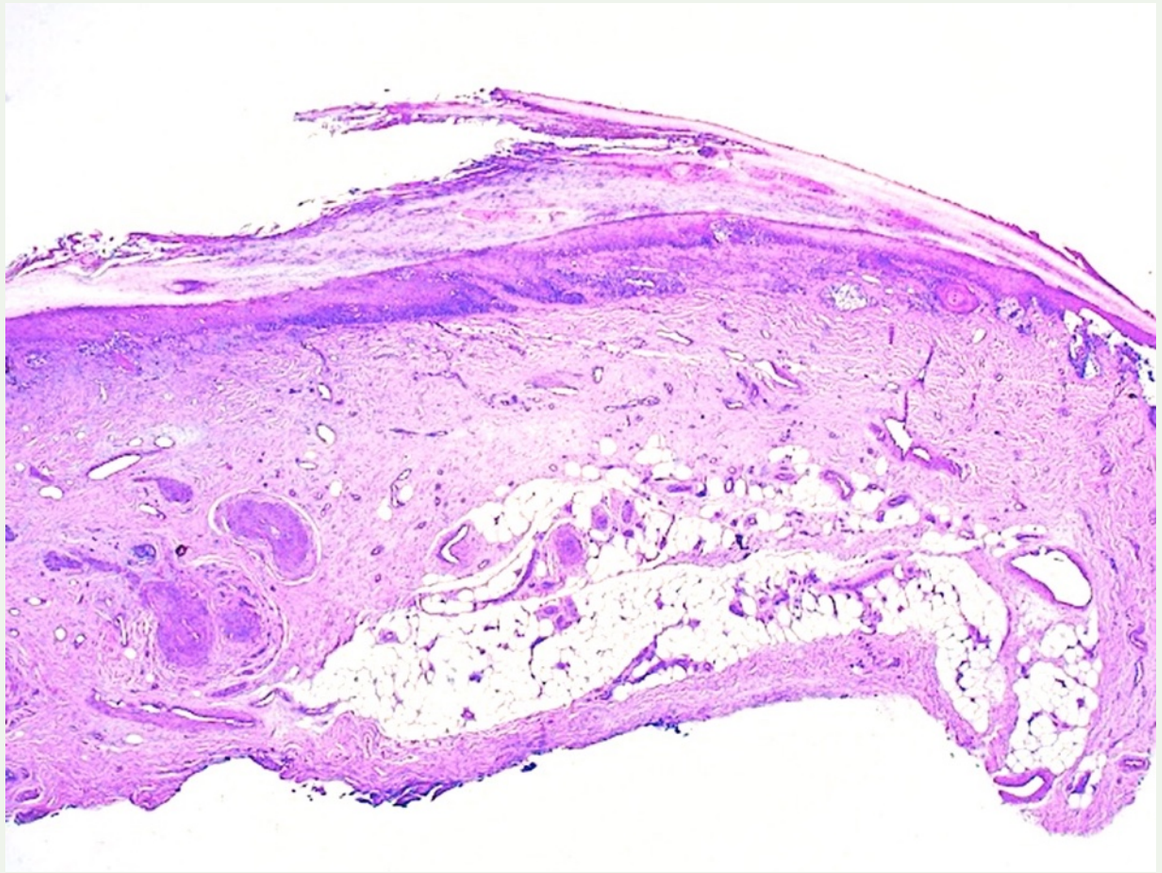
There is some uncertainty as to whether traditionally recognised histologic features (Figure 4.10) for melanoma are prognostically useful in SUM.

- Measurement of the Clark's level and Breslow thickness is hampered, due to difficulty in distinguishing the papillary from the reticular dermis, the absence of subcutaneous fat and the lack of a granular layer in the nail matrix. The number of melanocytes in the nail matrix is lower than in normal skin and most of these do not produce melanin in white-skinned people. There is a higher incidence of KIT mutations in acral melanomas compared to other melanoma subtypes, whereas BRAF mutations are less common.

Treatment

The treatment of subungual melanoma is primarily surgical. However, there are no evidence based guidelines as to the level of resection, and the body of evidence in the literature is poor. Choice of level of resection and reconstruction method should take into account both the risk profile of the tumour and future limb function. Traditionally, digital amputation

FIGURE 4.10 HISTOPATHOLOGICAL EXAMPLE OF SUBUNGUAL MELANOMA



This low power view of a longitudinal section of nail bed shows an inflammatory reaction against an element of intra-epidermal melanoma. This pattern of inflammation is a highly sensitive sign associated with subungual, mucosal and acral lentiginous melanoma.

has been the recommendation, since the lack of subcutaneous fat results in a close proximity of the nail bed to the bone. Consequently, many centres performed proximal amputations at the metacarpo- or metatarsophalangeal level. However, there is now a trend towards more limited resections that preserve function. For invasive SUM, functional amputations are usually performed at the distal or proximal interphalangeal level or at the neck of the middle phalanx (proximal phalanx in the thumb/great toe). The local recurrence rate seems not to be increased when a distal amputation is performed rather than a traditional proximal one.

It seems that in situ disease can safely be treated more conservatively than invasive disease. Options include excising the nail bed and skin grafting onto the underlying periosteum, or alternatively performing a minor amputation with preservation of the tendon insertions and a flap repair. This is in spite of the very small deep margins obtained.

Sentinel node biopsy should be discussed with and offered to patients with intermediate to high risk tumours, as for melanomas elsewhere. Patients with positive sentinel nodes are offered completion lymph nodes dissection and/or enrolment in trials. A staging PET-CT or CT should be performed if there is a suspicion of disease dissemination. Distant metastases are managed similarly to melanomas located elsewhere. ILI (isolated limb infusion) or ILP (isolated limb perfusion) may be offered in case of surgically non-resectable in-transit metastasis.

Section 5

Lentigo Maligna Melanoma

Key Points

- Lentigo Maligna (LM) is a slow growing melanoma precursor; the rate of conversion to invasive LM Melanoma (LMM) is unknown.
- LMM is often located on functionally and cosmetically sensitive areas of the head and neck in elderly people.
- LMM may be difficult to distinguish from LM
- LMM has a higher rate of local recurrence than other melanoma subtypes.

Introduction

The invasive form of LM is referred to as Lentigo Maligna Melanoma (LMM), one of the histological subtypes of melanoma.

LMM presents diagnostic, treatment and follow up challenges because of clinically indistinct margins over large areas in cosmetically and functionally sensitive areas of the head and neck, often in a background of extensive chronic sun damage, as well as a propensity to recur locally.

Epidemiology

LMM is typically found on the face and neck, where it is the most common subtype of melanoma. Peak incidence is in the 7th and 8th decades of life. LMM accounts for up to 15% of all invasive melanomas, with a rising incidence due to an increasing ageing population worldwide. The rate at which LM evolves to LMM is unknown; one study reported the lifetime

risk of developing LMM within a LM to be as low as 2.2% when diagnosed in 65 year olds and 4.7% when diagnosed in 45 year olds. However, other studies have reported conversion rates as high as 50%, with transition times varying from a few months to several decades. Despite these wide ranges in estimates, the most commonly quoted figures are around 20% lifetime risk.

Aetiology

Despite the requirement for chronic sun damage to the dermis in the diagnosis, chronic sun exposure has not been shown on multivariate or meta-analyses to be a risk factor. However, previous non-melanoma skin cancers increase the risk by up to 12 fold and sunburn episodes in the first 20 years of life may slightly increase it (1.1 fold).

BRAF mutations are less common in LM/LMM than melanomas occurring on non-chronically sun damaged skin, whereas KIT mutations, which are rare in non-chronically sun damaged skin, have been identified in LM/LMM in approximately 20%.

Clinical Diagnosis

Distinguishing LMM from LM can be difficult, with between 16% and 50% of excised LM containing LMM foci on histological examination. Macroscopic features that raise the suspicion of LMM include: increasing diameter, greater variation in colour, increasing border irregularity, elevation and white areas suggestive of regression (Figure 4.11).

Dermoscopy improves the diagnostic accuracy of diagnosing LMM over LM. The identification of the following additional dermoscopic features is strongly suggestive of LMM over LM:

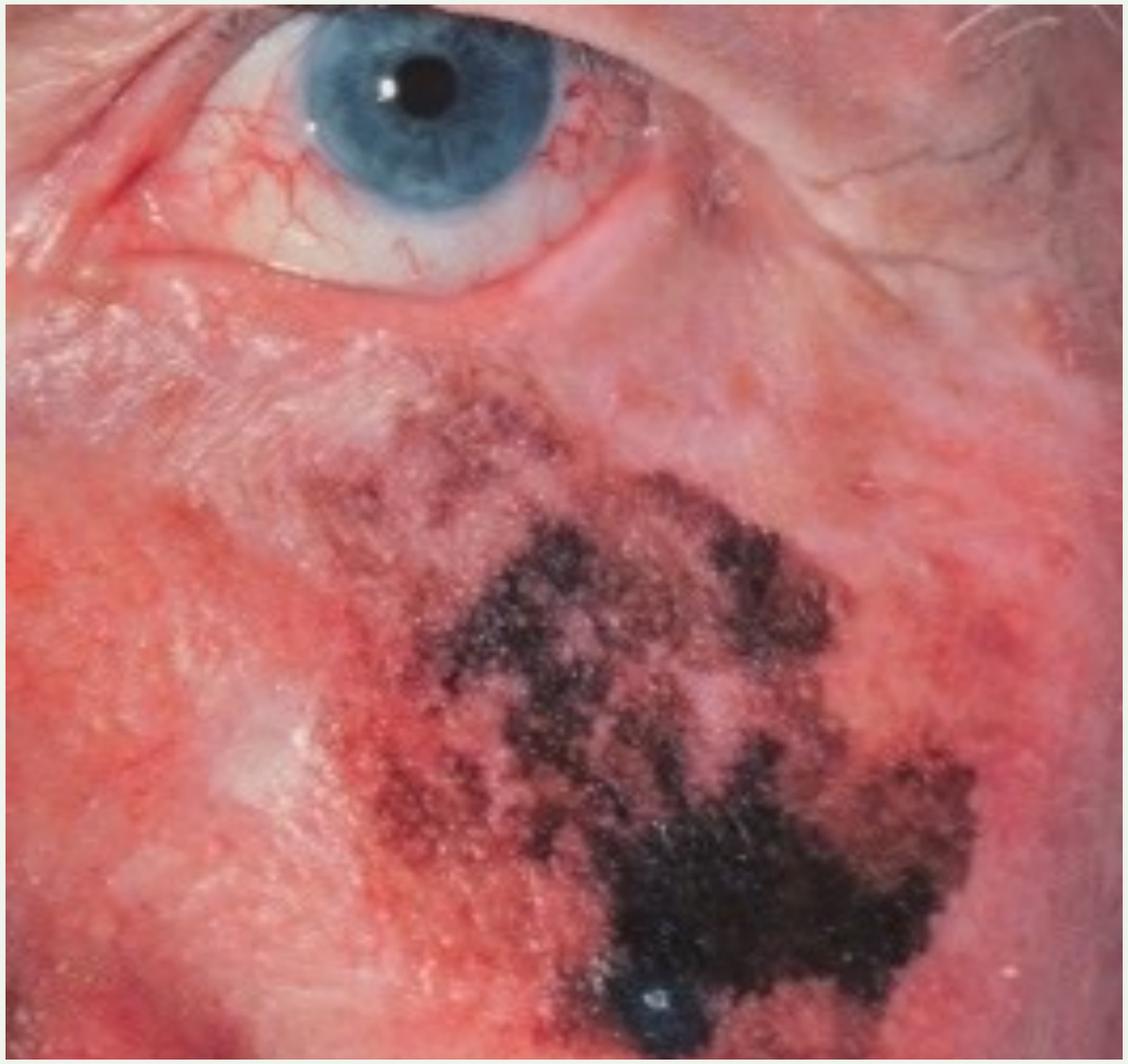
- no. of colours ≥5
- marked pigmented rhomboidal structures
- obliterated hair follicles
- red rhomboidal structures
- ulceration

- black structureless areas
- blue papular areas

Delineating the extent of the disease is clearly crucial for successful treatment. Atypical cells can extend far beyond visible margins and incomplete pathological margins after excision, following clinical assessment alone, are not uncommon.

When there is clinical suspicion of LM or LMM a biopsy should be performed. In general excisional biopsy is advocated; however, these tumours are often large and located in functionally and cosmetically sensitive facial areas. Therefore one or more incisional or punch biopsies should be performed from the most atypical parts of the lesion, often guided by dermoscopy.

FIGURE 4.11 CLINICAL EXAMPLES OF LENTIGO MALIGNA MELANOMA (FACIAL)



An example of an obvious Lentigo Maligna Melanoma on the left cheek, with an invasive component at the 6 o'clock margin.

Histopathology

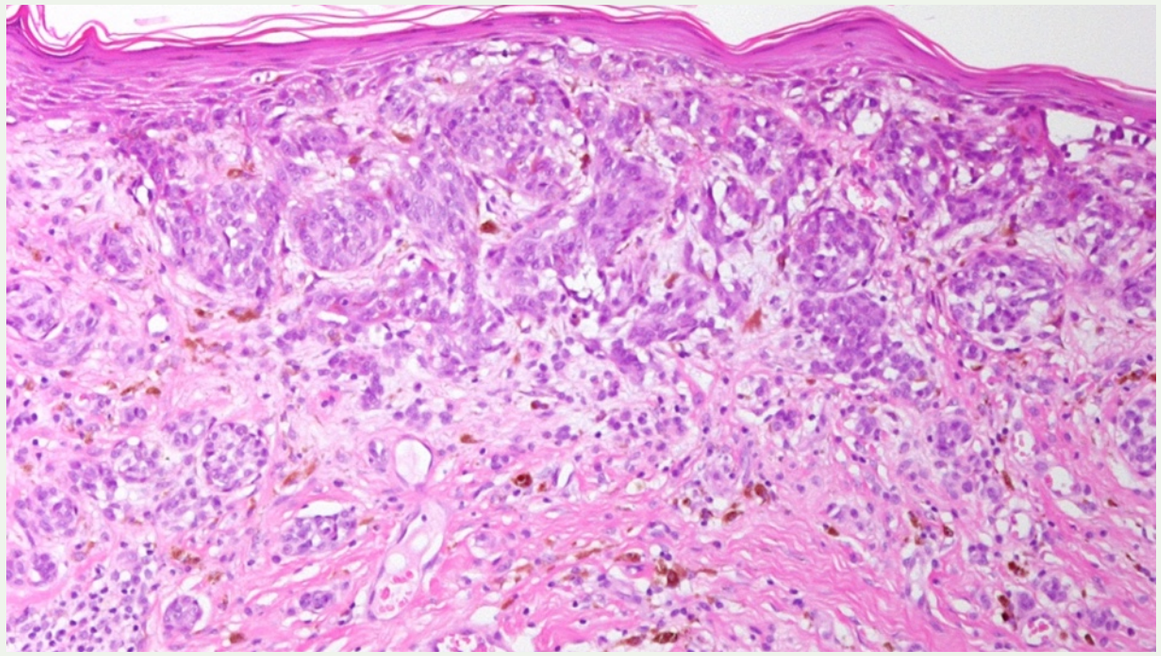
See Understanding Pathological Assessment *for background explanation of features.*

LMM is present in up to 15% of lentigo maligna lesions. The dermis is characterised by solar elastosis with ectatic vessels in the superficial vascular plexus. The melanocytes are hyperchromatic and most commonly show spindle shaped morphology, but lack the vesicular nuclei and prominent nucleoli commonly seen in other melanoma subtypes. There is a lack of dermal maturation, and perineural invasion is frequently seen, whereas mitotic activity usually is limited.

Treatment

Surgery is regarded the standard treatment of LMM, usually consisting of wide local excision (WLE) with a 10-20mm clinical margin, depending on the Breslow thickness and anatomical constraints. However,

Figure 4.12 Histological Features of Lentigo Maligna Melanoma



Low power view demonstrating the thinned dermis (solar elastosis) and melanoma invasion into the subcutaneous tissue.

LMM poses therapeutic challenges because of the often large size, indistinct clinical and pathological margins and location in functionally and cosmetically sensitive areas with limited local tissue availability for flap reconstruction. Consequently, a skin graft is often required. Furthermore, the LMM is

often surrounded by much more extensive LM, the extent of which may be particularly difficult to determine pre-operatively. The surgical options are as follows:

- wide local excision
- Staged surgical excision

Staged surgical excision (SSE) consists of preoperative delineation of the lesion using a Wood's lamp and thereafter excision of a marginal band surrounding the tumour at a 5-10mm margin, which is sent for permanent histology. The patient returns for subsequent excisions until negative margins are achieved. The tumour itself is excised last and the defect repaired. The advantages of this technique are sufficient marginal excision assessed by high quality permanent histopathological sections and avoidance of an open wound during the process.

Mohs micrographic surgery (MMS) is special form of SSE usually using frozen sections for histopathological evaluation of margins. Frozen sections offer convenience from a time conservation point of view, but introduce up to a 50% risk of false negative results due to artefacts. Therefore some use permanent sections instead of frozen sections ("slow Mohs"). MMS initially uses narrower margins than SSE and WLE and generally results in smaller excisions that potentially decrease the functional and cosmetic impact of the treatment. The main disadvantages of both SSE and MMS are the cost and time consumption.

SECTION 6

Desmoplastic Melanoma

Key Points

- Desmoplastic melanoma is usually atypical and difficult to diagnose both clinically and histologically.
- The risk of lymph node metastases is lower for pure desmoplastic melanomas than for other subtypes.
- Neurotropism occurs in many desmoplastic melanomas, but also in non-desmoplastic melanomas.
- Adequate margins may be difficult to obtain in presence of neurotropism, delaying definitive reconstruction and justifying consideration of adjuvant radiotherapy.

INTRODUCTION

The desmoplastic subtype of melanoma (DM) is a term used to describe an uncommon variant of cutaneous melanoma that shows spindle cell morphology and an abundance of collagen within the tumour. The term was first coined by Conley in 1971 and then modified by Reed and Leonard in their 1979 publication entitled "Neurotropic melanoma: a variant of desmoplastic melanoma", since these authors noted such tumours were typically invading nerves. However, whilst many desmoplastic melanomas also show neurotropism, it is not a universal feature.

EPIDEMIOLOGY

Desmoplastic melanoma represents around 2.7% all cutaneous invasive melanomas, with a mean age of patients 66 years and a 2:1 male to female ratio. Neurotropism is present in around 30-50% of desmoplastic melanomas, however, 30%

neurotropic melanomas do not display any desmoplasia, thus the two terms are not synonymous.

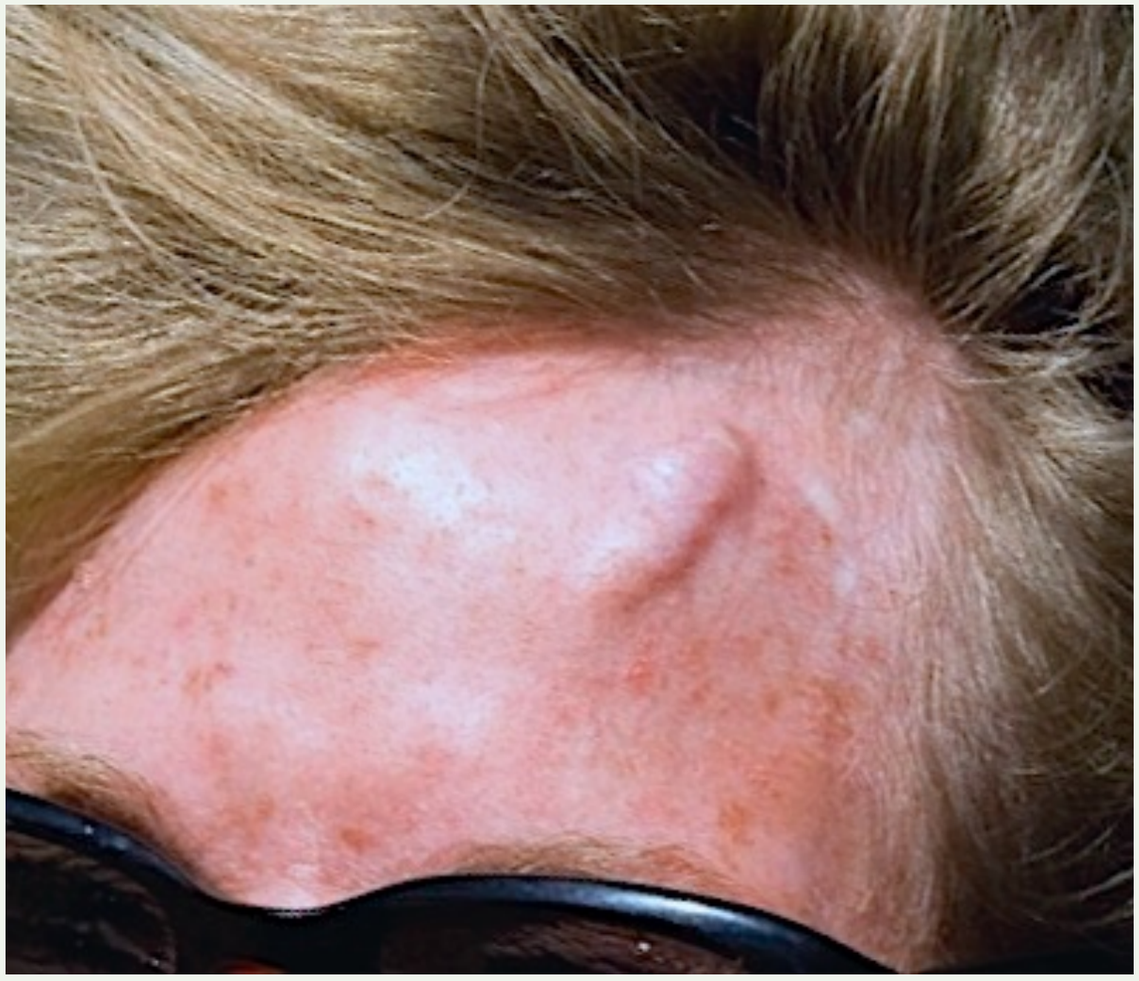
Aetiology

Desmoplastic melanoma typically occurs in sun exposed sites such as the head and neck (51%), the extremities (30%) and the trunk (17%). However, the interaction with other risk factors such as intermittent sun exposure and a family history of melanoma has not been fully characterised.

Clinical diagnosis

The presentation of DM is often atypical of a cutaneous melanoma, usually having a scar-like non-pigmented appearance (Figure 4.13). Consequently, the ABCDE rule and even dermoscopy can fail to correctly diagnose DM. Likely as a result of this apparently innocent appearance, the diagnosis is often delayed and the tumours are relatively large

Figure 4.13 Clinical Appearances of Desmoplastic Melanoma



Desmoplastic melanoma with neurotropism involving the left supraorbital nerve, presenting as an amelanotic firm mass.

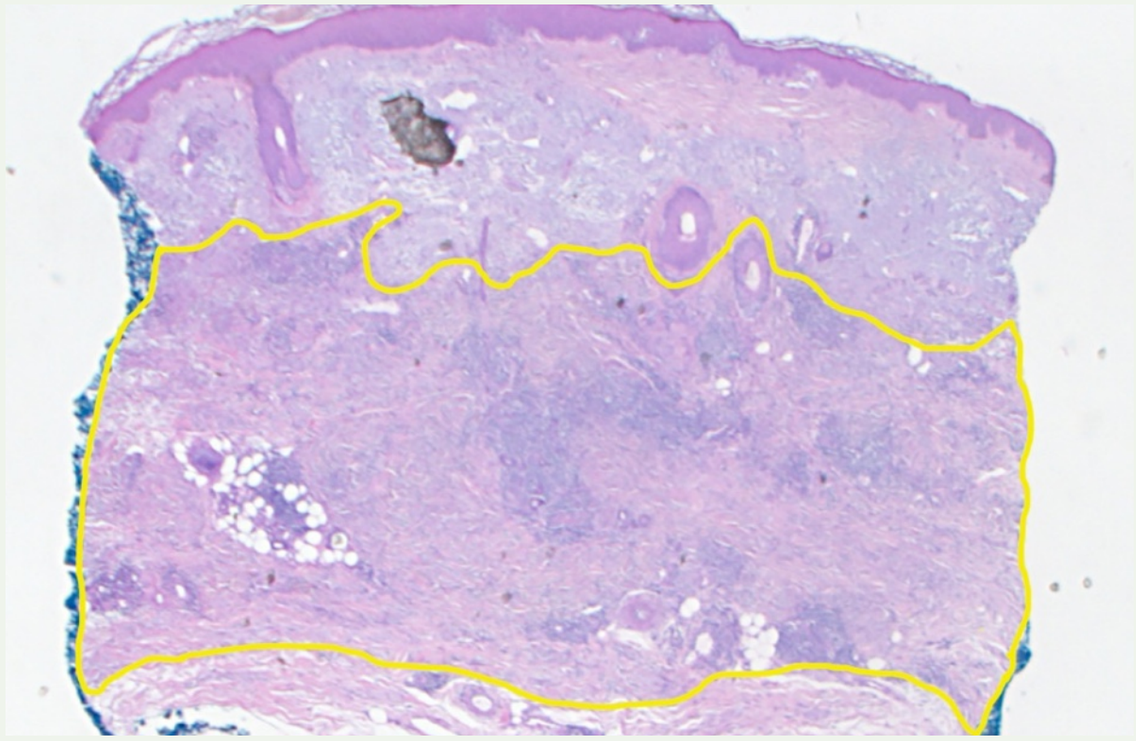
and thick compared to more classical appearing melanomas.

Histopathology

See Understanding Pathological Assessment *for background explanation of features.*

The histopathology of desmoplastic melanoma can at times be very subtle, (Figure 4.14) resembling benign fibrous and even neural tissue. For this reason, low grade desmoplastic melanomas may go unrecognised causing a delay in appropriate treatment. The tumours typically show bland spindle cells with abundant collagen deposition and frequently accompanying chronic inflammatory cells (Figure 4.15). In around 50% cases the DM is pure, and in the remaining 50% there is a mixture of DM and another melanoma subtype, such as superficial spreading melanoma or lentigo maligna melanoma. Neurotropism is an umbrella term to include any neural involvement by a melanoma. Within this term are three distinct phenotypes; 'perineural invasion', 'intraneural invasion' and 'neural transforming'. The first two types of neurotropism may exist either with or without desmoplasia, whereas the 'neural

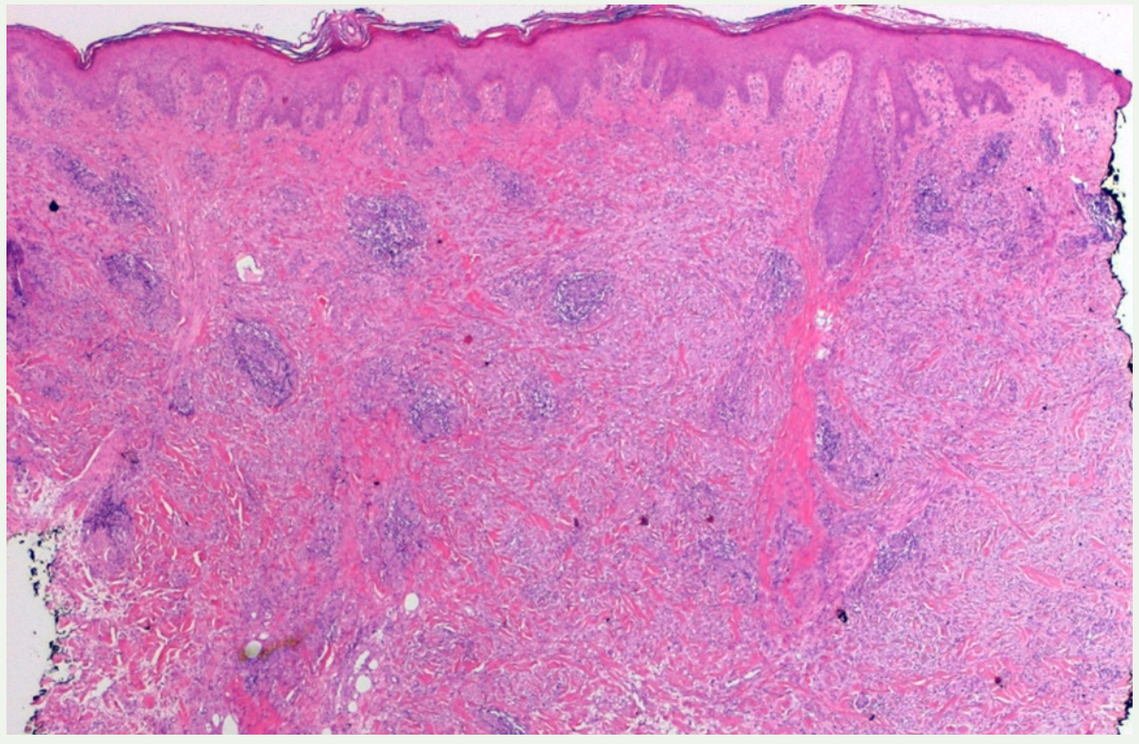
Figure 4.14 Subtle and Misleading Histological Appearances of Desmoplasia



Desmoplastic melanoma replacing the entire area outlined in yellow, which could easily be misinterpreted as fibrosis. The blue ink applied to the margins of the biopsy are visible at the borders.

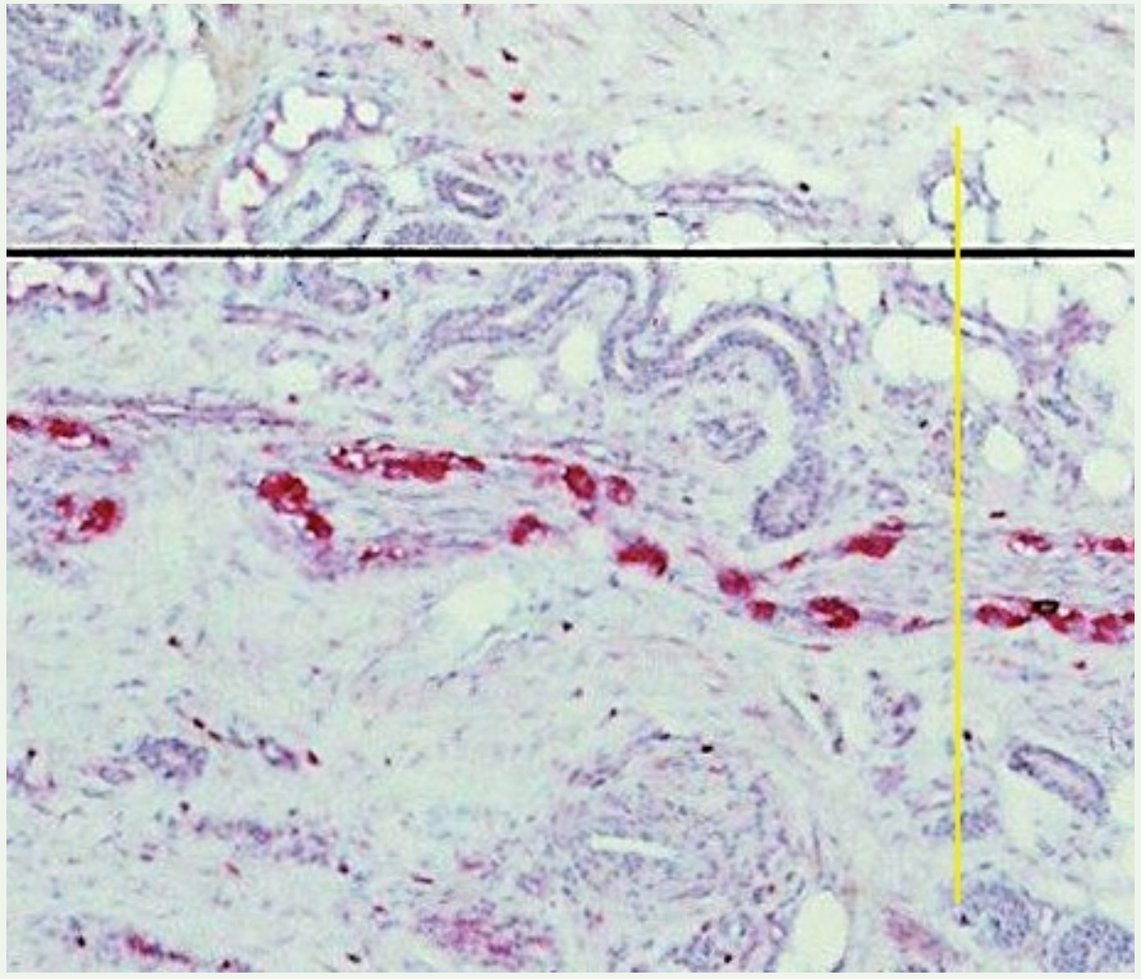
transforming' type only occurs in desmoplastic melanoma. Perineural invasion refers to the invasion into the perineural space, allowing spread along it, sometimes apparently producing skip lesions (Figure 4.16). Intraneural invasion describes

FIGURE 4.15 TYPICAL HISTOLOGICAL APPEARANCE OF DESMOPLASIA



Extensive dermal and subcutaneous desmoplastic melanoma.

FIGURE 4.16 HISTOLOGICAL APPEARANCE OF NEUROTROPISM



Axial sectioning of melanoma (red staining) infiltrating a nerve. Of note, the melanoma appears to 'skip' along the nerve, thus a section taken in the plane indicated by the yellow line may appear to show clear margins, despite tumour being present less than a millimetre away in both directions.

infiltration of the nerve fascicles themselves by tumour cells, tending to form contiguous lesions. Neural transformation describes the de-novo formation of nerve-like structures that are distinct from any pre-existing nerves.

Treatment

The relatively uncommon nature of desmoplasia and neurotropism in melanoma and the significant overlap in their co-existence has resulted in a paucity of good quality prognostic studies on the two entities. However, a consistent observation is that the rates of sentinel lymph node metastasis are lower in pure desmoplastic tumours than is typical for other cutaneous melanomas, especially given the greater median Breslow thickness. In contrast, neurotropism probably has little effect on the rates of SLN metastasis. Although SLN metastases are less common in pure DM than non-DM, they are still present in around 6-8% cases and therefore SLNB is justified.

Surgical resection of DM follows the same principles as for melanoma in general, with margins based upon the pathological tumour stage. However, where neurotropism is present, several operations may be required in order to obtain adequate histologically confirmed margins. In some cases, such as when cranial nerves are involved, this may not be technically feasible. If there is doubt as to the adequacy of the margins, then radiotherapy should be administered to reduce the risk of recurrence. Due to the potential difficulties in obtaining adequate surgical resection in a single stage, complex reconstructions should be avoided until the results of histological assessment have been reviewed.

Citations and Further Reading

1. RJ. Hutchinson. Senile freckle with deep staining - a superficial epithelioma of the cheek. Archives of Surgery, London, 1892, 3: 159.

2. Ackerman AB, Briggs PL, Bravo F. Differential Diagnosis in Dermopathology III. Philadelphia: Lea&Febiger 1993, 166–9.

3. Tannous ZS, Lerner LH, Duncan LM, et al. Progression to invasive melanoma from malignant melanoma in situ, lentigo maligna type. Hum Pathol 2000; 31: 705–8.

4. Flotte TJ, Mihm MCJ. Lentigo maligna and malignant melanoma in situ, lentigo maligna type. Hum Pathol 1999; 30: 533-6.

5. McKenna JK, Florell SR, Goldman GD et al. Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. Dermatol Surg 2006; 32: 493–504.

6. Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. Br J Dermatol 1987; 116:303–10.

7. Stevenson O, Ahmed I. "Lentigo maligna : prognosis and treatment options". Am J Clin Dermatol 2005; 6: 151–64.

8. Klauder JV, Beerman H. Melanotic freckle (Hutchinson), me´lanose circonscrite pre´cance´reuse (Dubreuilh). AMA Arch Derm 1955; 71: 2–10.

9. Dalton SR, Gardner TL, Libow LF et al. Contiguous lesions in lentigo maligna. J Am Acad Dermatol 2005; 52: 859–62.

10. Robinson JK. Use of digital epiluminescence microscopy to help define the edge

ACKNOWLEDGEMENTS

Michelle Avramidis BSc Photography

5

Melanoma Mimics

PASCALE GUITERA LILIAN ROCHA
SHU WANG RICHARD A. SCOLYER

Melanoma Institute Australia

Key Points

- Numerous non-melanocytic lesions can enter in the differential diagnosis of melanoma.
- Dermoscopy is an essential diagnostic tool.
- The main practical difficulties arising with the following types:
  - pigmented basal cell carcinoma
  - seborrheic keratosis
  - dermatofibroma
  - haemorrhagic or vascular lesion

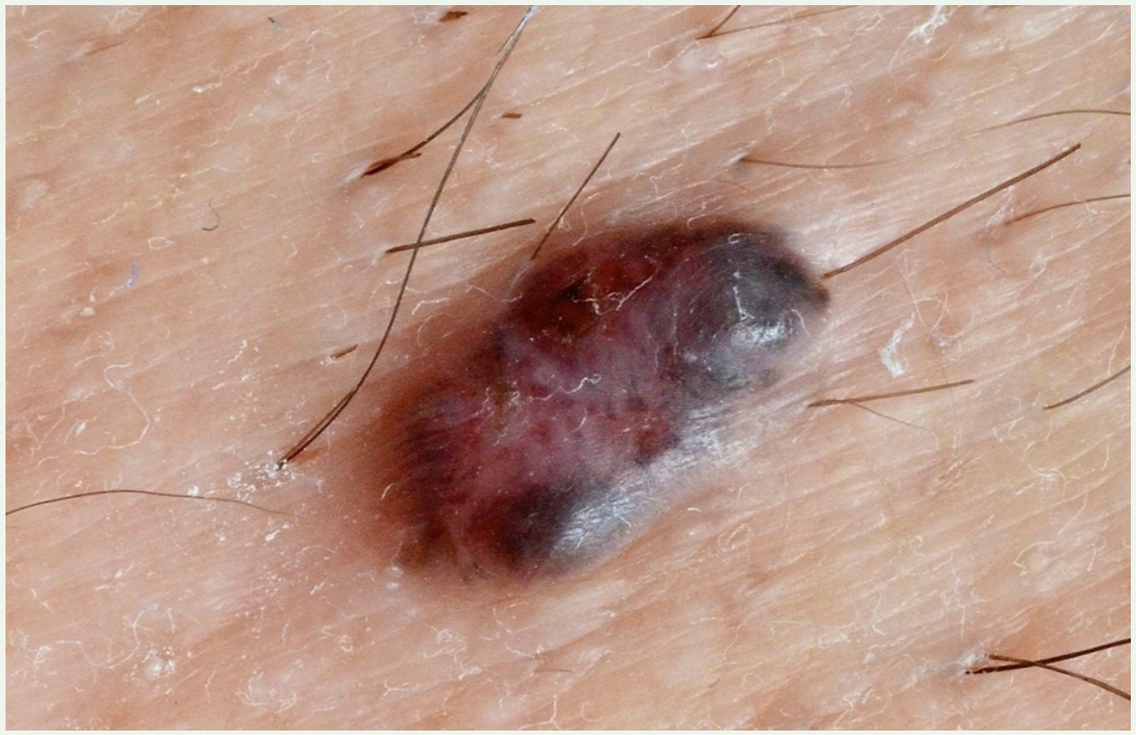
Basal Cell Carcinoma (BCC):

BCC is the most common cancer in humans; it is due to chronic sun-damage and is more common in elderly individuals. Risk factors for BCC include ultraviolet light (UV) exposure, light hair and eye colour, Fitzpatrick phototype I and II, ionising radiation and some heritable conditions, such as Basal cell naevus syndrome, Bazex syndrome and Rombo syndrome.

Usually the presentation is a friable, non-healing lesion on sun exposed skin. Characteristics may vary for different clinical sub-types, which include nodular, superficial, morpheaform, and pigmented BCCs.

The main dermoscopic criteria include: arborising vessels, superficial fine telangiectasia, blue-gray ovoid nests, multiple blue-gray globules, maple leaf-like areas, spoke wheel areas, in-focus dots, concentric structures, ulceration, multiple small erosions, shiny white-red structureless areas and chrysalis. For more details see The dermoscopy universe of basal cell carcinoma.

Figure 5.1 Basal Cell Carcinoma



A heavily pigmented basal cell carcinoma.

(Image 1 of 2)

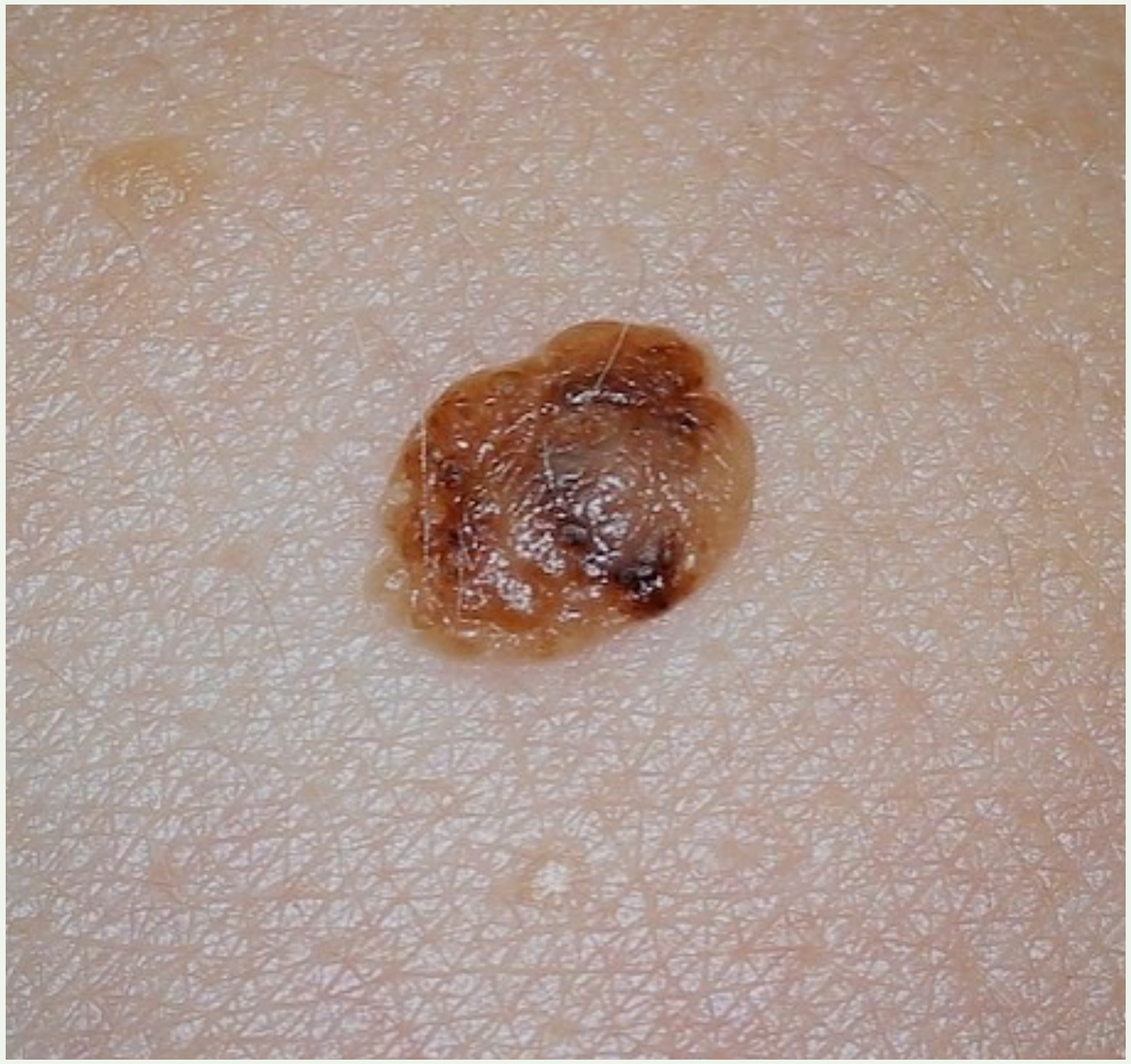
Seborrheic Keratosis or *Wart* :

Seborrheic keratosis is the most common of the benign epithelial tumours. Developing in middle-age, they appear as sharply demarcated, flesh colour, brown or black, with greasy texture. They are particularly common on chest, back and face. They can be itchy and rapidly arising. They can be also flat and homogeneous brown at early stage. They are not linked to sun exposure.

The main dermoscopy pattern are: milia-like cysts, comedo-like openings, fingerprint-like structures, fissures or ridges, moth-eaten border, hairpin blood vessels and white halo surrounding hairpin blood vessels.

They represent proliferation of monomorphous basaloid keratinocytes.

Figure 5.2 Seborrheic Keratosis



Clinical example of seborrheic keratosis.

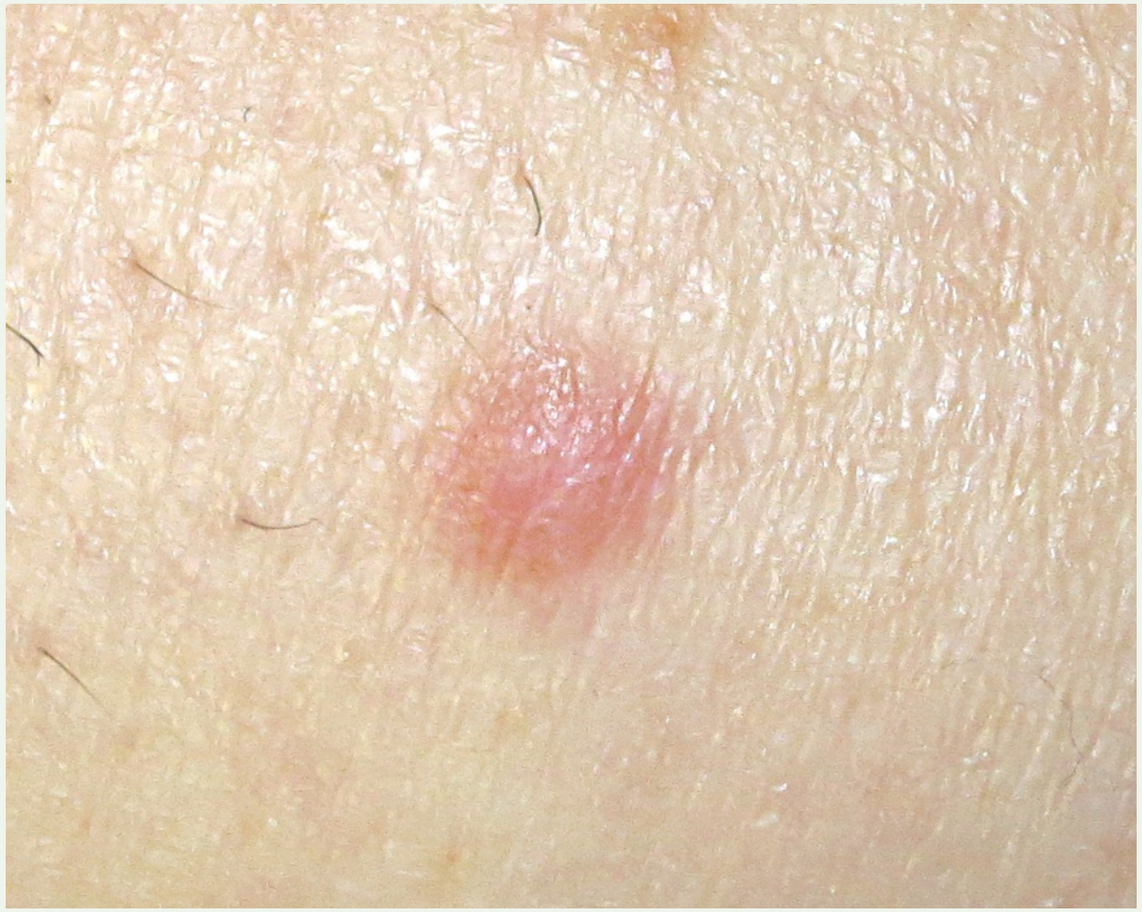
(Image 1 of 2)

Dermatofibroma:

A dermatofibroma is a fibrous papule of the skin that develops following an insect bite or other small trauma. Dermatofibromas typically appear as an asymptomatic papule or nodule that can be white, pink or pigmented. On palpation, lesions are firm and they can exhibit the characteristic "Dimple sign": lateral compression with thumb and index finger produces a depression or "dimple".

The main dermoscopy features are a central white patch and peripheral thin reticulation.

Figure 5.3 Dermatofibroma



Example of dermatofibroma showing a pink nodule.

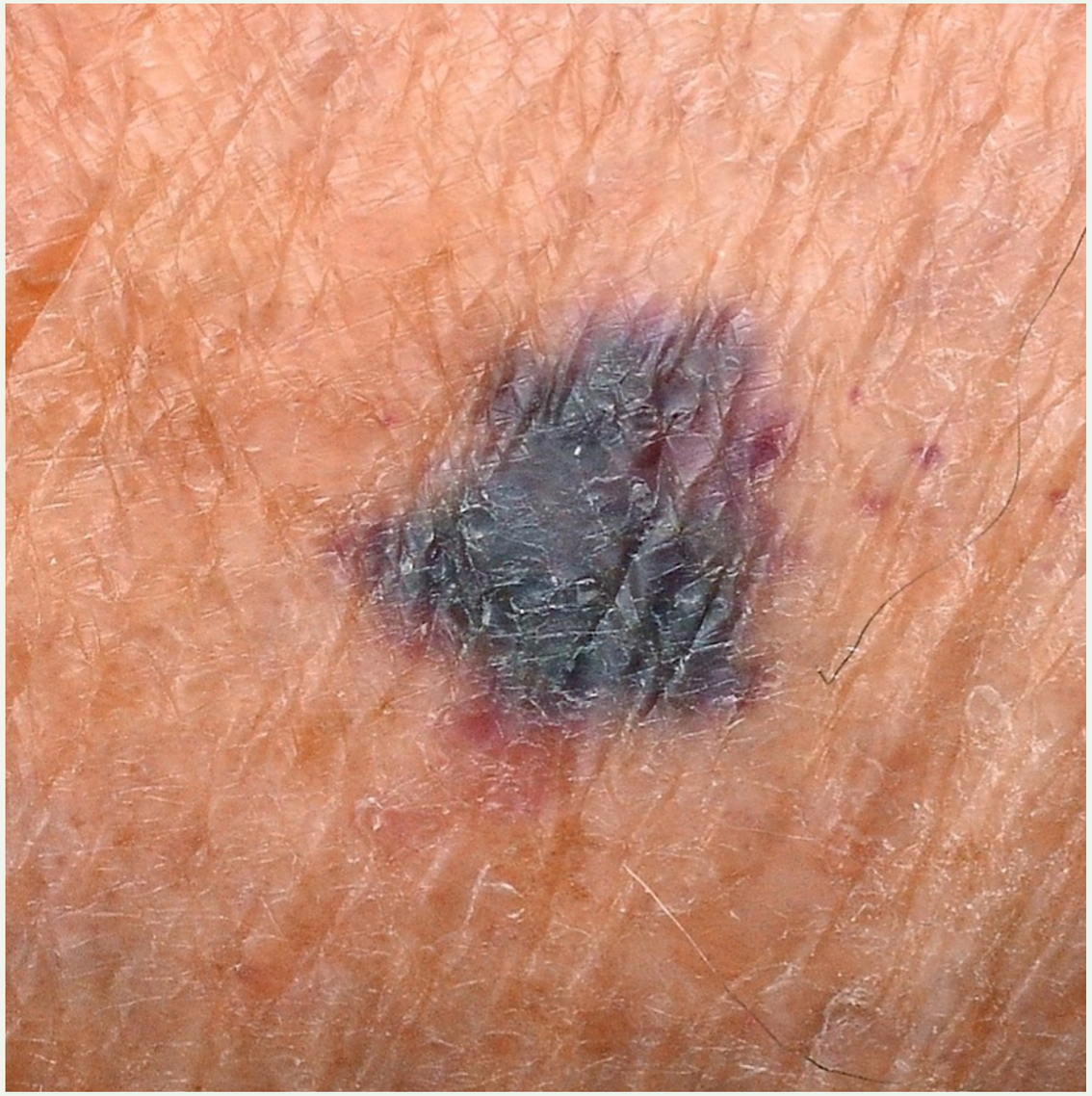
(1 of 2)

Haemorrhagic & Vascular Lesions:

Melanoma is commonly included in the differential diagnosis of lesions containing blood, especially when desaturated as in low flow cutaneous and mucosal angiomas.

Dermoscopy is very useful in identifying these conditions. Typically angiomas are seen to readily empty under gentle pressure from the dermatoscope plate. These lesions tend to have smooth outlines and there is a complete absence of any network structures. Intracutaneous haematomas, typically post traumatic, are also common.

Figure 5.4 Haemorrhagic & Vascular lesions



Darkly pigmented low-flow cavernous angioma on the lower leg.

(Image 1 of 2)

1 of 11

Citations and Further Reading

1. Klaus Wolff, Lowell A. Goldsmith, Stephen I. Katz, Barbara A. Gilchrest, Amy S. Paller, David J. Leffell. Fitzpatrick's Dermatology in General Medicine. Textbook. Vol.1, part7, seventh edition.

2. Tony Burns, Stephen Breathnach, Neil Cox, Christopher Griffiths. Rook's Textbook of Dermatology. Vol.1, eighth edition.

3. Lallas A et al. The dermoscopy universe of basal cell carcinoma. Dermatol Pract Concept. 2014;4(3):2.

ACKNOWLEDGEMENTS

Michelle Avramidis BSc Photography

6

Clinical and Instrument-Aided Diagnosis

PASCALE GUITERA SCOTT W. MENZIES
HELENA COLLGROS

Melanoma Institute Australia

Key Points

- Physician-detected melanomas are thinner than self-detected lesions.
- Nodular, desmoplastic and acral melanomas have a higher prevalence of light coloured variants.
- Dermoscopy improves the diagnostic accuracy for melanoma compared with naked-eye examination.
- Sequential digital dermoscopy imaging allows detection of melanomas that lack dermoscopy features of melanoma.
- Changes in melanocytic lesions, as determined by total body photography, in patients older than 50 years should be considered suspicious for melanoma.
- In vivo reflectance confocal microscopy is useful as a second opinion to confirm that a lesion lacking dermoscopic evidence of melanoma is truly benign, and for mapping the clinical margins of lentigo maligna or detecting amelanotic melanoma.

SECTION 1

Clinical Diagnosis

Important Points

- Most melanomas have features characterised by ABCDE rule.
- Many nodular melanomas are NOT characterised by ABCDE rule - if in doubt be suspicious.
- Many benign lesions are also characterised by ABCDE rule.
- Ugly duckling rule is useful for patients with atypical lesions.
- Amelanotic (non-pigmented) melanomas are difficult to diagnose.
- Dermoscopy significantly improves diagnostic skills.

INTRODUCTION

In Australia, self-detected melanomas are most commonly recognised by change in colour (58%), size (26%) and shape (22%). Irritation or itch occurs in only 13% of self-detected melanomas and pain in only 1.8%.

The features of most initial flat-phase melanomas are summarised by the ABCDE rule, although many dysplastic naevi also have the ABCD features of melanoma. However, a significant minority of melanomas do not present with classical features, thus a lesion that cannot be clearly diagnosed, may in fact be a melanoma. In keeping with this concept, is the "Ugly duckling" rule: it is a lesion that is different from the others and stands out.

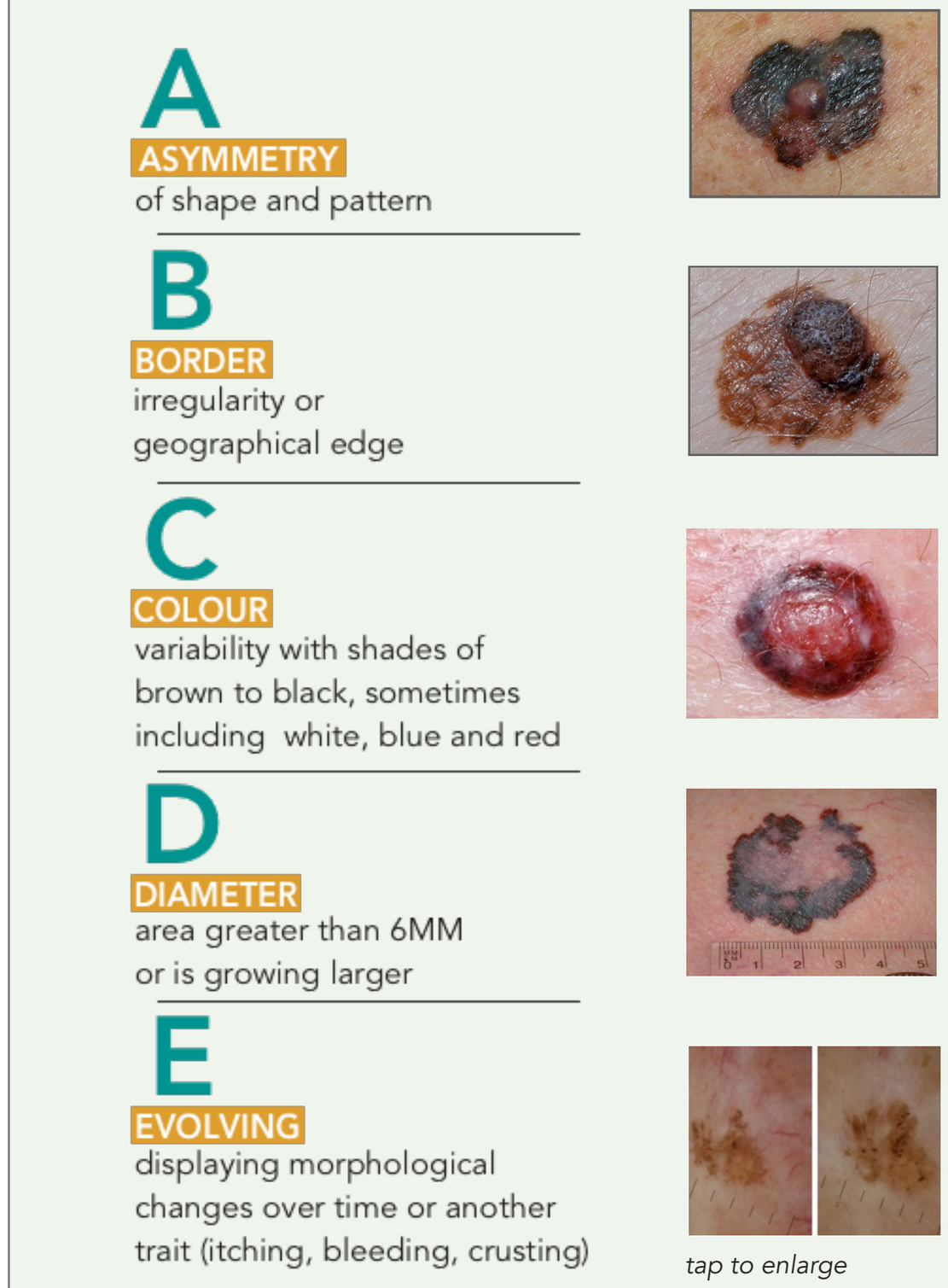
In this section we outline the ABCDE rule and its pitfalls due to notable exceptions that should also raise suspicion.

ABCDE Rule

The ABCDE rule is a mnemonic based system to describe concerning skin lesions (Figure 6.1). The ABCDE rule coupled with naked eye examination achieve a sensitivity of 71% and specificity of 81%.

The ABCDE rule works well for the diagnosis of typical superficial spreading melanomas such as that shown in Figure 6.2. However, other lesions, in particular amelanotic nodular melanomas (Figure 6.3), are not well detected by the rule. This rule should therefore be used with caution, particularly when trying to rule out the possibility of melanoma in a lesion.

Figure 6.1 ABCDE Rule



tap to enlarge

FIGURE 6.2 CLINICAL FEATURES OF MELANOMA

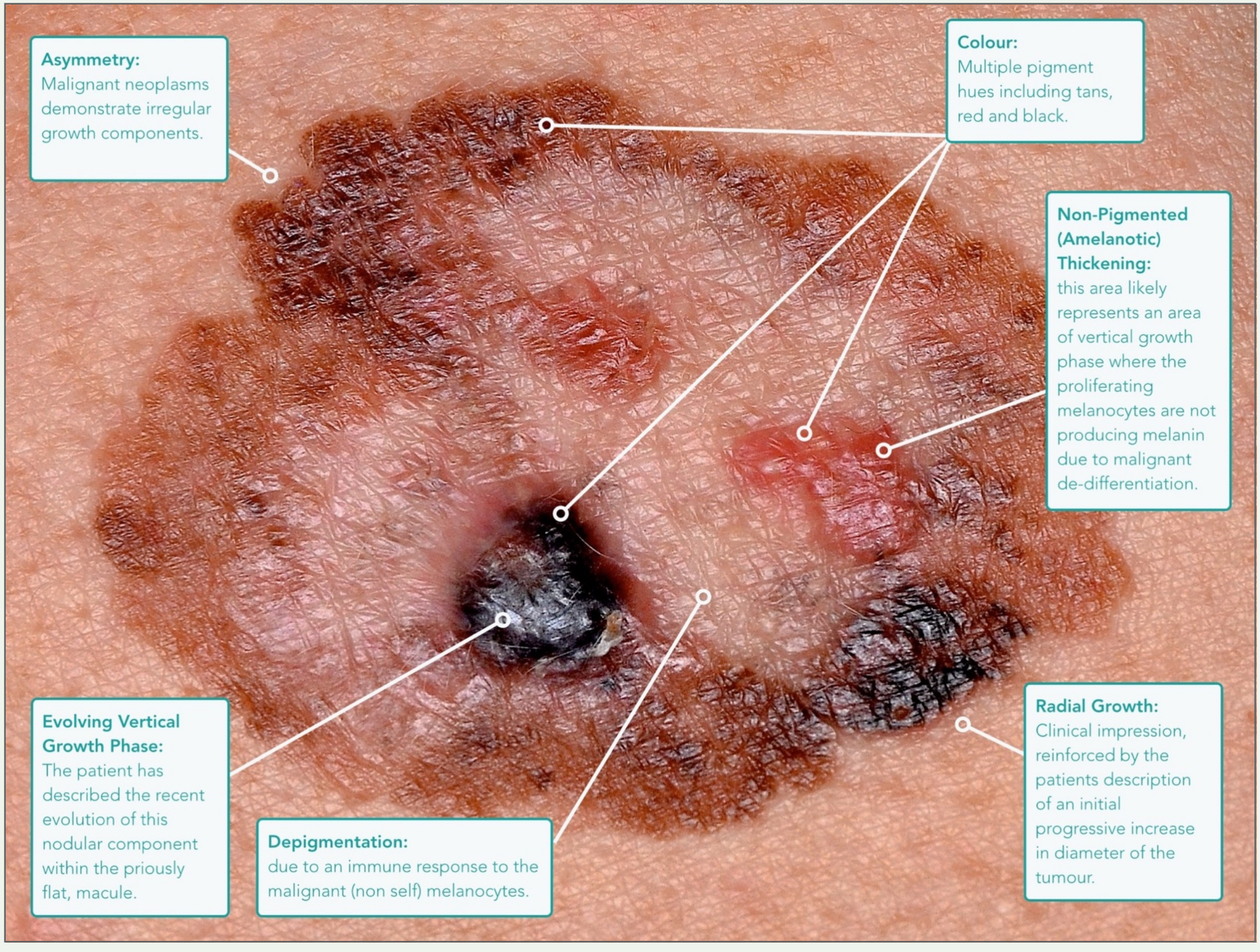
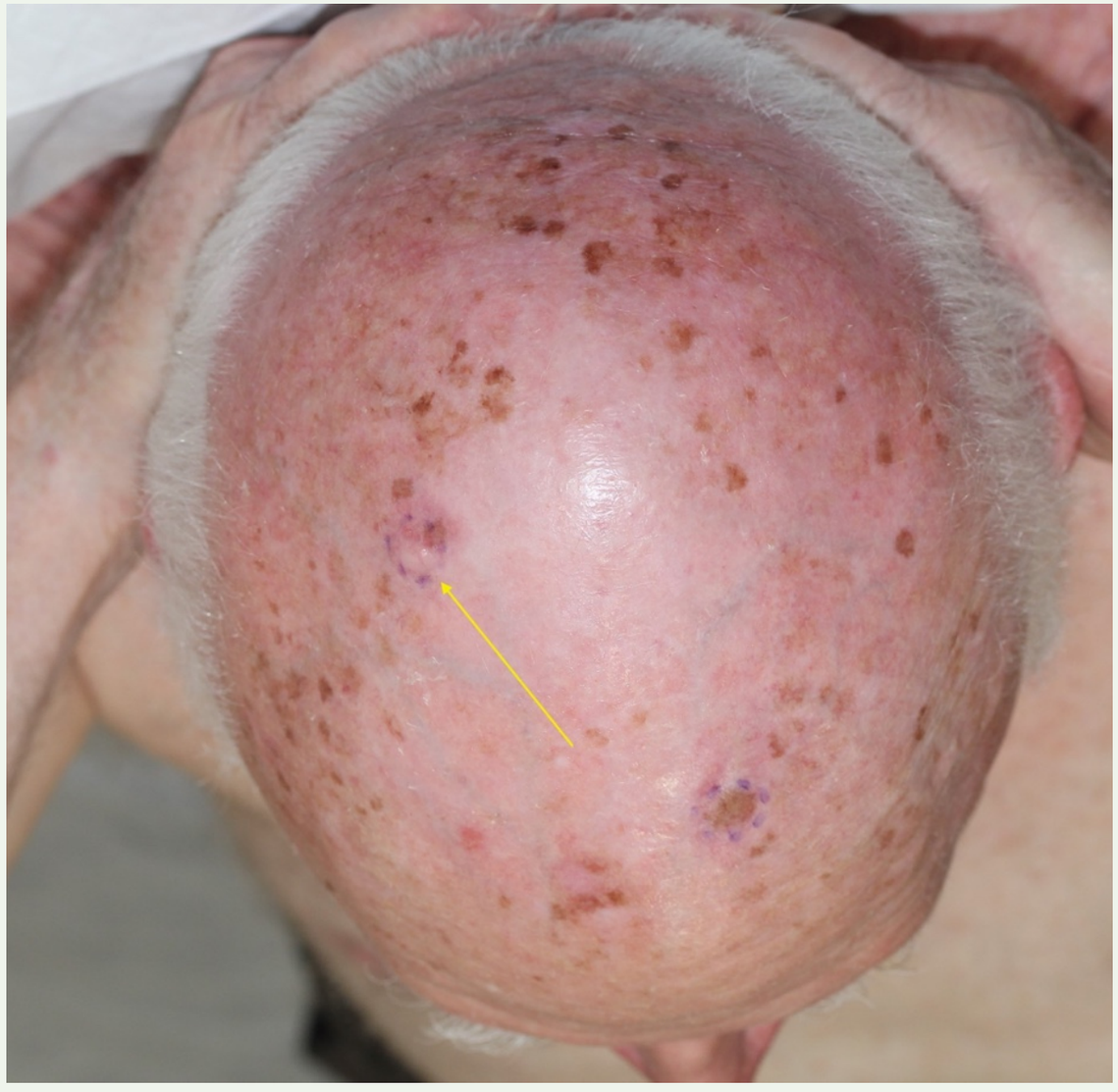


FIGURE 6.3 AMELANOTIC MELANOMA OF SCALP (DESMOPLASTIC)

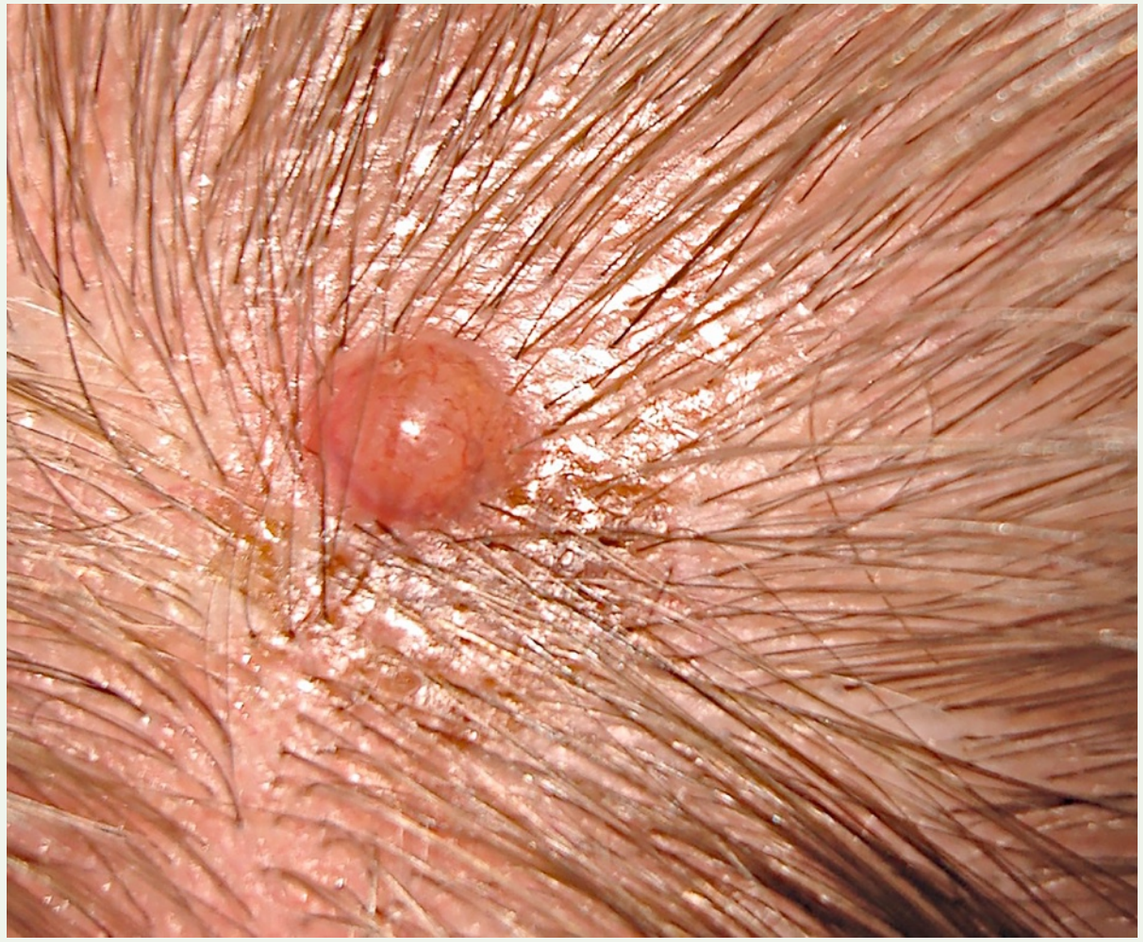


2.5mm Breslow thickness nodular amelanotic desmoplastic melanoma of the scalp, as indicated by the yellow arrow and purple pen marks around the lesion.

- A practical approach to a non-pigmented lesion, which does not fit well into the ABCDE rule, may be as follows:
  - assess for any thickness (nodular component):
    - if absent (macular); reassess in 3 months
    - if present; re-assess in 4 weeks:
      - if further change; biopsy
      - if no change; re-assess in 3 months

Despite the limitations of macroscopic lesion assessment and the ABCDE rule, this can be considerably improved by combining with dermoscopy (Figure 6.4) to around 90% sensitivity and 90% specificity. However, it should be remembered that even with dermoscopy and expert training, some melanomas will remain very difficult to diagnose due to atypical presentation (Figure 6.5). Therefore, any lesion that continues to evolve should be treated with suspicion.

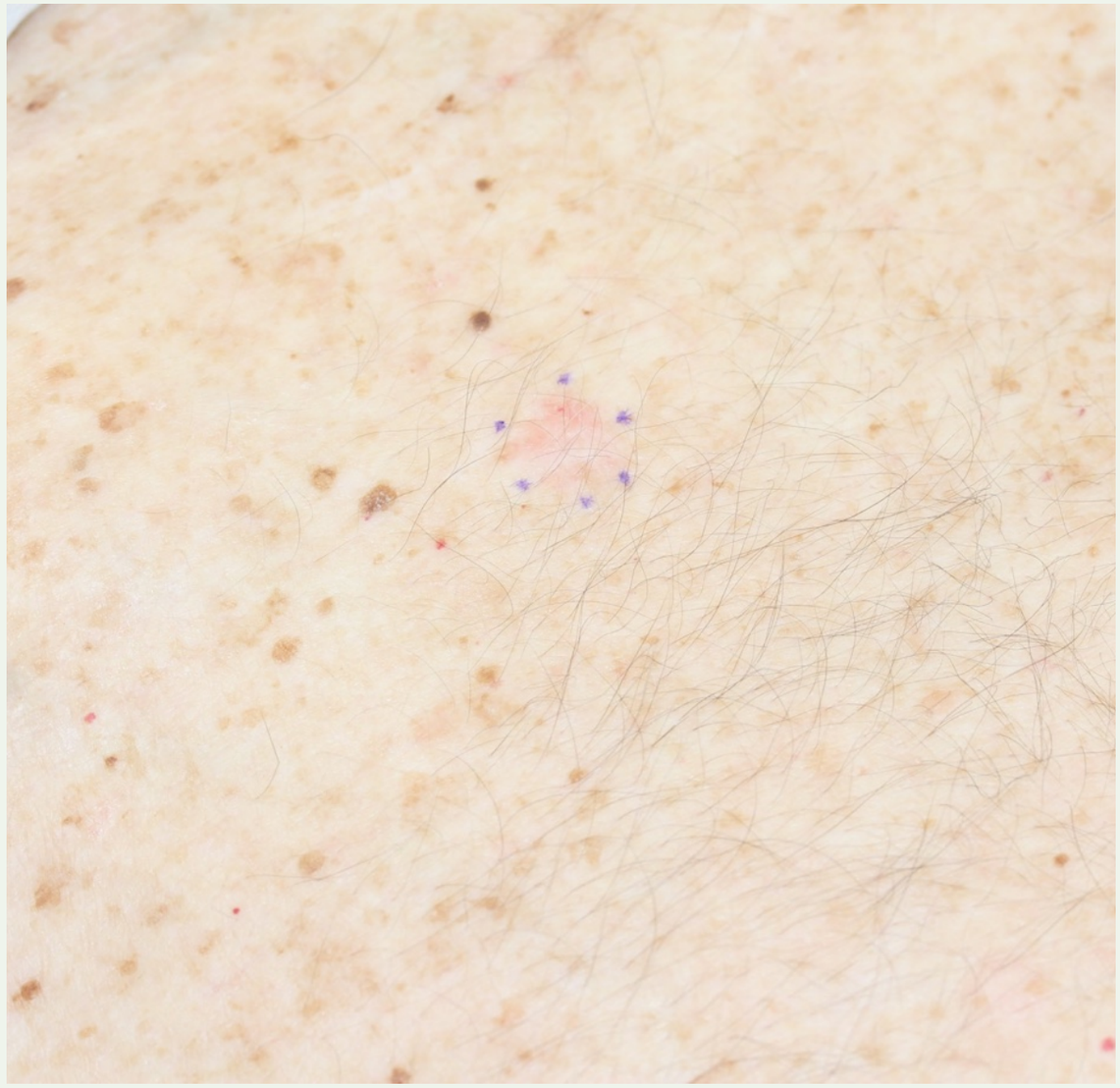
Figure 6.4 Dermoscopy Aids Clinical Diagnosis of Melanoma



An amelanotic nodular melanoma arising in the scalp.

(Image 1 of 3)

Figure 6.5 Very Subtle Appearance of Melanoma



Macroscopically indistinct melanoma (Breslow 0.80mm), as outlined by blue ink dots.

Dermoscopy Diagnosis

Technology

Dermoscopy (dermatoscopy, oil epiluminescence microscopy, surface microscopy) is a simple technique where a hand-held magnification device (usually X 10) is combined with either liquid or cross-polarised filters. This enables the visualisation of diagnostic morphologic structures in pigmented and non-pigmented skin lesions located in the epidermis and upper dermis, which are not seen with the naked eye. Cross-polarised devices enable visualisation of chrysalis structures (found in melanoma), however, some critical pigment features may not be visualised with these instruments (blue-white veil and milia-like cysts). New dermoscopes allow toggling from non-polarised to polarised light and offer the advantages of both techniques.

Evidence For Use

Dermoscopy has been shown to greatly enhance the clinical diagnosis of nearly all pigmented skin tumours and many non-pigmented lesions. However, its main impact has been to improve the diagnostic accuracy of melanoma compared to naked-eye examination. In a recent meta-analysis, the diagnostic odds ratio for melanoma using dermoscopy was 15.6 times higher compared with naked-eye examination. Sensitivity was higher for dermoscopy (90%) than for eye examination alone (71%), while there was no evidence of an effect on specificity (90% vs 81% respectively). However, in a randomised trial of naked-eye versus naked-eye plus dermoscopy examination, there was a 42% reduction (p=0.01) in patients referred for biopsy in the dermoscopy arm. Furthermore, a clinical trial of

sequential digital dermoscopy imaging compared with naked eye examination in primary care physicians demonstrated a 63.5% reduction in the benign pigmented lesion excision/referral rate ($p<0.0005$).

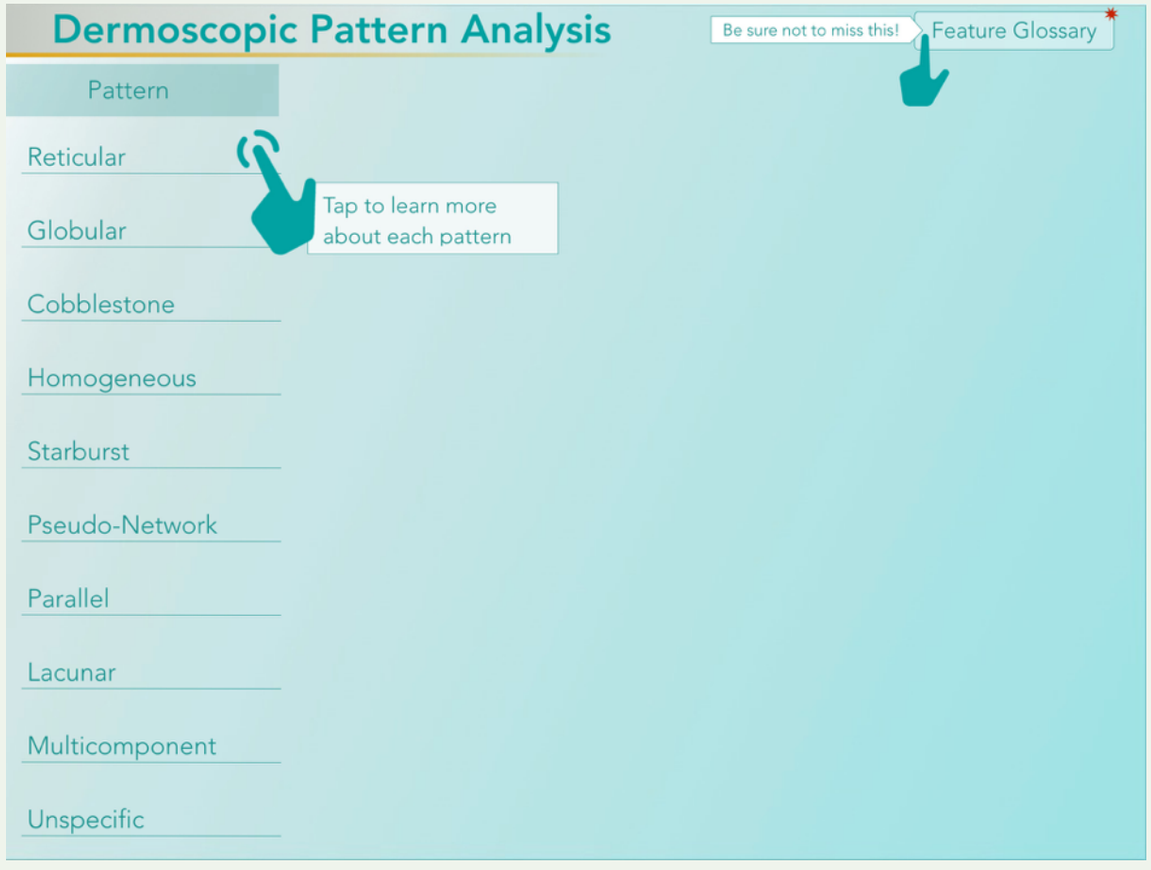
Dermoscopy therefore results in a very significant reduction in the ratio of benign to malignant melanocytic lesions excised by clinicians. So evidence is now available that dermoscopy decreases the need for biopsy in addition to improving the detection of melanoma compared with naked-eye examination.

In 2008, the evidence-based Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (CPGMMANZ) gave the recommendation that training and utilisation of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions. This was given the highest grade of recommendation (Grade A: the body of evidence can be trusted to guide practice).

Technique

A degree of training is required in order to successfully use a dermatoscope in clinical practice. Firstly, one needs to become familiar with the

Interactive 6.1 Pigmentation Pattern Analysis



patterns of pigmentation that may be seen (Interactive 6.1). Most benign lesions have a symmetry of the pattern of pigmentation (which is different from the symmetry of shape). Secondly, a structured approach to lesion analysis is required, using the two-step method that is recommended by experts. This method first distinguishes melanocytic from non-melanocytic lesions, then determines which melanocytic lesions are likely to be malignant. It is mostly defined by the negativity of melanoma

Interactive 6.2 Two-Step Dermoscopy Method for Pigmented Lesion Diagnosis

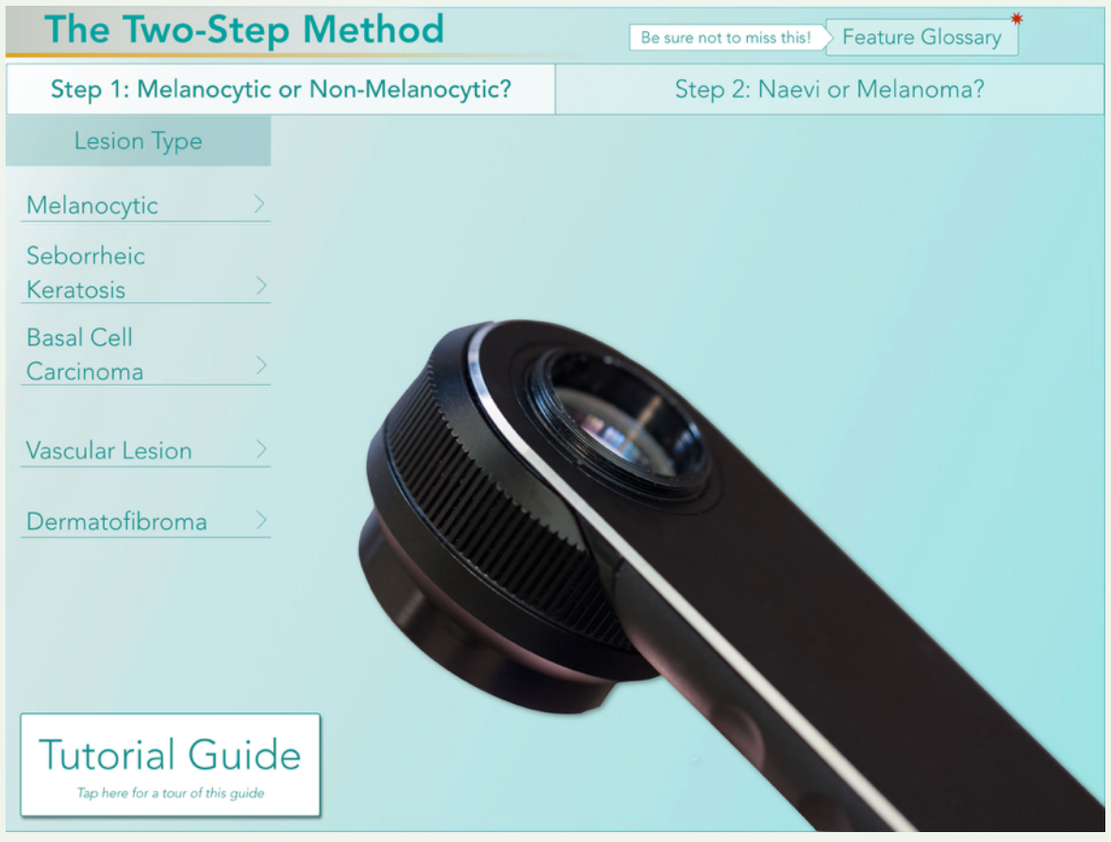
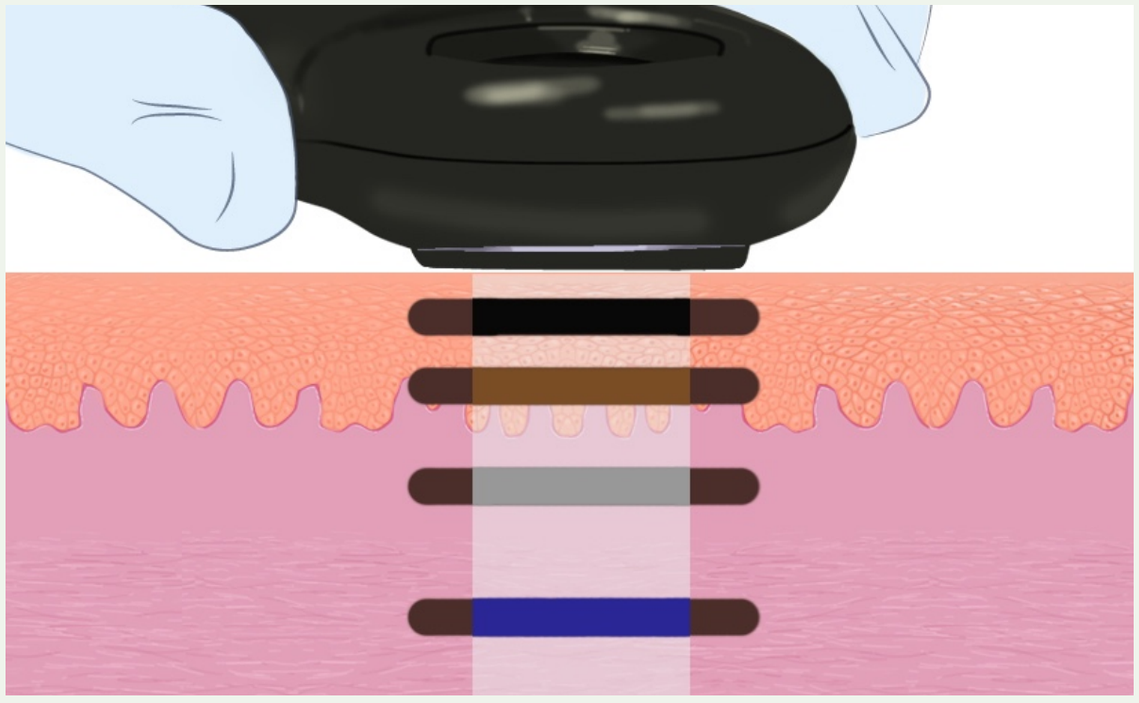


Figure 6.6 Tyndall Effect in Dermoscopy



The perceived colour of brown melanin pigment within a lesion varies according to its depth within the skin. This is due to greater scattering and hence reflection of blue than red light, which increases with the distance travelled through the skin and is known as the Tyndall Effect.

features. We have included a step-by-step guide to performing this technique (Interactive 6.2).

A point of particular note is that most benign lesions will have only one or two colours. Red and purple correspond to increased vascularity, bleeding or vascular lacuna like in haemangioma. Whereas other colours observed depend on the depth of melanin within the skin, due to the Tyndall effect (Figure 6.6):

- epidermis - stratum corneum: black
- epidermis - junction: brown
- upper dermis: gray
- lower dermis: blue

SECTION 3

Digital Dermoscopy Monitoring

INTRODUCTION

Sequential digital dermoscopy imaging (SDDI) involves the capture and assessment of successive dermoscopic images, separated by an interval of time, of one or many melanocytic lesions to detect suspicious change. This is performed in two settings: short-term digital monitoring (over a period of 3 months) for suspicious melanocytic lesions, and long-term surveillance (usually at intervals of 6-12 months). In a recent meta-analysis that grouped both short and long-term SDDI together, it was shown the number of lesions needed to monitor in order to detect one melanoma ranged from 31 to 1008, depending

upon the clinical setting (lower for short-term monitoring). For every additional month of monitoring, one additional melanoma was detected, with the chances of detecting a melanoma during surveillance shown to increase as the length of follow-up extended. Furthermore, the proportion of in situ melanoma and thin melanomas detected by SDDI were higher than expected in the general population.

The 2008 CPGMMANZ gave the recommendation to consider the use of SDDI for detecting melanomas that lack dermoscopic features of melanoma. This was given a Grade B recommendation: the body of evidence can be trusted to guide practice in most situations.

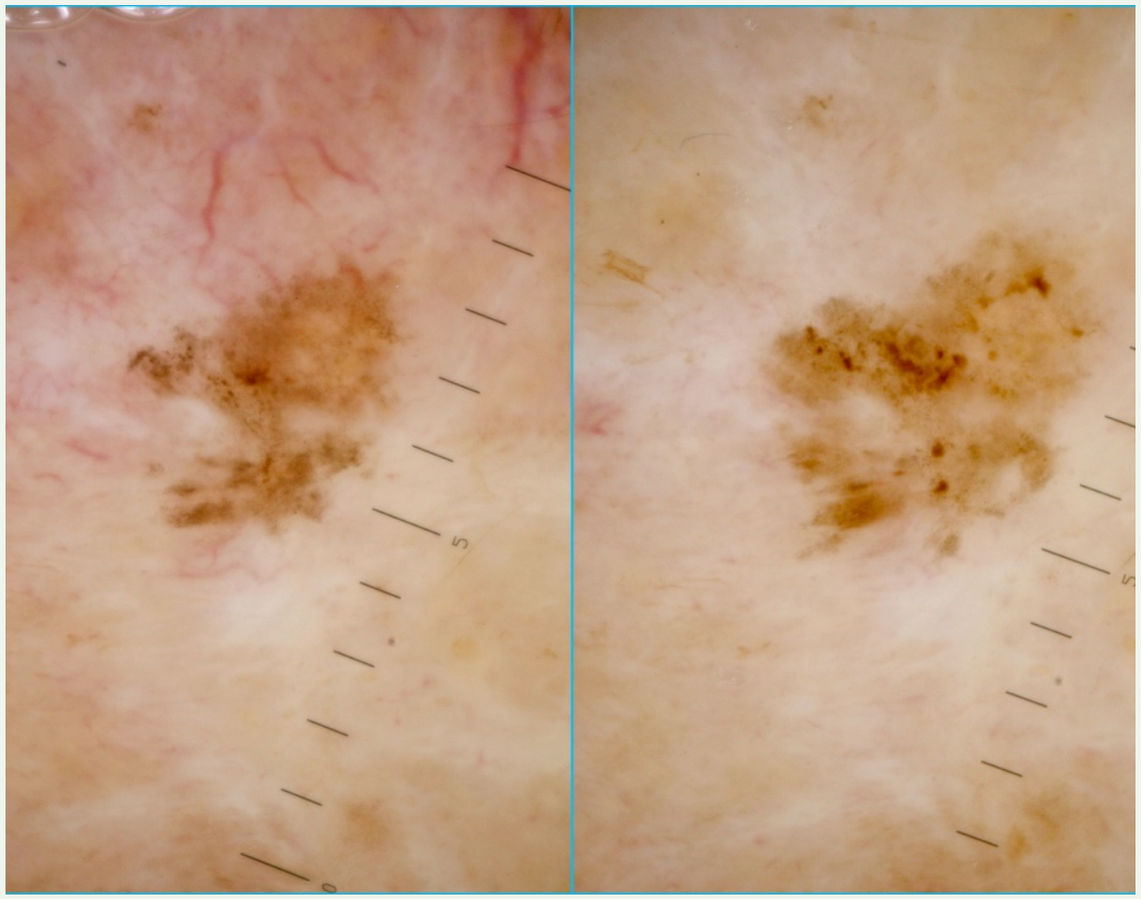
There are two standard approaches to SDDI, which ensure the technique is safe: short-term and long-term monitoring.

Short-Term Monitoring

Somewhat suspicious, flat to slightly raised melanocytic lesions (e.g. changing mildly atypical lesions or non-changing moderately atypical lesions), which would normally be observed for change or excised depending upon patient preference, can be monitored over a 3 month time period (2.5-4.5 months). After this time period, any observed change (except an increase or decrease in milia-like cysts, or pigmentation without architectural change consistent with tanning or lightening of the surrounding skin), leads to excision. Importantly, 99.2% of lesions that remain unchanged at 2.5 - 4.5 months are benign. While 94% of melanoma (non-lentigo maligna type) will change during the short-term interval, only 75% of lentigo maligna change at this time point. For this reason, a second monitored 3 month interval, between 6-12 months following the baseline image,

is recommended where the diagnosis of lentigo maligna is being excluded.

FIGURE 6.7 SHORT-TERM MONITORING

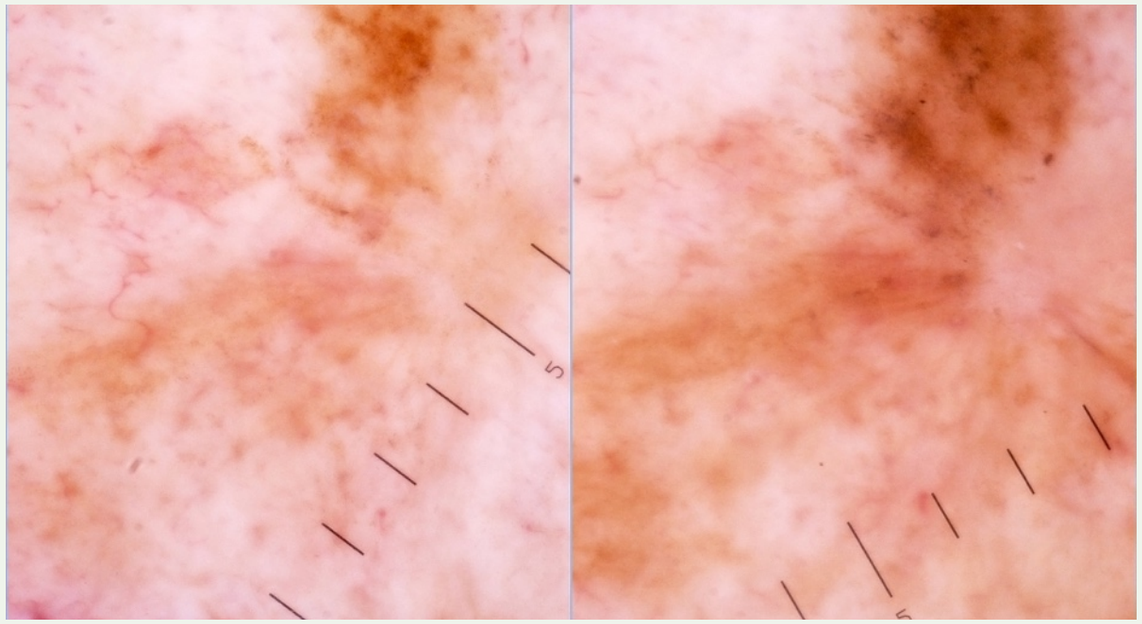


Baseline image in left panel, with right panel image taken 3 months' later, showing evolution of the lesion. Histologically confirmed diagnosis of melanoma in situ.

LONG-TERM MONITORING

Naevi or pigmented macules are monitored over standard surveillance periods (6-12 months), usually for patients with multiple atypical naevi or for follow-up of lesions that have had short-term monitoring. During long-term monitoring of a

FIGURE 6.8 LONG-TERM MONITORING



Long term monitoring demonstrates evolution of a pigmented lesion from baseline (left) over 9 months (right). Excision biopsy confirmed in situ melanoma.

lesion, only certain changes require excision of it (this is different to short term monitoring). They are:

- enlargement
- shape change
- regression
- appearance of new colours
- appearance of known dermoscopy features of melanoma

Within such significantly changed lesions, naevi tend to enlarge symmetrically over time whereas melanoma tends to enlarge asymmetrically. Over the long-term monitoring period, three characteristics are more predictive of changes in melanoma versus naevi:

- Observation of broadening of the network
- Increased black dots and globules
- Focal increase in pigmentation

Both atypical and banal naevi change in size over long-term monitoring more frequently in young people. Amongst people aged 0-20 years 13% of banal naevi show an increase in size, whereas only 1.5% enlarge in adults over 40 years. Similarly, 10% of atypical naevi enlarge in people aged under 28 years in contrast to only 3% in adults over 48 years.

Section 4

Total Body Photography

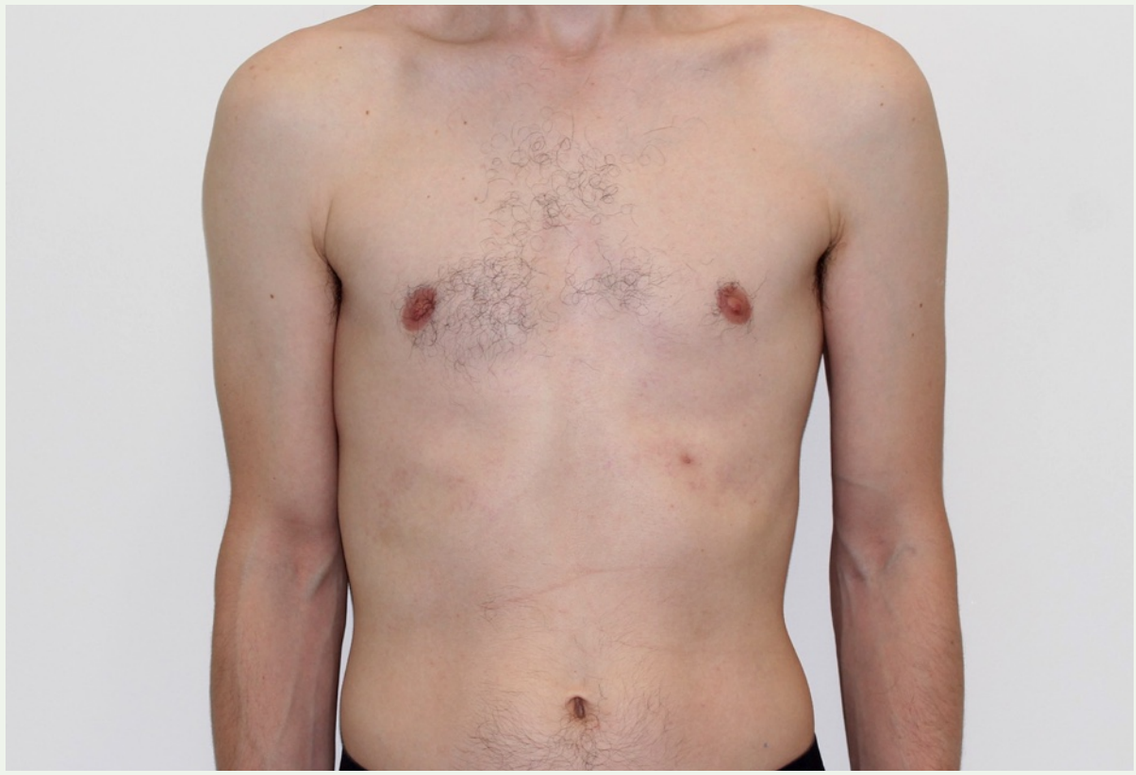
Introduction

Total body photography (TBP) allows early identification of new or changing skin lesions and also decreases the need for excision of stable lesions. It is primarily used in people with:

- multiple naevi
- naevi that are not easily seen (e.g. on the back)

It is known that patients with multiple dysplastic naevi have a significantly greater incidence of changed naevi when followed with total body photography. In an Australian cohort of high-risk patients followed by baseline TBP and dermoscopy, many of whom had multiple atypical naevi, patient age was a fundamental determinant of managing changed naevi. Only 0.4% of new and 3% of changed naevi in adults younger than 50 years of age were melanomas. In contrast 30% of new and 22% of changed lesions in older people were melanomas.

Figure 6.9 Standard Views Taken during Total Body Photography



Anterior torso.

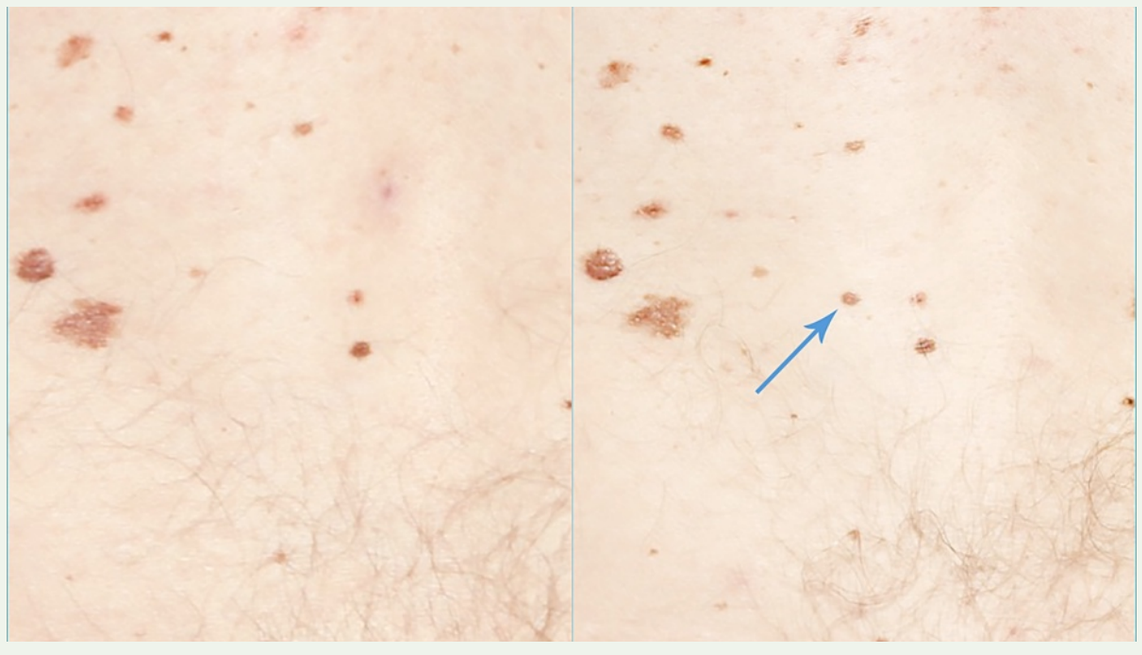
1 of 14

Usage

Due to the low rates of melanoma in younger adults found with changing naevi, TBP tends to be used in a two-step approach. When changing or new lesions are considered benign by dermoscopy criteria, short-term digital dermoscopy monitoring can be used. When lesions appear suspicious, then excision is recommended. Such an approach decreases excision rates for benign and stable lesions while detecting an increasing proportion of early, thin melanomas. In one clinic using this approach, 35% of suspicious pigmented lesions biopsied were melanomas.

TBP plays a significant role in self-screening. In one study, 32% of all malignancies were found by patient self-screening using TBP, and the detected melanomas were thin, in contrast to the thicker self-detected melanomas commonly self-reported.

Figure 6.10 Total Body Photography Detection of Melanoma



Serial TBP detected this new pigmented lesion (blue arrow in the right panel), which was then monitored with dermoscopy at 3 month intervals.

Citations and Further Reading

1. McPherson M, Elwood M, English DR, Baade PD, Youl PH, Aitken JF. Presentation and detection of invasive melanoma in a high-risk population. J Am Acad Dermatol 2006;54:783-92

2. Grob JJ, Bonerandi JJ. The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. Arch Dermatol. 1998 Jan;134(1):103-4.

3. Chamberlain AJ, Fritschi L, Giles GG, Dowling JP, Kelly JW. Nodular type and older age as the most significant associations of thick melanoma in Victoria, Australia. Arch Dermatol 2002;138:609-14.

4. Swetter SM, Boldrick JC, Jung SY, Egbert BM, Harvell JD. Increasing incidence of lentigo maligna melanoma subtypes: northern California and national trends 1999-2000. J Invest Dermatol 2005;125:685-91.

5. Holman CD, Armstrong BK. Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: An analysis separating histogenetic types. J Natl Cancer Inst 1984;73:75-82.

6. Menzies SW, Crotty KA, Ingvar C, McCarthy WH. Dermoscopy: An Atlas. 3rd ed. Sydney: McGraw-Hill Book Co.; 2009.

7. Blum A, Simionescu O, Argenziano G, Braun R, Cabo H, Eichhorn A, et al. Dermoscopy of pigmented lesions of the mucosa and the mucocutaneous junction: results of a multicenter study by the International Dermoscopy Society (IDS). Arch Dermatol. 2011; 147(10): 1181-7.

8. Lin J, Koga H, Takata M, Saida T. Dermoscopy of pigmented lesions on

Acknowledgements

Michelle Avramidis BSc
Photography

Roula Drossis MSc BSc
Illustrations

7

Biopsy Techniques

RICARDO VILAIN JONATHAN STRETCH
KIERAN POWER

Melanoma Institute Australia

Key Points

- Accurate diagnosis of any pigmented lesion is crucial to its appropriate ongoing management.
- The type of biopsy performed can impact upon the accuracy of diagnosis and assessment of its microstaging.
- Wherever possible an **excision biopsy** should be performed; punch, incision or shave biopsies should be reserved for circumstances where excision biopsy is difficult.
- Subtotal biopsy specimens may lead to an incorrect diagnosis due to sampling error or suboptimal pathological assessment and may also make accurate pathological staging impossible.

Biopsy Types

The accurate histopathological diagnosis of any skin lesion with a potential diagnosis of melanoma is crucial for appropriate patient care. The type of biopsy performed will impact upon the information that can be determined and can have implications for the overall accuracy of the diagnosis. Where possible an excision biopsy should be performed.

Punch, incision or shave biopsies are generally associated with potential significant limitations. They may be acceptable where excision biopsy will prove difficult, e.g. for large pigmented lesions or those located on cosmetically or functionally sensitive anatomic sites. In these situations it may be preferable for the biopsy strategy to be determined by the treating specialist. Subtotal biopsy specimens may lead to an incorrect diagnosis due to sampling error or suboptimal pathological assessment and may also make accurate pathological staging impossible.

Excision Biopsy

Excision biopsy is performed by removing the lesion with at least a 2mm margin, typically as an ellipse, to the depth of the subcutis. This normally allows primary closure of the resultant wound. Using this technique, histological sampling of the entire lesion can take place. This is critical for optimal histopathological assessment and diagnosis as well as the accuracy of assessment of important histological parameters including tumour depth and mitotic rate, which are paramount in guiding the ongoing treatment needs of the patient.

It is accepted that an excision biopsy may not always be practical, for example if the size of the lesion may not allow primary closure or where subsequent reconstruction choices would be affected by the definitive diagnosis. At cosmetically

sensitive or anatomically constrained locations a punch or incision biopsy can be considered.

Shave Biopsy

A shave biopsy is performed using either a scalpel or curved flexible blade. The technique used and depth of the lesion, together with the overall thickness of the skin at the site of the lesion, will all influence the quality of the biopsy and its usefulness. However, shave biopsies generally provide more of a lesion than punch or incision biopsies. Superficial shave biopsies commonly transect the lesion, particularly at its deep margin; resulting in an inability to accurately microstage the Breslow thickness of melanoma and can adversely impact the patient's overall management strategy and the opportunity to consider the issue of lymphatic mapping and sentinel node biopsy.

Incision & Punch Biopsies

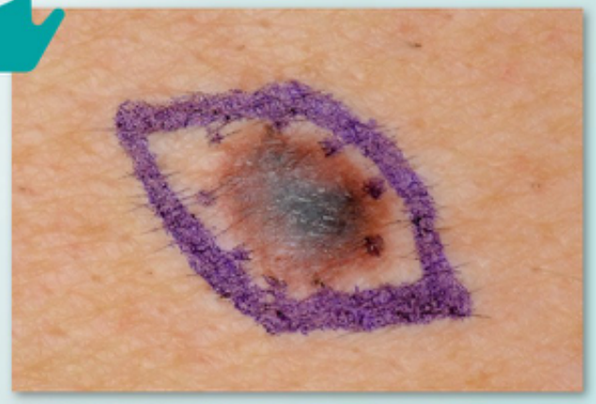
An incision biopsy is performed by creating an elliptical incision through part of the lesion (typically including some normal perilesional skin) affording direct closure of the resultant wound. The punch biopsy is essentially a variation of this using a circular blade, which can range in size from 1.0 to 8.0mm in diameter (3.0 to 5.0mm being most commonly used). Examples of each are illustrated below. The incision biopsy will often yield greater information as more tissue can be sampled than with a punch biopsy. However, the punch can be more straightforward to perform and often negates the need for suturing, requiring only a simple dressing.

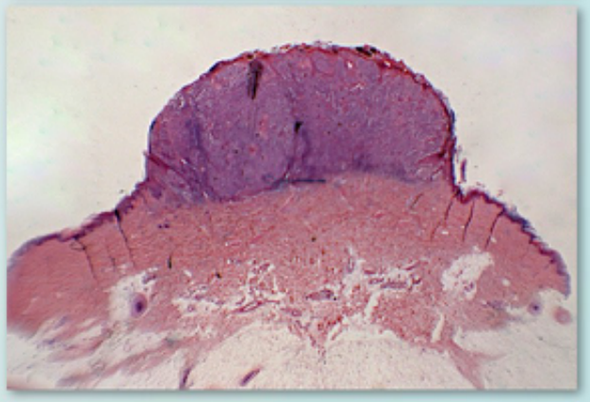
These techniques are inherently tissue sampling procedures and even with multiple biopsies, may not be truly representative of the entire lesion. The specimens obtained can also be more prone to misdiagnosis because some of the important

Interactive 7.1 Types of Biopsy

Types of Biopsy

Excision





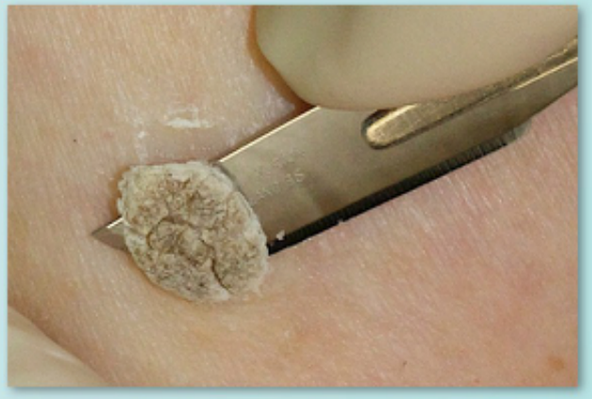
Advantages

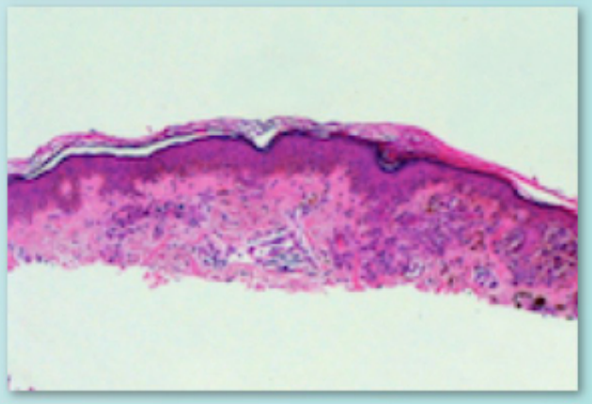
- Totally removes lesion.
- Facilitates accurate histological assessment.
- Most often biopsy of choice.

Disadvantages

- Most readily feasible for lesions affording direct closure.
- A partial biopsy may be preferable where direct closure is not possible.

Shave





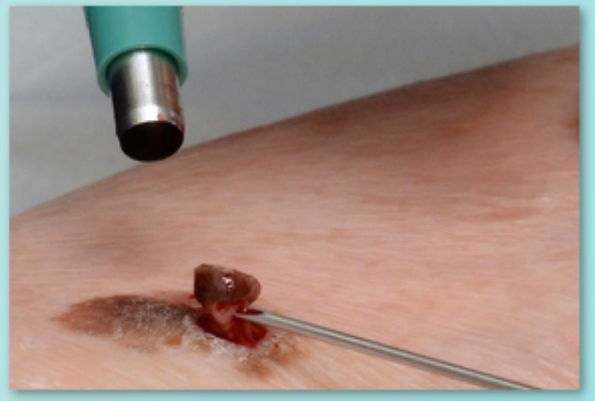
Advantages

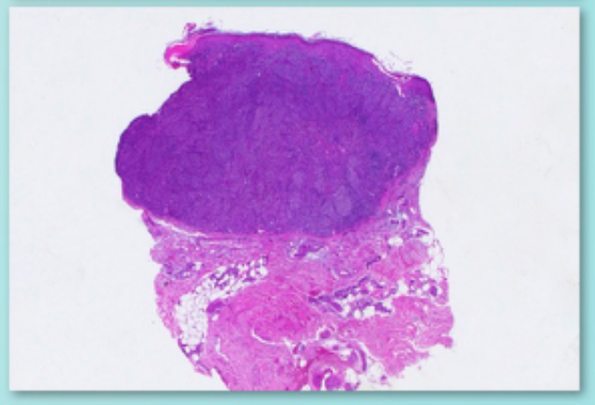
- Quick to perform.
- Potentially treats benign conditions.

Disadvantages

- Margins (deep and peripheral) often involved by lesion.
- Increased risk of inaccurate diagnosis.

Punch & Incisional





Advantages

- Quick to perform.
- May confirm clinical diagnosis and suggest tumour thickness.

Disadvantages

- Often does not complete management of lesion.
- Sampling error may miss relevant pathology.
- Greatly increased risk of melanoma misdiagnosis (punch).

features for pathological diagnosis cannot be adequately assessed and they may make assessment of the relevant histological parameters more difficult, thus potentially hindering the definitive treatment plan. Notwithstanding these potential limitations incisional and punch biopsies do have a place in the diagnostic armamentarium where excision biopsy is not practical. The specialist who will provide the ongoing and definitive care for the patient may be the most appropriate clinician to make this decision.

Discussion

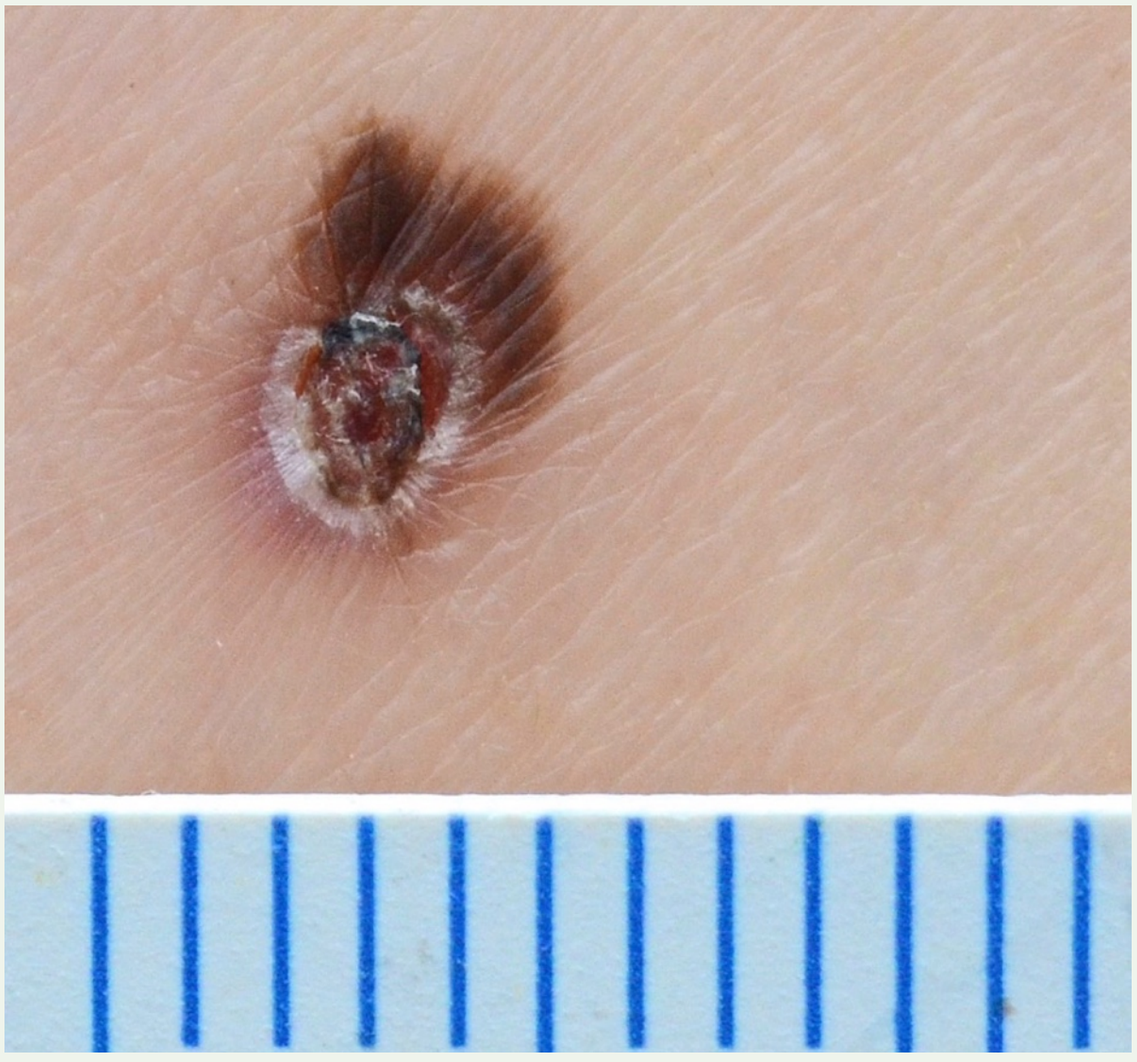
There can be little doubt that the approach individual clinicians use in selecting biopsy techniques is heavily driven by their training and the format of their clinical practice, including the types of pathology most commonly encountered. It is perhaps understandable that clinicians who manage a diverse range of skin conditions are primarily focused on establishing a tissue based diagnosis. Undoubtedly shave and punch biopsies rapidly facilitate this process in many instances. However, when the diagnosis of melanoma is a realistic contender in the differential diagnosis of a cutaneous lesion, it is more appropriate that the clinician should consider the question as to why an excision biopsy cannot be performed. Not only does an excision biopsy facilitate accurate pathological diagnosis, but also melanoma misdiagnosis is greatly increased in partial biopsies, especially punch biopsies. Ongoing management decisions about wider re-excision margins, and the utility of sentinel node evaluation (albeit lymphatic mapping and node ultrasonography, or formal sentinel node biopsy) are entirely dependent on the accurate histopathological characterisation of the entire lesion.

All too commonly, clinicians in specialist melanoma centres are referred patients following shave and

punch biopsies of melanoma; the accompanying histopathology report makes it impossible for the clinical management decisions outlined above to be appropriately decided. At best, the residual lesion may be amenable to a completion excision biopsy, which may provide further useful information. However, the biopsy artefact produced by the preceding shave or punch biopsy frequently precludes this.

Apart from the implicit diagnostic limitations of subtotal (shave and punch) biopsies, the longer term consequences to the residual lesion (particularly if it was considered to be a naevus) warrant discussion. The wound within the biopsied melanocytic lesion subsequently heals by processes that include acute inflammation, angiogenesis, fibroblast activation and collagen production. As part of this wound healing process, a range of growth factors (including bFGF, VEGF, PDGF and TGF-β) are produced that are also known to be

FIGURE 7.1 INAPPROPRIATE SUBTOTAL (PUNCH) BIOPSY OF SMALL LESIONS



This melanocytic lesion with maximal dimensions of 4mm, apparently of concern to a clinician, was biopsied with a 2mm punch. The sample obtained and residual lesion are both likely to present diagnostic and ongoing management problems.

promoters of neoplasia. The impact of these factors on the residual melanocytic lesion following subtotal biopsy is considered to contribute to the development of regenerating naevi, pseudomelanoma and possibly the transformation of dysplastic naevi into melanoma. Although subtotal biopsy of a melanocytic lesion may result in a pathology report that does not identify malignancy, subsequently the residual lesion frequently undergoes clinically apparent change. How the clinician and patient interpret this can be problematic and potentially hazardous. Furthermore, distinguishing a regenerating naevus from a melanoma in any subsequent biopsy may be very difficult for the pathologist and sometimes impossible.

In summary, when a diagnosis of melanoma is contemplated on the basis of the clinical history or morphological features of a lesion, excision biopsy is almost invariably the optimal form of biopsy.

8

Histogenesis

JONATHAN STRETCH RICHARD A. SCOLYER

Key Points

- Melanoma is a carcinoma that develops from melanocytes or melanocytic naevus cells.
- Melanocytes reside in basal layer of the epidermis where they produce and deliver melanin to surrounding keratinocytes.
- Melanin forms a cap over the outer surface of keratinocytes' nuclei to shield the DNA from UV radiation.
- Melanocytes connect with each other via their dendrites to form a network; melanoma cells can induce pre-cancerous changes in nearby cells within the network, creating a "field effect".
- Wide excision removes residual tumour cells and unstable melanocytes in the vicinity of the primary melanoma.

Histogenesis of Melanoma

Melanocytes and melanocytic naevus cells are both derived from neuroectoderm and represent varying points of developmental evolution from the same tissue origin. Melanoma is a malignant tumour that can evolve from either of them.

Development and Function

The melanocyte's primary role in the skin is to produce and deliver melanin to the surrounding keratinocytes, where it shields their DNA from ultraviolet radiation. Melanocytes can be induced to increase melanin synthesis in response to ultraviolet-induced keratinocyte DNA damage. The reactions that generate melanin occur within a cytoplasmic organelle called the melanosome. Within melanosomes, two principal types of melanin polymers are formed: eumelanin and pheomelanin. Eumelanin is coloured dark brown-black and displays greater photoprotective properties than pheomelanin. The balance of eumelanin to pheomelanin determines skin and hair pigmentation, with darker hues being the result of high eumelanin-to-pheomelanin ratios. Melanosomes packed with melanin polymers are exported to melanocyte dendritic processes where they are packed into vesicles and secreted, following which they are taken up by surrounding keratinocytes. Keratinocytes breakdown the vesicles and redistribute the melanin as an apical cap over the nucleus, thereby shielding the genomic DNA from UV radiation.

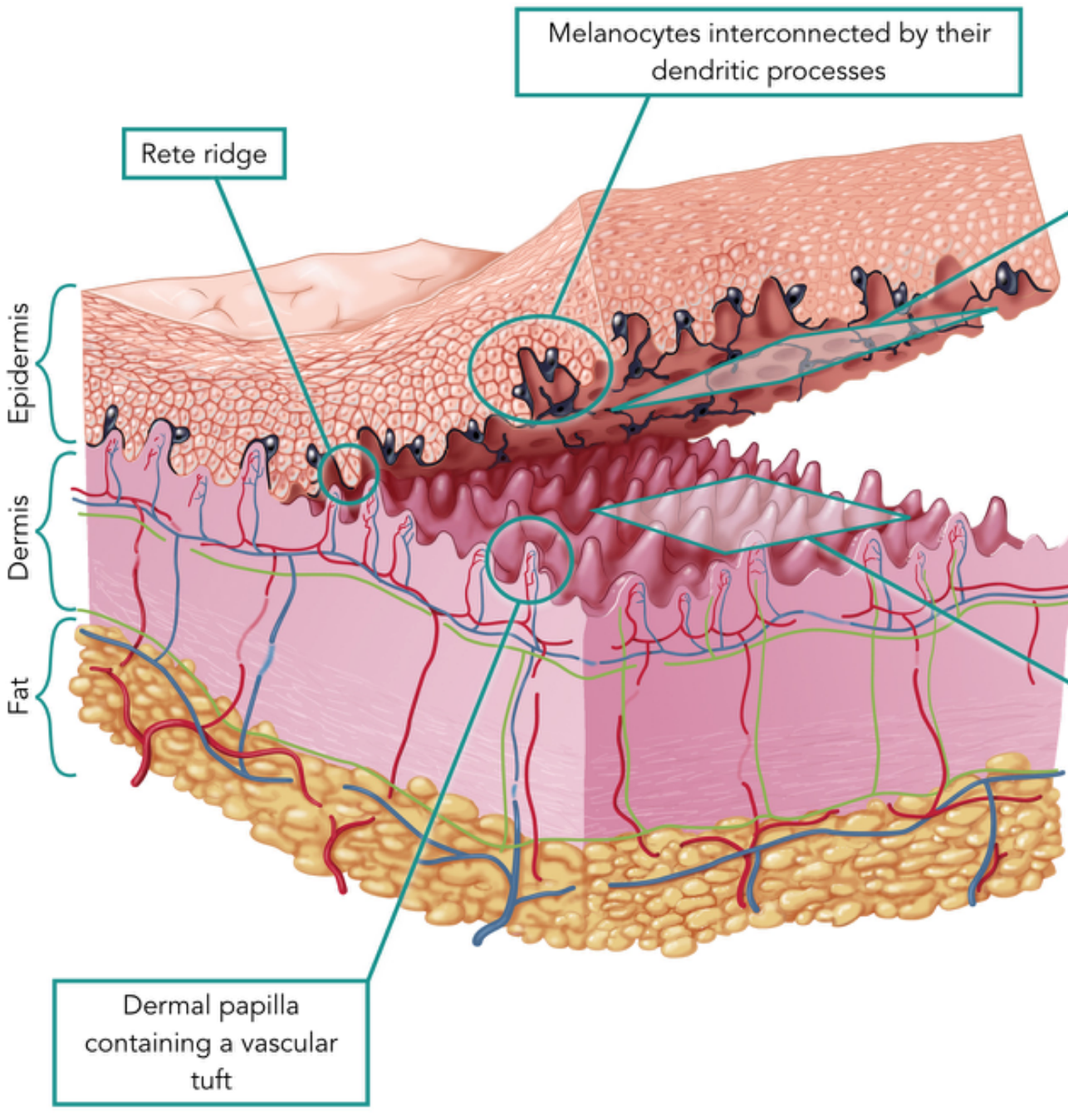
Understanding the Dermo-epidermal Junction

The skin is essentially composed of epidermis and dermis, with normal melanocytes distributed along the dermo-epidermal junction and associated adenexal structures including hair follicles, sebaceous and sweat glands.

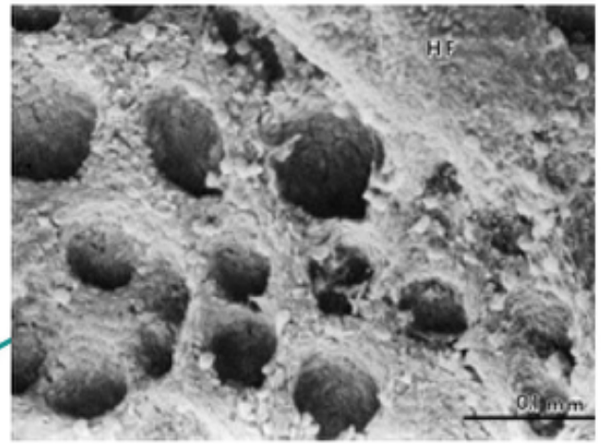
Interactive 8.1 Topography of the Dermo-Epidermal Junction

Topography of the Dermo-Epidermal Junction

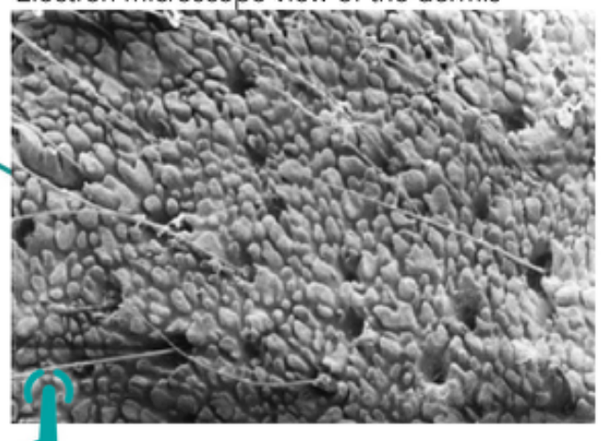
Illustration of the melanocytic network at the dermo-epidermal junction in normal skin



Electron microscope view of the epidermis



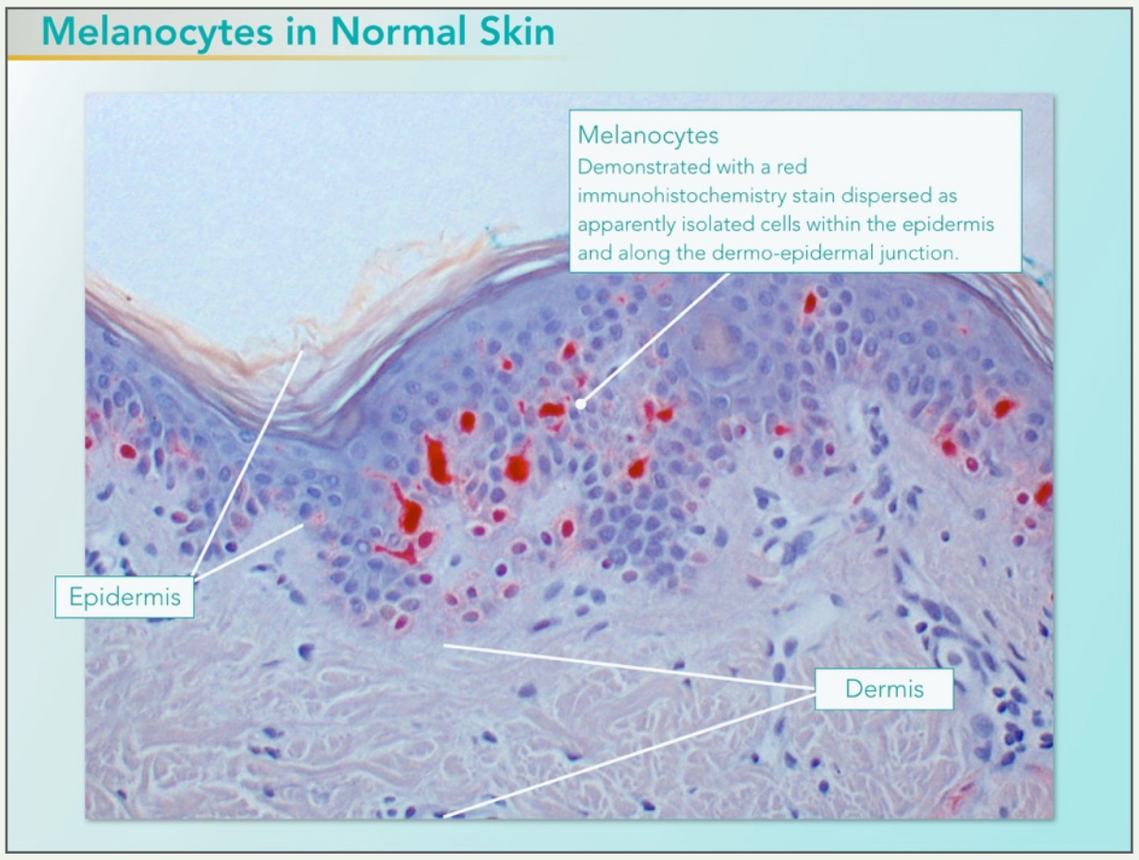
Electron microscope view of the dermis



Tap images for more detailed views

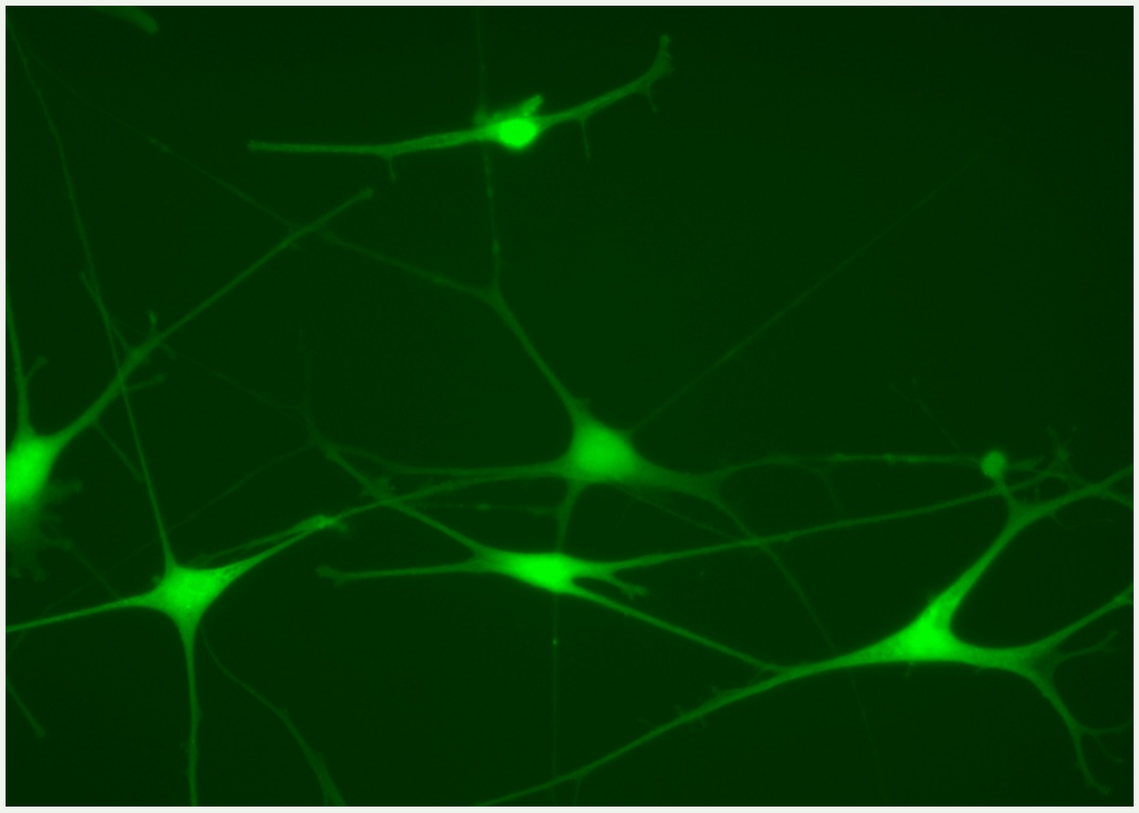
Conventional histological tissue sections generally give the impression that melanocytes at the dermoepidermal junction of normal skin are isolated from each other, interspersed between the basal keratinocytes (Figure 8.1). In reality they are part of a highly interconnected melanocytic network linked by their dendritic processes (Figure 8.2).

FIGURE 8.1 HISTOLOGICAL SECTION OF NORMAL DERMO-EPIDERMAL JUNCTION



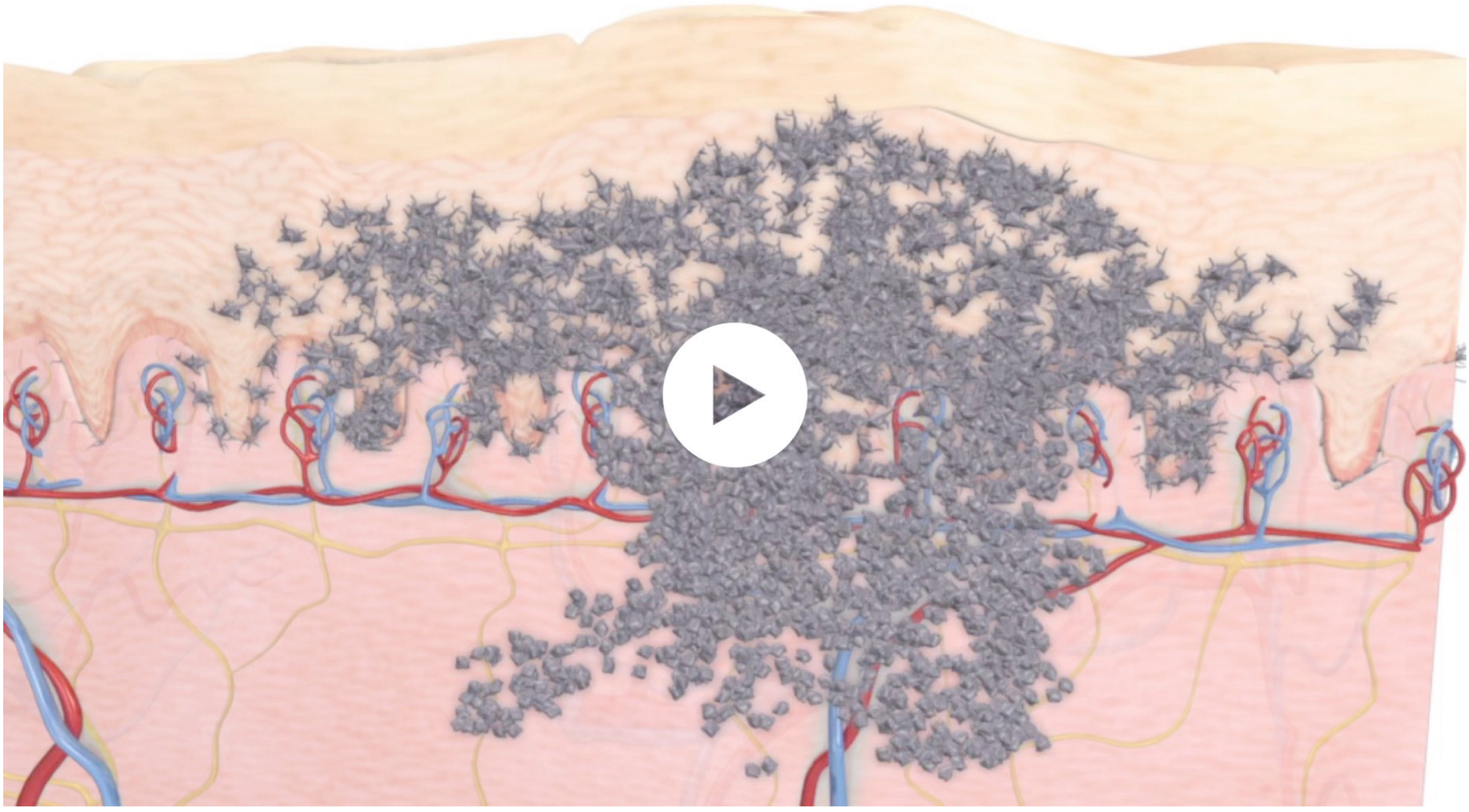
Melanocytes normally show a complex dendritic morphology, with multiple processes extending over and between adjacent keratinocytes. The usual density of melanocytes approximates 1 melanocyte

FIGURE 8.2 INTERCONNECTION OF MELANOCYTES



Microscope view of melanocytes in culture demonstrating their dendritic connections. Note the morphology of the melanocytes' bodies is different than in vivo

Video 8.1 The Junctional Melanocytic Network and Evolution of Melanoma



to 10 keratinocytes although this varies depending on the anatomical location. Melanocytes are distributed regularly throughout the basal epidermis, although their density can be higher in flexural skin (axilla, groin), during pregnancy and in sun-damaged skin, where the density can double.

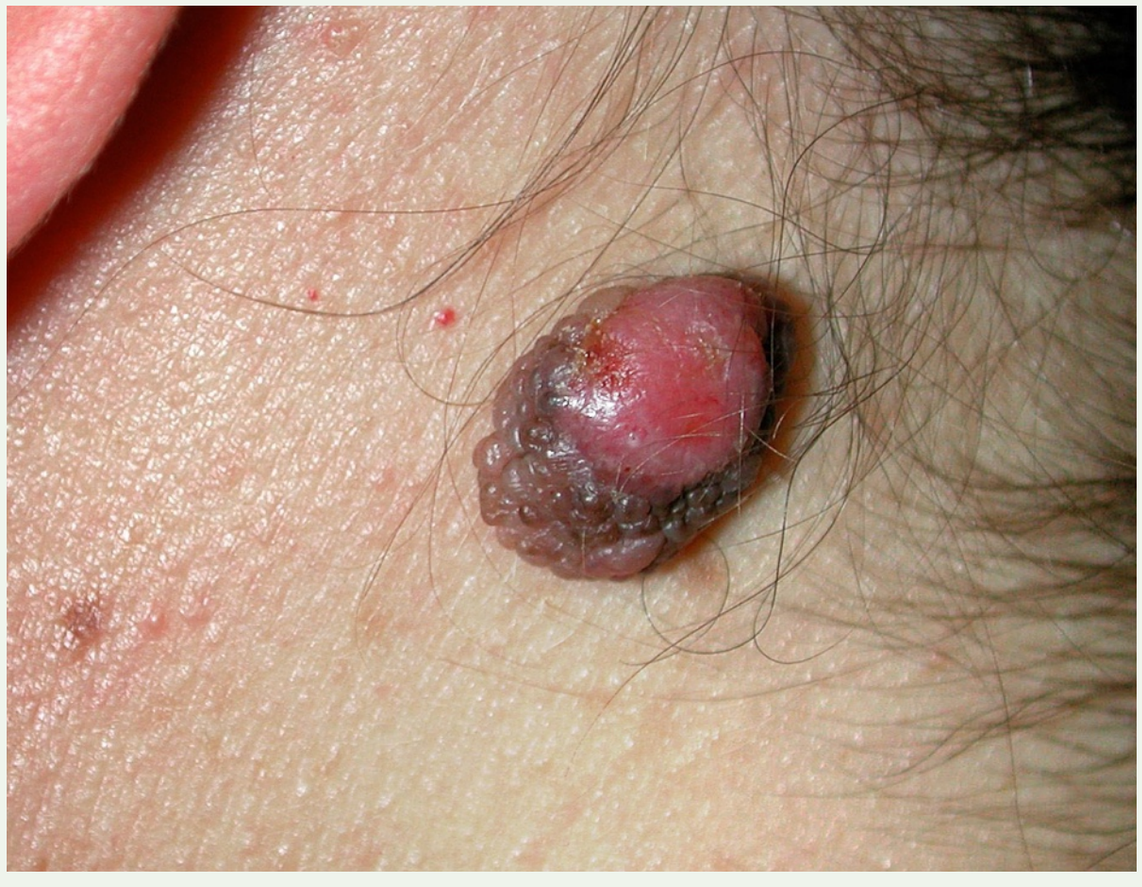
Melanin pigment is not routinely identified within melanocytes, but within the cytoplasm of keratinocytes over the superficial surface of the nucleus. Melanin undergoes degradation during keratinocyte maturation and the normal upward migration of keratinocytes within the epidermis. As a consequence, melanin is typically not visible within the cornified layers. When melanin pigment is abnormally deposited within the superficial (papillary) dermis, it is termed pigment incontinence. As such, pigment incontinence reflects damage to the basal epidermal layer and a release of pigment. This is typically a consequence of immune cell mediated damage. Melanin can lie free within the dermis or be engulfed by macrophages, which are termed melanophages.

Common Naevi

Congenital naevi are formed in utero or become clinically apparent within the first months of life. They can be large or garment-like but are more commonly small or medium size. Large congenital naevi are sometimes defined as being larger than the palm of the patient's hand. The remaining neural crest cells destined to form **acquired naevi** and the melanocyte population of the skin migrate to become associated to the dermo-epidermal junction of the skin. During childhood and adolescence, promoted by sunlight exposure, these cells proliferate and aggregate and become clinically apparent as various forms of acquired naevi (junctional, compound and dermal). Although occasional new naevi can develop later in adult life, the process of evolving acquired naevi is normally complete between the ages of 18 - 30 yrs. It is this

fact that forms the basis for public awareness programs urging patients to report new moles for assessment. Unfortunately, a misunderstanding about this process causes significant concern from parents of young children as their normal acquired naevi become apparent.

FIGURE 8.3 MELANOMA ARISING IN NAEVI



This patient presented with this melanoma arising in a naevus. Sentinel lymph node biopsy showed evidence of metastasis to a neck node.

The immunocytochemical profile and cell culture characteristics of both naevus cells and melanocytes overlap substantially, reflecting their common embryological origin.

Melanoma can therefore evolve from any of these melano/naevocytic cells. It is variously estimated that 40-60% of melanoma arises from a pre-existing naevus (Figure 8.3). The remainder arise from neoplastically transformed melanocytes existing as essentially individual cells.

Primary Melanoma and the Surrounding Melanocytic Network

When a primary melanoma arises in skin, the tumour lies within a surrounding background of apparently histologically normal melanocytes. However, these adjacent *normal* melanocytes may also have significant genomic changes that can predispose to

further tumours developing. These genomic mutations may occur both as a result of a similar environmental exposure and as a consequence of signalling through the melanocytic network from the overt tumour cells. The dendritic interconnectivity between a primary melanoma and the surrounding melanocytes is depicted in Video 8.1.

The concept of oncogenically transformed, histologically normal, melanocytes at a distance from the identifiable tumour has been elegantly demonstrated by Boris Bastian and colleagues in acral melanoma. They have established that histologically normal junctional melanocytes at some distance from the primary tumour have been at least partly biologically transformed. These transformed cells are at risk of progressing to further malignancy, representing a potentially unstable "field effect". Consequently, it now appears that oncological progression in the field beyond the histologically identifiable tumour may represent a better explanation for 'local recurrence' than residual tumour.

The principle of wide local excision (WLE) of melanoma may therefore serve two purposes; firstly, to remove any adjacent pre-cancerous cells and secondly, to remove any residual tumour or peritumoural satellites. However, residual tumour is infrequently detected in WLE specimens after a complete excision biopsy with 2-3mm clinical margins, unless the primary tumour has advanced features on microstaging. Therefore, the benefits of WLE are likely to be predominantly due to removal of the field effect, consistent with the greater margins used in melanoma compared to most other skin cancers.

Although there is currently no directly applicable data to validate the application of Bastian's findings with acral melanoma to melanomas occurring at other anatomical sites, it appears highly relevant.

Clinical experience with recurrent/multiple melanoma arising outside histologically established adequate excisions of lentigo maligna melanoma adds substance to the concept of field changes extending beyond clinically or histologically apparent neoplasia.

It is interesting to contemplate that the original melanoma surgeons extremely widely excised primary melanomas, based on their caseload of mostly very advanced tumours with high risks of peritumoural lymphatic involvement. More conservative excision margins are in use today, but clinical trials are still underway to define what constitutes the optimal excision margins. However, it seems inevitable that melanoma will continue to require a wider excision margin than most other cutaneous tumours.

Citations and Further Reading

1. North JP, Kageshita T, Pinkel D, LeBoit PE, Bastian BC. Distribution and significance of occult intraepidermal tumor cells surrounding primary melanoma. J Invest Dermatol. 2008 Aug;128(8):2024-30. doi: 10.1038/jid.2008.41. Epub 2008 Mar 6. PubMed PMID: 18323782; PubMed Central PMCID: PMC2825251.

ACKNOWLEDGEMENTS

Animated Biomedical Productions

Animation

9

Histopathological Assessment & Synoptic Reporting

RICARDO VILAIN RICHARD A. SCOLYER

Melanoma Institute Australia

Key Points

- Histopathological diagnosis of melanocytic tumours can be particularly challenging and definitive diagnoses are not always possible.
- The tabular synoptic report format systematically documents the important histological features that determine a melanoma's staging according to the American Joint Committee on Cancer (AJCC) guidelines.
- The broad range of details available in the histopathology report, including Breslow thickness, collectively form important prognostic indicators that can optimise patient management strategies.

Introduction

The appropriate care of patients with skin lesions that include melanoma in their differential diagnosis requires a fundamental comprehension of the histopathology of these conditions. The nomenclature that has been developed to describe these lesions is fundamentally linked with their associated pathobiology.

At the outset of any discussion of diagnostic melanocytic pathology, it is important to highlight the specific difficulties that the clinical histopathologist often faces in establishing tissue diagnoses that enable the managing clinicians to evolve optimally appropriate treatment strategies. Establishing a confident diagnosis of invasive melanoma as opposed to a melanocytic tumour of uncertain malignant potential (sometimes referred to by the acronym MelTUMP) is a frequent issue in histopathological practice.

- This chapter will review the fundamental histopathological features associated with the diagnosis of primary cutaneous melanoma in its most common forms and highlight the valuable utility of the synoptic histopathology report.

Section 1

Understanding Pathological Assessment

Introduction

Melanoma is an invasive and metastasising tumour that originates from melanocytes. Melanomas can arise from either single melanocytes (60%) or as part of a melanocytic naevus (40%). However, as mentioned earlier, the risk of any individual naevus becoming a melanoma is around 1 in 100,000.

Melanoma can be subdivided into the pre-invasive and the invasive forms. The pre-invasive forms are known as melanoma in situ and lentigo maligna/ Hutchinson's melanotic freckle. The invasive forms are melanoma and lentigo maligna melanoma.

We discuss here the associated histological features of melanoma, together their diagnostic significance.

Melanoma In Situ

Melanoma in situ represents the intra-epidermal or radial growth phase of melanoma. There is no invasion through the underlying junctional basement membrane, and therefore no capacity for metastasis.

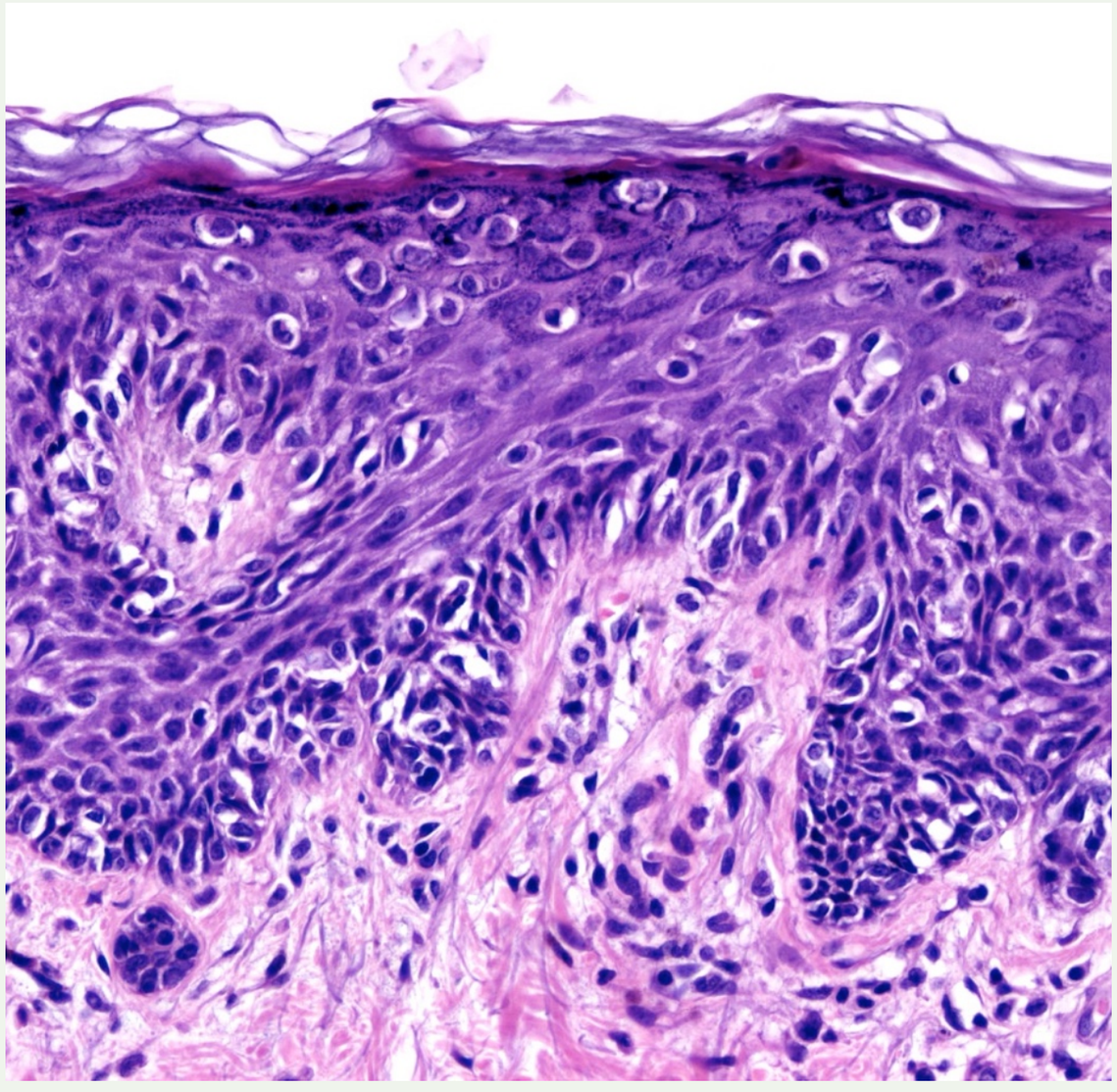
There is no single criteria that defines melanoma in situ, however a universal feature is the deviation from the normally ordered appearance of benign melanocytes and naevi. Four of the most frequent alterations seen include:

1. prominent single cell growth
2. confluence of irregular and variably sized melanocyte nests
3. prominent pagetoid spread
4. widespread cytological atypia.

The proliferation of single melanocytes dominates most in situ melanomas. These melanocytes are irregularly distributed along the basal layer epidermal layer, extending into adnexal epithelium (hair follicles and sweat glands) and also fusing into melanocyte nests. Large 'skip areas' of seemingly uninvolved epidermis appear nestled in between zones with dense aggregates of atypical melanocytes. Differences in the pattern and density of melanocyte growth, which can be most apparent at the tumour periphery, contribute to an appearance of asymmetrical growth.

Melanocyte nests vary in size, shape and in their distance to one another. Importantly, confluent growth between differently sized nests is a feature not commonly encountered in either benign or dysplastic naevi. The degree of nest expansion can be such that they grow over the walls of the rete ridges and extend into the supra-papillary plate or deep into adnexal epithelium.

FIGURE 9.1 HISTOLOGICAL FEATURES OF MELANOMA IN SITU



Widespread proliferation of melanocytes along the basal epidermal layer, typical of in situ melanoma.

The spread of atypical melanocytes into the epidermal granular layer and beyond (pagetoid spread) is a particularly useful feature in the assessment of melanoma in situ. The involved epidermis can also demonstrate useful clues to the presence of a melanoma in situ. The epidermis can be irregularly atrophic, exhibiting total loss of the normal rete ridge architecture. This co-exists with a zone of thickened epidermis, typically associated with regions exhibiting florid pagetoid spread.

The underlying papillary dermis frequently exhibits the same fibroplasia seen in dysplastic naevi. An underlying irregularly distributed inflammatory component is typically present. An intense but patchy inflammatory infiltrate can be a highly significant clue within a small biopsy of melanoma in situ of acral skin.

Invasive Melanoma

Several requirements must be met to establish a diagnosis of invasive melanoma. A collection of atypical architectural and cytological features must exceed what would be acceptable for either an unusual naevus or a highly dysplastic naevus.

The presence of asymmetrical features within the architectural and cytological elements of the lesion most readily betrays the malignant nature of melanocytic lesions. Melanomas frequently display an irregular growth pattern, generating an asymmetrical silhouette that is best observed at low power. A low power inspection will reveal an epidermis of variable thickness that may also be ulcerated. The junctional melanocytes typically show all the hallmarks of in situ melanoma. The presence of this component helps to establish that the lesion is a primary tumour rather than a metastasis.

An invasive dermal component is characteristically identified as densely cellular sheets and expansile nodules of tumour cells which destroys or disrupts the normal appearance of the dermis. High power inspection of the dermal component typically shows the same atypical cellular features encountered within the intra-epidermal melanoma. Cellular pleomorphism and nuclear atypia in addition to a high mitotic rate, are usually sufficient to confirm the malignant nature of the invasive melanoma cells. However, any of these elements may be missing and so other features will need to be assessed.

Melanoma cells typically do not 'mature' with depth. As a result, the cells within the deepest levels of the dermis will appear of similar size to cells throughout the superficial layers. The absence of maturation is also apparent in the failure to observe single cell dispersion of the deepest tumour cells. Instead, melanoma typically continues to grow as densely cellular nests and sheets. Aberration in pigment production is also common in melanomas, demonstrating an irregular distribution, with clusters and single cells showing melanin production throughout all layers of the dermis. In contrast, pigment in the dermal component of compound naevi is restricted to the superficially located naevocytes. The melanin pigment is typically finely granular, sparse and evenly dispersed in the cytoplasm of benign naevocytes, but acquires a coarse texture and appears at a variable cytoplasmic concentration throughout a melanoma.

A high mitotic rate is not universally encountered in melanoma, but if present is a highly significant finding. However, mitoses may be present in regenerating and traumatised naevi, as well as naevi under hormonal influence (e.g. during pregnancy). However, abnormalities in the structure of the mitotic spindle, as well as deeply located mitoses, are not features seen in benign naevi. The presence of abnormal mitoses or deep mitoses is highly

significant and warrants a high degree of suspicion for the presence of melanoma.

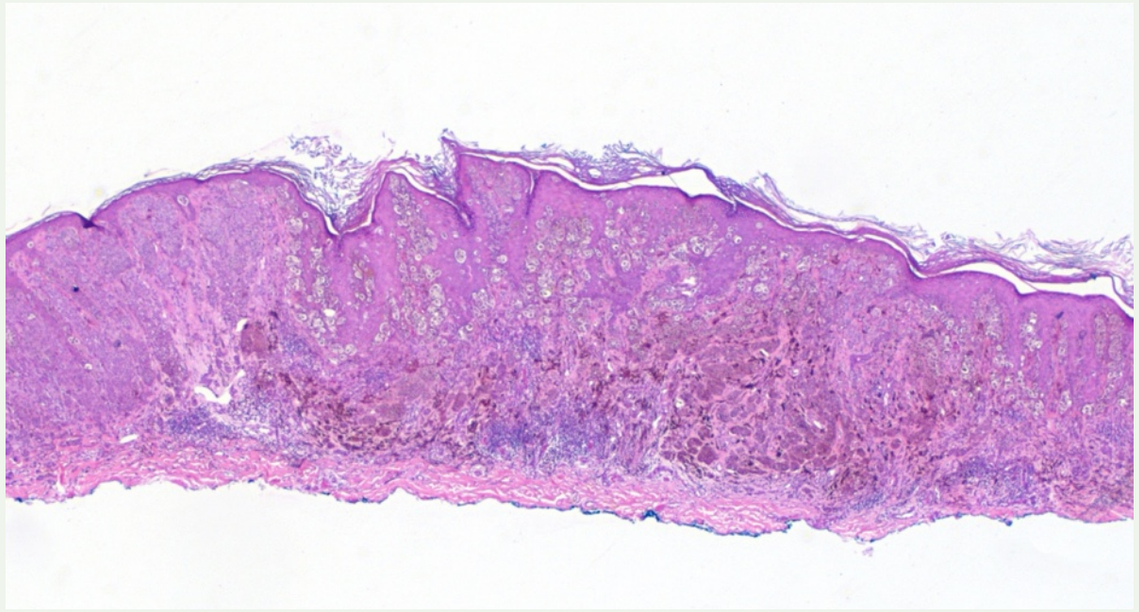
It must be stressed that not of all these features need to be present to support a diagnosis of melanoma. For a difficult borderline lesion, displaying ambiguous histological features, determination of the malignant potential may ultimately depend on interpreting the histology in the context of the lesion's history and dermoscopic appearance as well as the patient's own clinical profile and medical history.

Superficial Spreading Melanoma

Superficial spreading melanoma (SSM) is characterised by laterally proliferating melanocytic tumour cells within the epidermis together with poor definition of the lateral extent of this process (Figure 9.2). This frequently correlates with the clinical observation of indistinct margins of these tumours. The epidermal part of the tumour typically extends beyond the underlying dermal component. Main architectural changes within the epidermis are poor circumscription of melanocytes, single melanocytes predominating over nests, dyscohesive nests, and haphazard, widespread Pagetoid (upward migration above the basal layer) distribution of melanoma cells. Cytologically, epidermal melanoma cells are most commonly large and pleomorphic with abundant eosinophilic cytoplasm, vesicular nuclei and large, eosinophilic nucleoli, which may be multiple. Mitoses are frequently seen.

The dermal component of SMM can exhibit increased mitotic activity, brisk and asymmetrical infiltration of inflammatory cells, and occasional regression (fibrosis with neovascularisation). The normal sequence of melanocytic maturation is lacking or unapparent with the cells at the deepest extent of the dermal invasion being cytologically indistinguishable from those within the superficial papillary dermis. The cells are generally of the epitheloid subtype.

FIGURE 9.2 HISTOPATHOLOGICAL EXAMPLE OF A SUPERFICIAL SPREADING MELANOMA



In this classical example of superficial spreading melanoma, the epidermis is heavily infiltrated by large round pale melanoma cell, showing upward migration toward the keratin layer (i.e. pagetoid spread). A population of heavily pigmented cells are seen in the subjacent dermis, representing invasive melanoma.

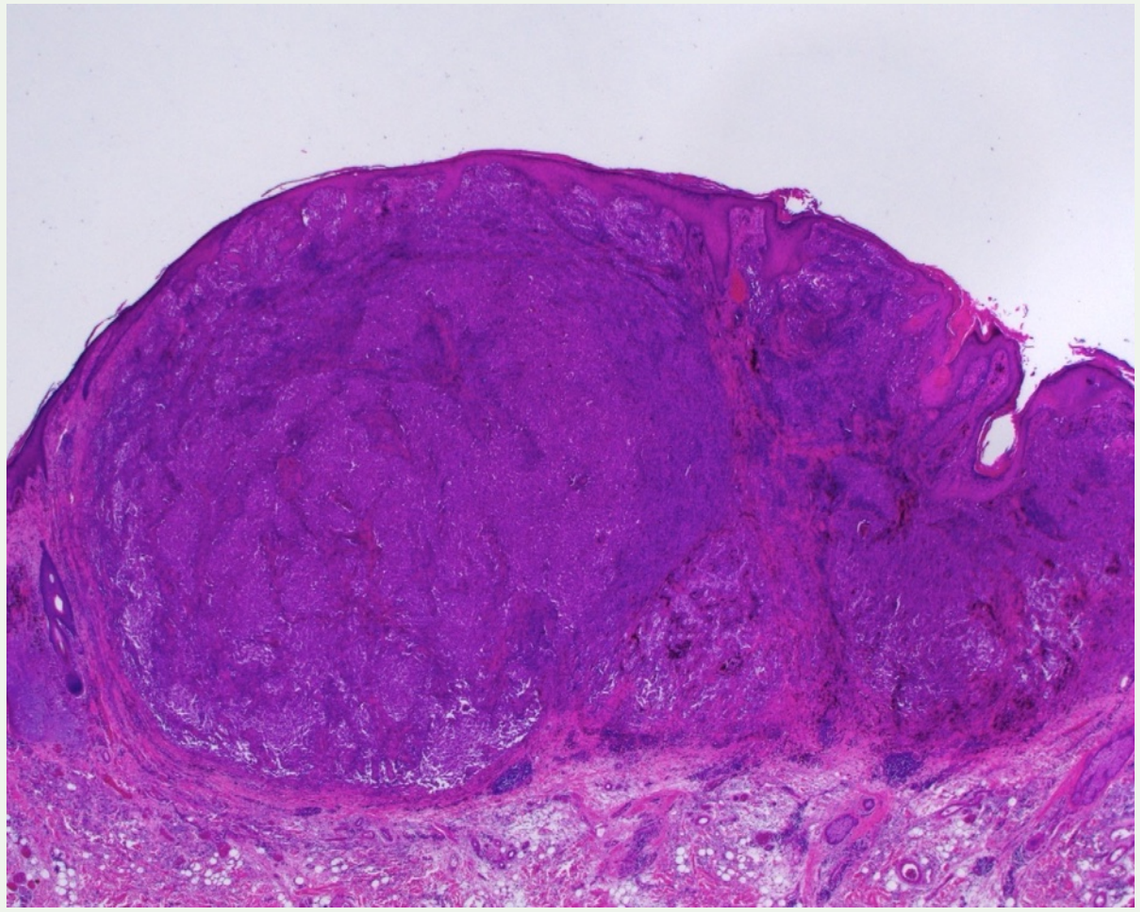
(1 of 3)

Nodular Melanoma

Nodular melanoma (NM) shares many histologic features with SSM (Figure 9.3), but differs particularly by commonly demonstrating sharp lateral circumscription and an epidermal component that is limited to the underlying dermal extension of the tumour. This correlates with the nodular clinical appearance of NM. The epidermal component of NM is characterised by epithelioid melanocytes with abundant cytoplasm, vesicular nuclei and prominent nucleoli. While single cells may predominate over nests, Pagetoid spread is less abundant than in SSM. Ulceration is common.

The vertical growth phase usually begins at an early stage in NM. Consequently, the dermal component is usually characterised by large nests and sheets of cytologically atypical melanocytes, correlating with the aggressive downward growth. An elevated mitotic rate is common in NM.

Figure 9.3 Histopathological example of a Nodular Melanoma



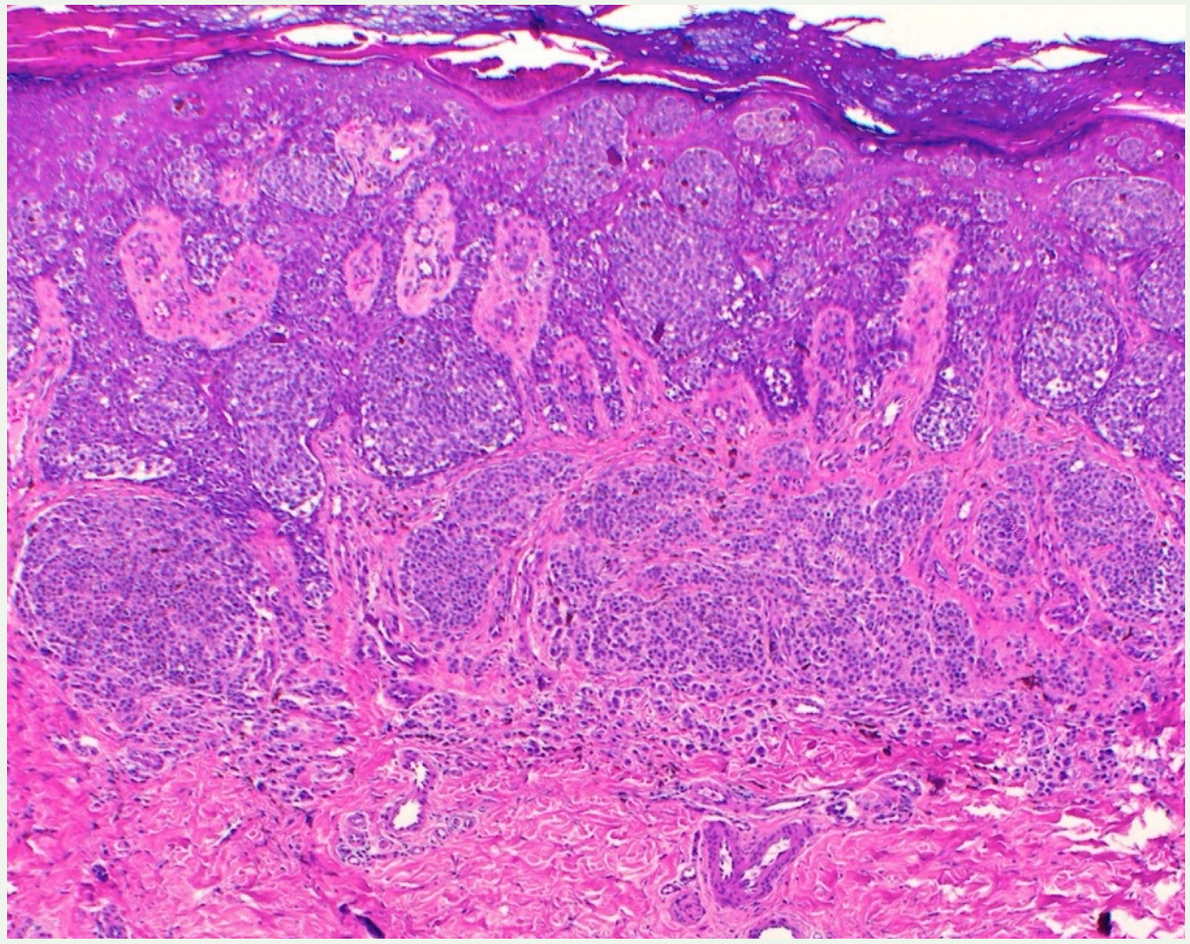
This nodular melanoma shows the characteristically rapidly expansile pattern of growth, which confers the tumour a protuberant appearance and in part explains the use of the term 'nodular'.

Acral Melanoma

The melanocytes in acral melanoma (AM) are present as nests and single cells along the dermal epidermal junction. In the epidermis pagetoid spread is often extensive. Pagetoid spread is also commonly seen in benign acral naevi, but much less widespread. Both epidermal and dermal melanocytes are most commonly hyperchromatic and spindled and nucleoli are often not apparent.

Dermal invasion is characterised by fascicles, nests and single cells through the dermis. The cells are often tracking down along sweat ducts and blood vessels. There is limited maturation with progressive descent through the dermis. Ulceration is frequently found, whereas mitotic activity is variable.

Figure 9.4 Histopathological and Clinical example of Acral Melanoma



This image of acral melanoma shows a markedly disordered epidermis almost completely over run by melanoma spreading as single cells and also forming large nests. The haphazardly distributed population of cells in the dermis signifies invasive melanoma.

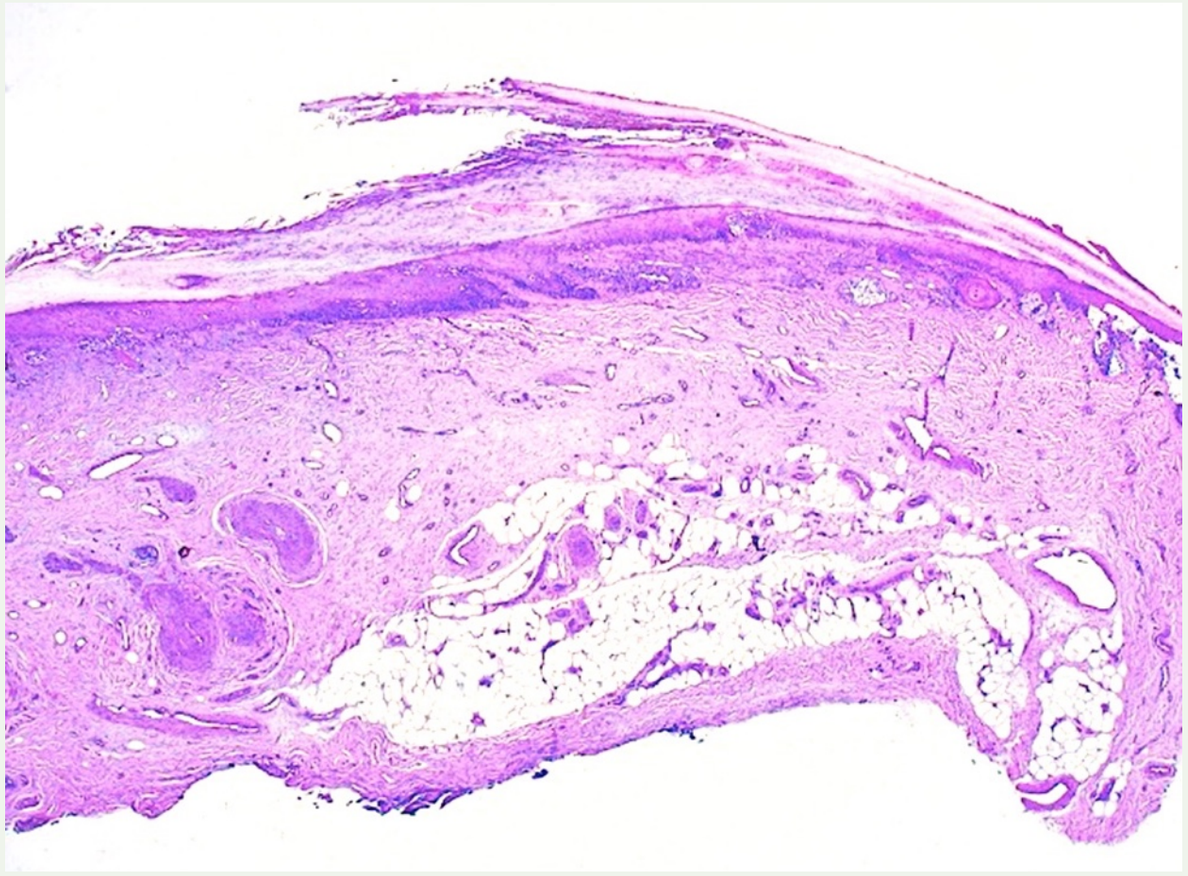
(Image 1 of 4)

Subungual Melanoma

Subungual melanoma (SUM) is generally considered a variant of acral melanoma. SUM can be diagnostically challenging for the pathologist, especially in subtotal biopsies or in previously biopsied specimens, which may be associated with worrying cytology and architecture such as mitoses and pagetoid epidermal growth ("pseudo melanomas"). In addition, over-diagnosis of malignancy in melanocytic lesions displaying single cell invasion of the nail matrix epithelium may occur. However, this is a nonspecific histopathological finding, particularly at acral sites. Repeat biopsies may be needed.

There is some uncertainty as to whether traditionally recognised histologic features for melanoma are prognostically useful in SUM. Measurement of Clark level and Breslow thickness is hampered due to difficulty in separating the papillary from the

Figure 9.5 Histopathological example of Subungual Melanoma



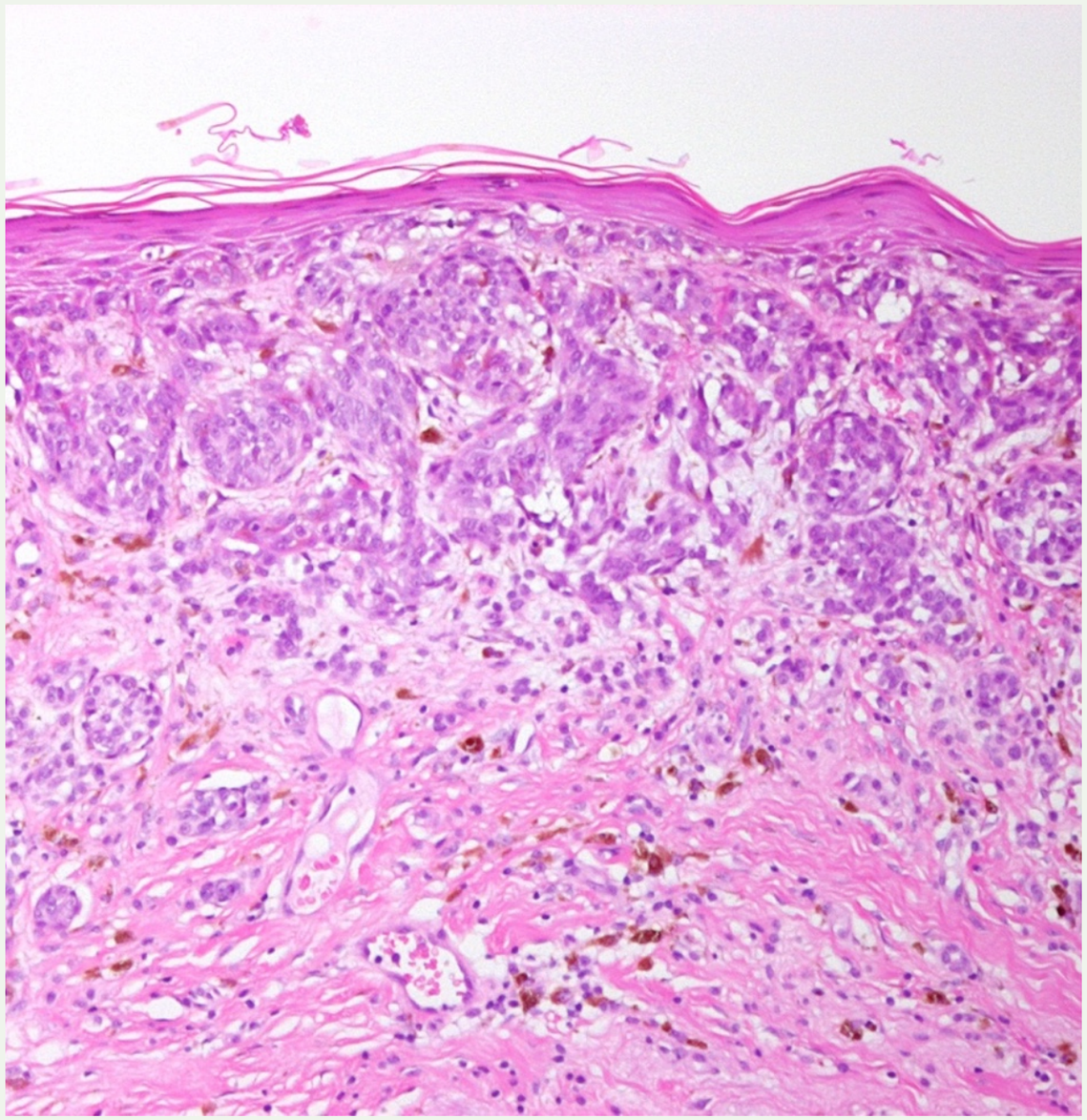
This low power view of a longitudinal section of nail bed shows an inflammatory reaction against an element of intra-epidermal melanoma. This pattern of inflammation is a highly sensitive sign associated with subungual, mucosal and acral lentiginous melanoma.

reticular dermis, absence of subcutaneous fat and lack of a granular layer in the nail matrix. The number of melanocytes in the nail matrix is lower than in normal skin and most of these do not produce melanin in white skinned people. There is a higher incidence of *KIT* mutations in acral melanomas compared to other melanoma subtypes, whereas BRAF mutations are less common.

Lentigo Maligna Melanoma

Lentigo maligna melanoma (LMM) is present in up to 15% of lentigo maligna lesions. The melanocytes are hyperchromatic and most commonly show spindle shaped morphology, but lack the vesicular nuclei and prominent nucleoli commonly seen in other melanoma subtypes. There is lack of dermal maturation, and perineural invasion is frequently seen, whereas mitotic activity usually is limited.

Figure 9.6 Histological Features of Lentigo Maligna Melanoma

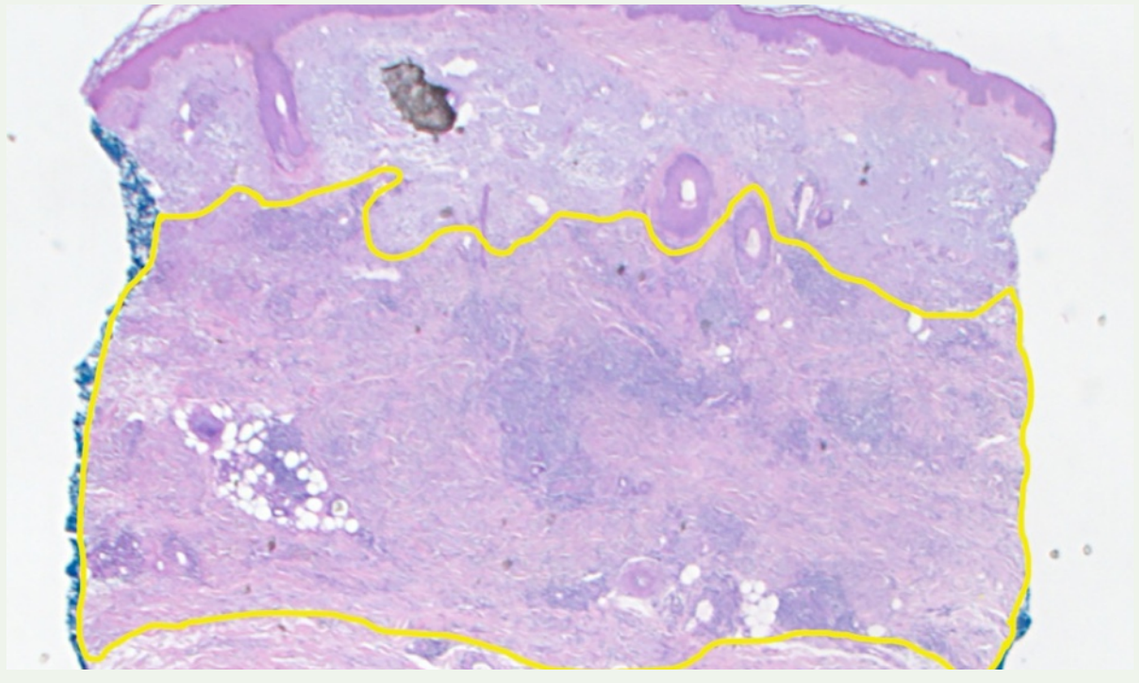


Low power view demonstrating the thinned dermis (solar elastosis) and melanoma invasion into the subcutaneous tissue.

Desmoplastic Melanoma

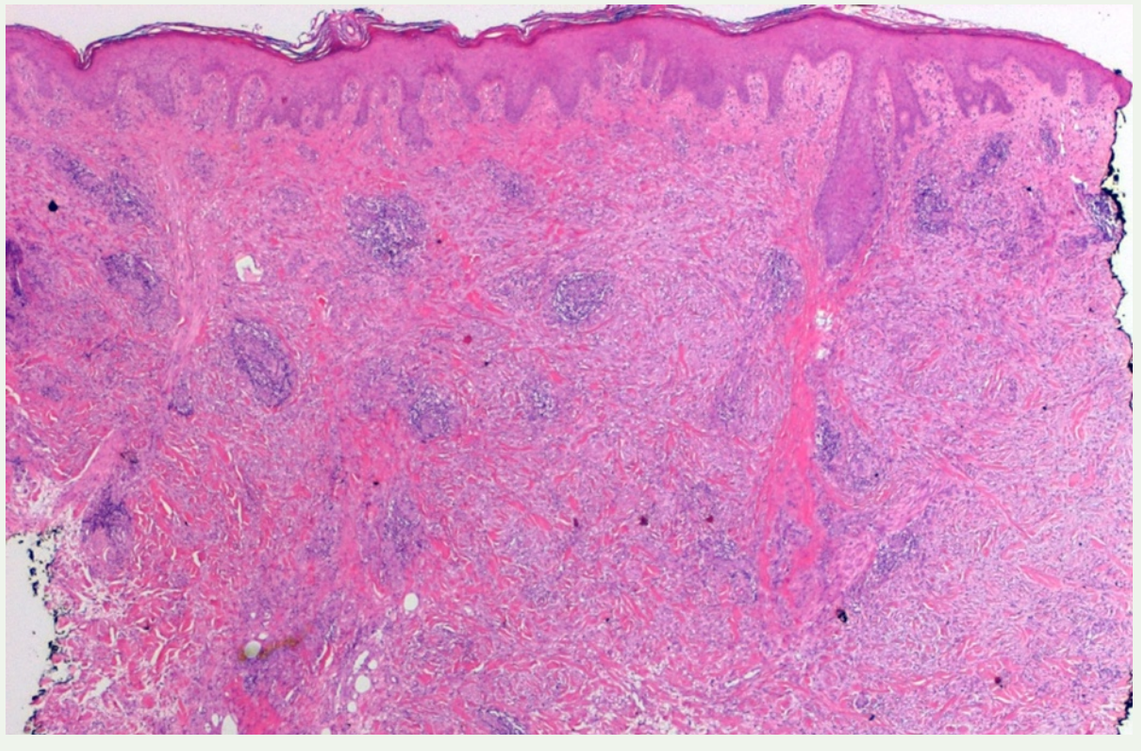
The histopathology of desmoplastic melanoma can at times be very subtle, (Figure 9.7) resembling benign fibrous and even neural tissue. For this reason, low grade desmoplastic melanomas may go unrecognised causing a delay in appropriate treatment. The tumours typically show bland spindle cells with abundant collagen deposition and frequently accompanying chronic inflammatory cells

Figure 9.7 Subtle and Misleading Histological Appearances of Desmoplasia



Desmoplastic melanoma replacing the entire area outlined in yellow, which could easily be misinterpreted as fibrosis. The blue ink applied to the margins of the biopsy are visible at the borders.

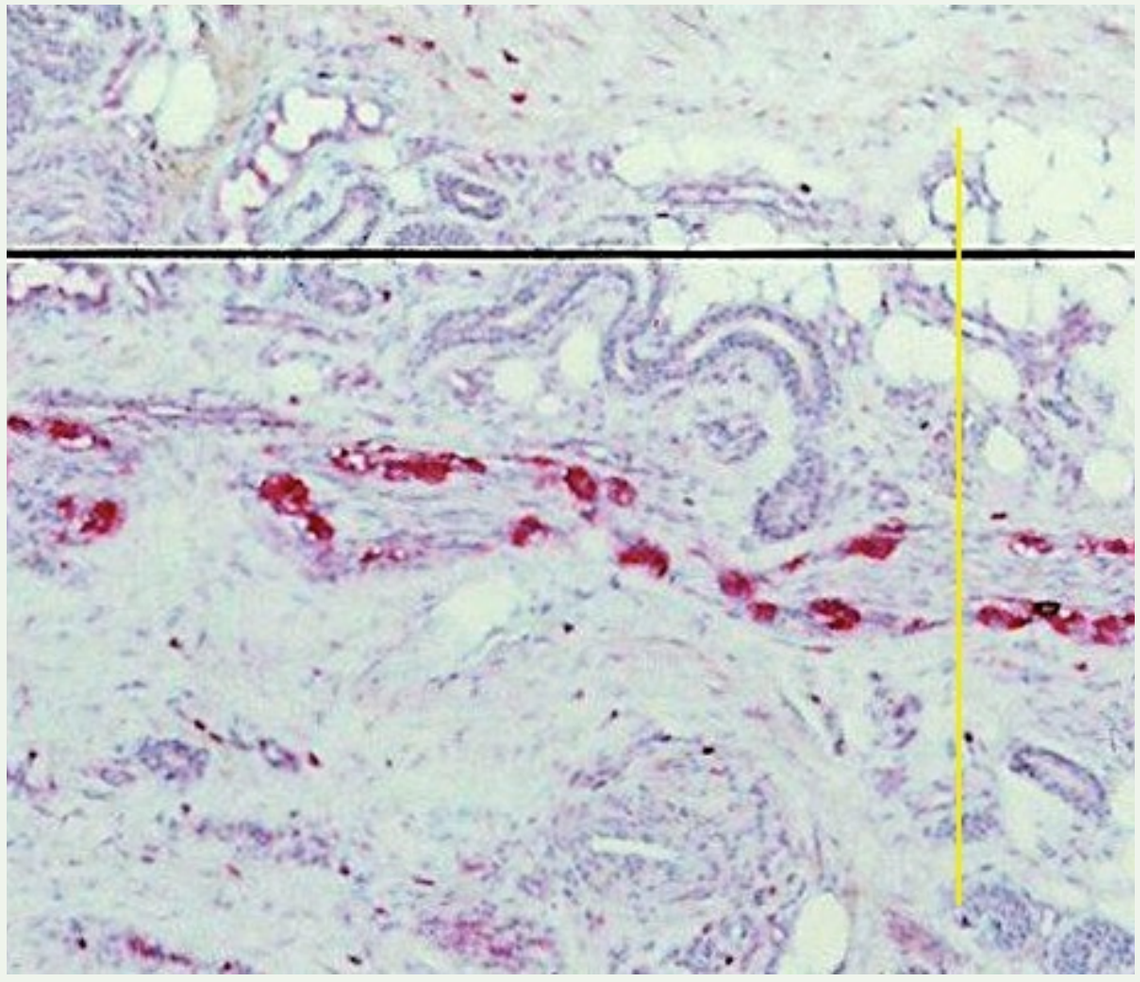
Figure 9.8 Typical Histological Appearance of Desmoplasia



Extensive dermal and subcutaneous desmoplastic melanoma.

(Figure 9.8). In around 50% cases the DM is pure, and in the remaining 50% there is a mixture of DM and another melanoma subtype, such as superficial spreading melanoma or lentigo maligna melanoma. Neurotropism is an umbrella term to include any neural involvement by a melanoma. Within this term are three distinct phenotypes; 'perineural invasion', 'intraneural invasion' and 'neural transforming'. The first two types of neurotropism may exist either with or without desmoplasia, whereas the 'neural transforming' type only occurs in desmoplastic melanoma. Perineural invasion refers to the invasion into the perineural space, allowing spread along it, sometimes apparently producing skip lesions (Figure 9.9). Intraneural invasion describes infiltration of the nerve fascicles themselves by tumour cells, tending to form contiguous lesions. Neural transformation describes the de-novo formation of nerve-like structures that are distinct from any pre-existing nerves.

FIGURE 9.9 HISTOLOGICAL APPEARANCE OF NEUROTROPISM



Axial sectioning of melanoma (red staining) infiltrating a nerve. Of note, the melanoma appears to 'skip' along the nerve, thus a section taken in the plane indicated by the yellow line may appear to show clear margins, despite tumour being present less than a millimetre away in both directions.

Section 2

Synoptic Reporting

Introduction

Synoptic reports represent a methodical and succinct manner in which to present a tumour's pertinent features. The report's format is typically tabular, systematically documenting the histopathological prognostic features that determine a patient's prognosis. The information contained in the report is of singular importance in guiding treatment choices and thus the clarity of communication is essential. The synoptic proforma generates a report that is not only easier to read, but also acts as an aide-mémoire to the reporting pathologist, ensuring more complete and consistent reports.

Elements of The Synoptic Report

Synoptic reports vary and most will include more than the core minimum required. However, the following summaries cover the elements most commonly relevant.

Patient Details

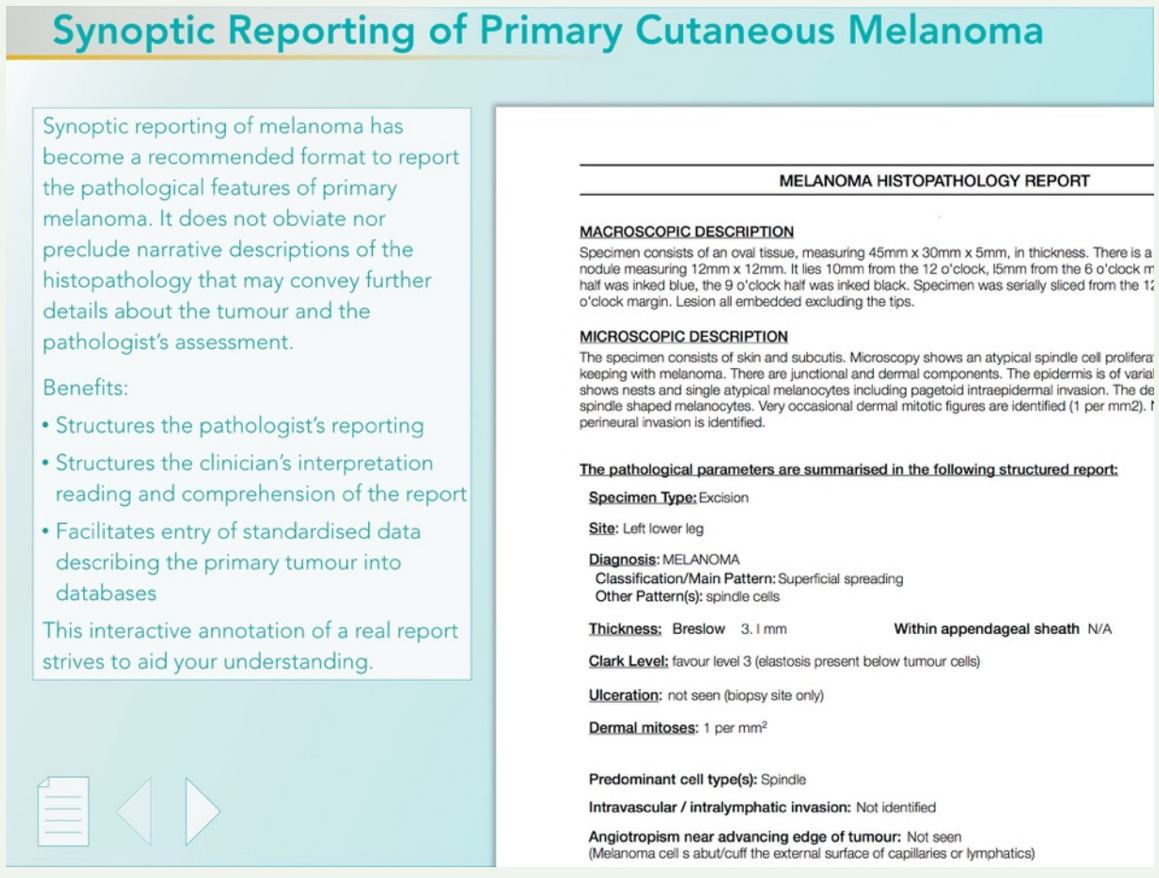
At least two patient identifiers and the requesting doctor's contact details are mandatory requirements for all histopathology requests. These requirements are necessary to minimise the risk of issuing an incorrect report to a patient.

Tumour Site

Knowledge of the anatomical origin is important in the interpretation of melanocytic lesions arising in acral, breast and genital skin. These sites are more likely to give rise to lesions exhibiting features which would elsewhere be interpret as evidence for a diagnosis of melanoma. Careful documentation of

the tumour site aids in directing further therapy and also helps in distinguishing locally recurrent disease versus an in-transit metastasis.

Interactive 9.1 A Guide to the Melanoma Synoptic Report



Correlation of the sections of a synoptic report with how they would appear in printed form. Tap the image above to launch the guide

Clinical History and Differential Diagnosis

The clinical impression of the lesion can aid the interpretation of histological findings. Lesions which are recurrent, arise rapidly, or have a strong dermoscopic impression of malignancy warrant a high degree of suspicion during their histological assessment. Large irregularly pigmented macular lesions are susceptible to under representation, which can result in a false negative diagnosis. Conversely, a history of partial biopsy or trauma and current or recent pregnancy can generate histological changes that mimic malignancy. A history of prior melanoma is an important clinical detail. Cutaneous melanomas with a totally regressed junctional component and primary dermal melanomas are both known to occur rarely. However, the presence of a melanoma in the dermis without tumour in the overlying epidermis most commonly represents a cutaneous metastasis. The documentation of known distant metastases at the

time of biopsy is important to correctly stage a patient with melanoma according to the AJCC staging guidelines.

Specimen Type

Incisional biopsies are typically performed for lesions which are either very large, have a low index of suspicion or occur in sites which are cosmetically sensitive (face) or surgically challenging (digits). However, incomplete or unrepresentative biopsies can impair the histopathological interpretation of not only the initial biopsy but also the assessment of the residual lesion within the re-excision specimen. Incomplete biopsies may not provide sufficient tissue to characterise enough features of malignancy to warrant a diagnosis of melanoma. Incomplete excision at the deep surgical plane also impairs assessment of tumour thickness. Reactive changes induced by surgical trauma can mimic malignancy in otherwise benign naevi. Finally, documentation of the nature of the biopsy also serves to provide an opportunity to identify mislabeled specimens.

Macroscopic Findings

A careful macroscopic examination directs tumour sampling towards critical areas such as foci suspicious for invasion, regression or narrowly excised margins. The documentation of the appearance of the lesion can also function as an aid for identification purposes.

Microscopic Description

Synoptic reports should be accompanied by a detailed description of the key diagnostic features used to render a diagnosis of melanoma. It affords the pathologist the opportunity to express the degree of certainty surrounding the diagnosis which could influence management decisions.

Breslow Thickness

Tumour thickness (more commonly termed Breslow thickness) provides the single most important prognostic feature of clinically localised primary cutaneous melanoma. The measurement is typically made to the nearest 0.01mm and it is calculated from near the top of the epidermal layer (granular layer), to the deepest invasive cell. The depth of melanoma invasion is staged according to the AJCC four point scale (T1: ≤1.0mm; T2: 1.01-2.0mm; T3: 2.01-4.0mm; and T4: ≥4.01mm).

The precise determination of tumour thickness can be complicated by the extension of tumour along nerves (neurotropism), lymphatics and capillaries (angiotropism) and through the walls of adnexal structures (periadnexal extension). For these instances, there is insufficient evidence in the medical literature to indicate which measurement best predicts a patient's prognosis. The best practice is to provide dual measurements, a Breslow thickness for direct tumour invasion in addition to an estimate of Breslow thickness corresponding to the deepest invasion along nerves, vessels or the involved adnexal structure (hair follicle or sweat glands).

Surgical Margins

The superficial excisional margin of melanoma (in situ and invasive) and the deep resection margin clearance of invasive melanoma are both provided to the nearest 0.1mm for narrow clearances (less than 2.0mm) and to the nearest 1.0mm for wider clearances (greater than 2.1mm). The precise determination of excision margins can be difficult to establish in cases where the tumour cells at the periphery merge with the surrounding sun-affected, but benign melanocytes.

Ulceration

Tumour ulceration is identified by the loss of the epidermis overlying an invasive melanoma. It is

measured in its extent in diameter or as a percentage of tumour width. It is a strong adverse prognostic finding that is used to define strata within the 'T' category of the AJCC staging protocol. Incisional biopsies can result in trauma induced changes that may be indistinguishable from genuine tumour ulceration.

Mitotic Rate

The number of mitotic figures counted in a square millimetre of invasive melanoma is a powerful adverse prognostic marker for clinically localised, thin (<1.0mm) melanomas. The number of mitoses in adjacent, non-overlapping, high powered fields equating to $1mm^2$ are counted in the area of tumour harbouring the highest frequency of mitotic figures.

Neurotropism

Neurotropism is defined by the invasion of melanoma cells through the perineural sheath of nerves located at or beyond the tumour's periphery. The excision margin clearance to the closest focus of neurotropism should be documented in the report. Neurotropic melanomas show higher rates of local recurrence as the result of unrecognised incomplete or narrow excision. Due to the higher rate of recurrence, melanomas exhibiting a significant degree of neurotropism are more likely to undergo greater wider local excision and/or adjuvant radiotherapy.

Lymphovascular Invasion

While not consistently identified as an independent prognostic marker, the presence of melanoma within the lumen of capillaries and lymphatics is considered to portend a poor patient prognosis.

Satellites

The presence of a discrete tumour deposit of at least 0.05mm in diameter and separated from the main tumour mass by at least 0.3mm, is interpreted

to represent an intra-lymphatic metastasis. Its presence is considered to be prognostically synonymous with in-transit metastases and local metastases. The presence of satellite lesions serves as the third criterion in the 'N' category of the AJCC system.

Clark Level

Tumour thickness can be measured as a function of the dermal compartment involved by an invasive melanoma. A melanoma's Clark level can be used to document the presence of in situ disease only (Clark level I), early infiltration of the papillary dermis (Clark level II), expansile infiltration of the papillary dermis (Clark level III), extension into reticular dermis (Clark level IV) or penetration into subcutaneous fat (Clark level V). Breslow thickness is a prognostically superior and more reproducible measurement, but the Clark level can provide complementary information when a Breslow thickness is not possible to quantify. Infrequently, a tumour with a thickness of less than 1.0mm and without ulceration or mitoses, but showing invasion of the reticular dermis or deeper, can be upstaged from a category T1a to T1b on the basis of the Clark level (i.e. Clark level III or IV).

Regression

Melanoma can elicit an intense T-cell mediated immune response that can, in some occasions, result in the complete eradication of the tumour at the primary site. The presence of a large number of lymphocytes surrounding and disrupting tumour nests (as tumour infiltrating lymphocytes) is identified in the synoptic report as evidence of early regression and is interpreted as a favourable prognostic factor. Intermediate and late regression are recognised by the partial or total replacement of tumour by newly formed collagen, which is usually also accompanied by new vessel formation and melanin ingesting macrophages (melanophages). There is contradictory evidence as to the prognostic

significance of intermediate and later regression. However, its presence at the resection margin is considered a significant risk for incompletely excised disease.

Desmoplastic Melanoma Component

Melanomas that exhibit a spindle cell morphology in association with a densely fibrotic tumour stroma are classified as 'desmoplastic' melanomas. Patients with this melanoma subtype show higher survival rates and a lower frequency of lymph nodes metastases. However, their greater propensity for recurrence typically mandates greater marginal clearances (>2cm) and adjuvant radiotherapy. Failure to correctly identify the extent of the tumour is due to a combination of their subtle histological features, propensity for neurotropism and highly infiltrative growth pattern.

Associated Melanocytic Lesion

While of no prognostic value, the documentation of a melanoma associated naevus is very helpful in correlating the histopathological findings with the clinical impression and lesional history. Knowledge of the presence of an associated naevus can also aid in the correct interpretation of a residual benign melanocytic component within the wide local excision specimen.

Melanoma Subtype

When corrected for tumour thickness, the traditional classification of melanoma into superficial spreading, nodular, lentigo maligna melanoma, acral-lentiginous and desmoplastic subtypes offers no definitive prognostic information. Nonetheless, there is increasing evidence identifying differences in the genetic abnormalities underlying these various subtypes and their characterisation serves to highlight the variability in the clinical presentation and histological appearance of melanoma.

Lymph Node Status

The presence of metastatic disease within the nodal basin of an otherwise clinically localised melanoma, is the strongest predictor of poor patient survival. In the synoptic report, the documentation of the lymph node status requires the total number of lymph nodes to be counted, the number of sentinel lymph nodes to be separately noted and the number of lymph nodes with metastatic disease to be tallied. The precise characteristics of the metastatic melanoma within the lymph node has to be carefully described; in sentinel lymph nodes, the size and location of the metastasis and the presence of extranodal extension can be used to determine the probability of finding additional metastases in non-sentinel lymph nodes.

Citations and Further Reading

1. Thompson JF, Scolyer RA. Cooperation between surgical oncologists and pathologists: a key element of multidisciplinary care for patients with cancer. Pathology. 2004;36(5):496–503. doi:10.1080/00313020412331283897.

2. Culpepper KS, Granter SR, McKee PH. My approach to atypical melanocytic lesions. J Clin Pathol. 2004;57(11):1121–31. doi:10.1136/jcp.2003.008516.

3. McCarthy SW, Scolyer RA. Pitfalls and important issues in the pathologic diagnosis of melanocytic tumors. Ochsner J. 2010;10(2):66–74.

4. Cassarino DS, Cabral ES, Kartha R V, Swetter SM. Primary dermal melanoma: distinct immunohistochemical findings and clinical outcome compared with nodular and metastatic melanoma. Arch Dermatol. 2008;144(1):49–56. doi:10.1001/archdermatol.2007.16.

5. American Joint Committee on Cancer. AJCC Cancer Staging Handbook.; 2010:52. doi:10.1007/978-0-387-88443-1.

6. Balch CM, Murad TM, Soong SJ, Ingalls AL, Halpern NB, Maddox WA. A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. Ann Surg. 1978;188(6):732–42.

7. Scolyer RA, Judge MJ, Evans A, et al. Data set for pathology reporting of cutaneous invasive melanoma: recommendations from the international collaboration on cancer reporting (ICCR). Am J Surg Pathol. 2013;37(12):1797–814. doi:10.1097/PAS.0b013e31829d7f35.

8. Baer SC, Schultz D, Synnestvedt M, Elder DE. Desmoplasia and neurotropism: Prognostic variables in patients with stage I melanoma. Cancer. 1985;74:2242–2247

10

Stage Classification and Survival

OMGO NIEWEG RICHARD A SCOLYER

Melanoma Institute Australia

Significantly updated to reflect new AJCC staging guidelines.

Key Points

- AJCC/UICC melanoma classification and TNM staging system form the worldwide standard for disease staging
- Enables estimation of prognosis for patients
- Selects patients for clinical trials
- Provides standardised nomenclature for communication between clinicians

Introduction

The stage of a person's cancer is defined as the classification of its extent. The stage reflects the severity of the disease. The word 'staging' has two meanings; to assign a stage to the disease and to perform diagnostic tests to enable this assignment. This chapter deals with the former and concerns cutaneous melanoma.

Melanoma is staged according to the TNM staging system that is based on: the primary tumour extent (T), the presence or absence of regional lymph node metastases and (sub-)cutaneous disease in the region between the primary tumour and the regional lymph node basin (N), and whether there are metastases (M) in more distant sites.

The Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer Staging (AJCC) determine the TNM classification. The system is derived from the patient, tumour and survival data of more than 46,000 patients diagnosed since 1998 with stage I-III disease from ten centres in the United States, Europe, and Australia. Given the rapidly evolving management of stage IV patients, the decision was made to refrain from analysing data from stage IV patients treated during the past 5 years. Instead, the previous 7th Edition AJCC stage IV database containing information on some 10,000 patients who presented with or developed stage IV disease was used for the current edition as the primary data source, supplemented by recent clinical trial data.

A uniformly accepted staging classification system is a vital requirement for clinicians and researchers.

The purposes of staging cancer are fivefold:

- Estimating the patient's prognosis
- Helping clinicians choose appropriate treatment
- Standardising information exchange about patients

- Facilitating comparison of the outcome of different diagnostic and therapeutic options
- Assisting in the design, conduct and anaylsis of clinical trials

The stage of a melanoma is largely determined by pathological evaluation, but physical examination, imaging and blood tests also play a role. The stage of the primary melanoma is solely based on histological information, while the lymph nodes are initially assigned a clinical stage based on physical examination or imaging findings, and subsequently often a pathological stage. The presence of distant metastases can be determined by pathological examination, imaging or physical examination and the M stage is refined by the lactate dehydrogenase (LDH) level in the serum.

The staging system has evolved in successive iterations as more sophisticated diagnostic techniques have become available and more is learned about the biology of the disease and prognostic factors. With the rapidly increasing knowledge of the molecular aspects of melanoma, there is likely to be a shift of staging parameters in a new direction in the future.

The current **UICC/AJCC** TNM classification discussed here was published in 2017 and is presented in Figure 10.6, Figure 10.7 and Figure 10.8.

Staging Primary Melanoma

The Breslow thickness forms the basis of the T-stage (Figure 10.6). It is determined histologically by measuring the deepest extent from the top of the granular layer or, in the presence of an ulcer, from its bottom. T1 lesions are thin melanomas and have the best prognosis, T2 and T3 lesions are of intermediate thickness and T4 are thick. Ulceration is defined as the full thickness absence of an intact epidermis with associated host reaction

(characterised by a fibrinous and acute inflammatory exudate) above the primary tumour based on histopathological examination and is an unfavourable parameter. The absence and presence of ulceration divides each stage into a or b. The prognosis for each ulcerated T stage (Tb) matches the subsequent non-ulcerated T stage (Ta).

Staging Regional Disease

Lymph nodes

The number of involved lymph nodes in the nodal basin to which the primary melanoma drains governs the N stage. The method of detecting the nodal metastases refines the N stage, since it serves as an indirect indicator of the extent of the involvement of individual lymph nodes (Figure 10.7). Therefore clinically occult metastases detected by sentinel node biopsy are in a lower subcategory than those identified by physical examination or imaging techniques. Matted metastatic lymph nodes are an unfavourable feature. There is no lower threshold for the size below which nodal involvement can be considered as meaningless, since it appears that even the smallest tumour deposit will eventually become clinically relevant if left undisturbed.

Microsatellite, satellite and in-transit disease

Microsatellite, satellite and in-transit metastases are also included in this N stage.

Microsatellites are defined as microscopically detected foci of metastatic tumour cells in the skin or subcutaneous tissue adjacent or deep to, but discontinuous from the primary tumour. However, they must not be separated only by fibrosis or inflammation that may signify regression of the intervening tumour.

Satellite metastases are clinically detected cutaneous or subcutaneous metastases occurring

within 2 cm of, but discontinuous from, the primary melanoma.

In-transit metastases are (sub-)cutaneous disease manifestations occurring >2 cm from the primary melanoma in the region between it and the regional lymph node basin. Occasionally, in–transit metastases may occur distal to the primary site.

Microsatellites, satellite and in-transit metastases have the same pathophysiology, originating from melanoma cells trapped in the intradermal or subcutaneous lymph vessels and also have a similar influence on prognosis.

Staging Systemic Disease

Distant metastases generally originate from tumour cells migrating through the blood stream, but also include lymph vessel metastases in the nodal basin and beyond. The M stage is categorised according to the site of distant metastases (Figure 10.8).

Dissemination to the skin, soft tissue (including muscle) and distant lymph nodes is associated with a better prognosis than involvement of the lungs. Lung metastases in turn are more favourable than lesions in visceral sites and brain metastases carry the worst prognosis.

The M staging is further refined by the LDH level in the blood; an increased serum LDH value generally portends a poor prognosis. However, although LDH exists in four different enzyme classes, their elevation in melanoma patients does not follow a specific pattern.

Stage Grouping and Prognosis

The stage grouping combines the T, N and M stages into categories with a similar prognosis (Figure 10.1). The survival percentages by stage are presented in Figure 10.3 and the survival curves for each stage I, II and III in Figure 10.2.

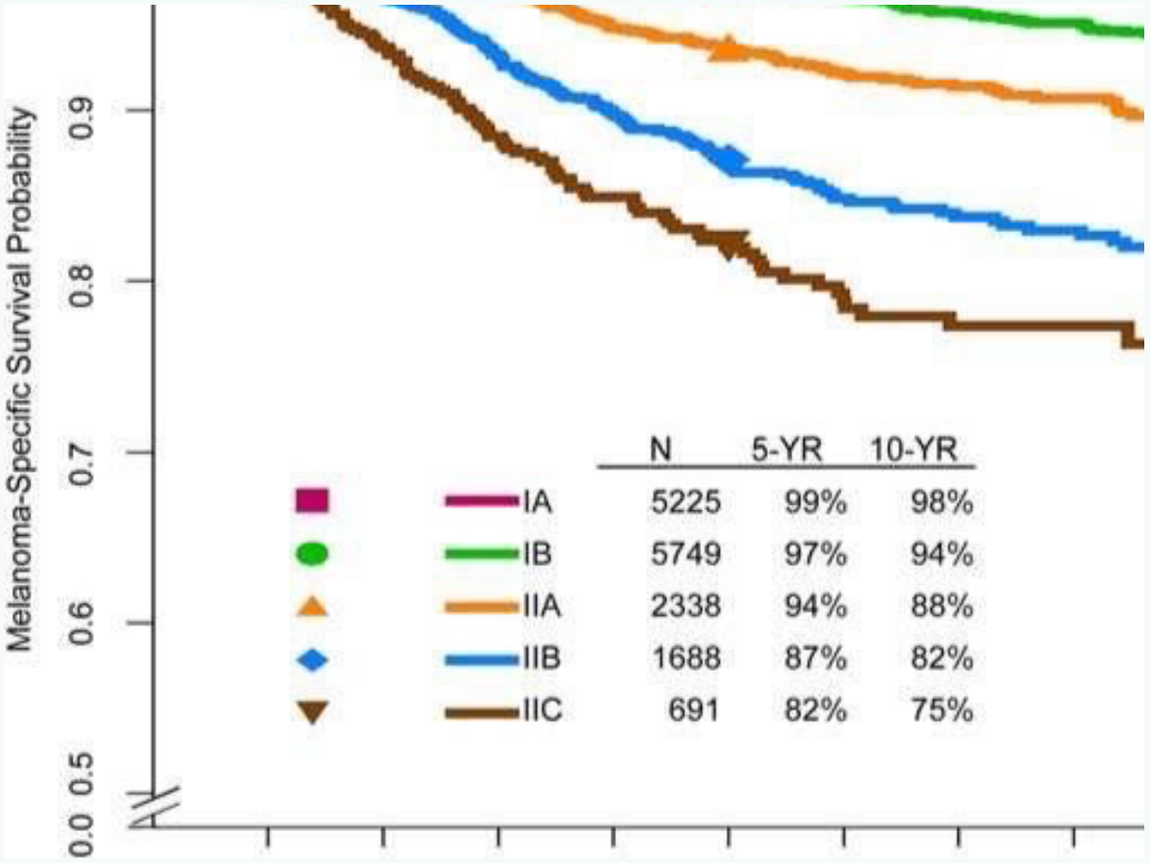
FIGURE 10.1 STAGE GROUPINGS

Clinical Staging* (cTNM)				Pathological Staging† (pTNM)			
T	**N**	**M**	**Stage**	**T**	**N**	**M**	**Stage**
Tis	N0	M0	0	Tis	N0	M0	0
T1a	N0	M0	IA	T1a T1b	N0 N0	M0 M0	IA
T1b T2a	N0 N0	M0 M0	IB	T2a	N0	M0	IB
T2b T3a	N0 N0	M0 M0	IIA	T2b T3a	N0 N0	M0 M0	IIA
T3b T4a	N0 N0	M0 M0	IIB	T3b T4a	N0 N0	M0 M0	IIB
T4b	N0	M0	IIC	T4b	N0	M0	IIC
				T0	N1b or N1c	M0	IIIB
				T0	N2b/c or N3b/c	M0	IIIC
				T1a/b-T2a	N1a or N2a	M0	IIIA
				T1a/b-T2a	N1b/c or N2b	M0	IIIB
				T2b/T3a	N1a-N2b	M0	IIIC
				T1a-T3a	N2c or N3a/b/c	M0	IIIC
				T3b/T4a	Any N ≥ 1	M0	IIIC
				T4b	N1a-N2c	M0	IIIC
				T4b	N3a/b/c	M0	IIID
Any T	Any N	M1	IV	Any T	Any N	M1	IV

**Includes microstaging of the primary melanoma and clinical/radiological evaluation for metastases.*

†Includes microstaging of the primary melanoma and pathological evaluation of the regional lymph nodes (except Stage 0 or IA patients).

Figure 10.2 Survival Curves



Stage I & II subgroups Kaplan-Meier curves for melanoma-specific survival

Used with permission of the American College of Surgeons, Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Figure 10.3 Survival Percentage by Stage

Stage	Five-Year (%)	Ten-Year (%)
IA	99	98
IB	97	94
IIA	94	88
IIB	87	82
IIC	82	75
IIIA	93	88
IIIB	83	77
IIIC	69	60
IIID	32	24
IV	Not provided	

Stage IB and above are based on patients who were pathologically staged for nodal status.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Changes in the 8th Edition

The previous (7th) edition of the staging classification was adopted in 2010. The 8th edition has been used since 1 January 2017 and is based

on a new contemporary international database that will enable ongoing development of prognostic tools that will be useful for clinical decision-making. Any system needs to balance nuance with practicality. As more precise discrimination of various stages has become possible over the years, so the system has increased in complexity. This is again true for the new edition. There are numerous changes, of which the most notable ones are mentioned here.

T-changes

Breslow thickness has become even more important. A melanoma with a Breslow thickness <0.8 mm without ulceration is now classified as T1a, as it was recently found that the prognosis is considerably worse for lesions 0.8-1.0 mm thick. In the 8th edition, tumour thickness measurements are recorded with rounding to the nearest 0.1 mm, not to the nearest 0.01 mm as before. This change was prompted by the inherent lack of precision in measuring melanomas, especially thicker ones.[9] The tumour mitotic rate was removed as a staging criterion.

N-changes

The N categorisation of regional dissemination has become more complex in the new edition. The terms "microscopic" and "macroscopic" lymph node involvement descriptors are redefined as "clinically occult" for sentinel biopsy detected disease and "clinically detected" disease for metastasis detected by physical examination or imaging. A positive sentinel node is assigned cN1a, which becomes pN1a if completion node dissection reveals no further disease and pN1a(sn) if no completion node dissection is performed.

Microsatellites, satellite and in-transit metastases are now better defined.

M-changes

Non-visceral distant soft tissue metastases are now categorised as M1a. Brain metastases are now a separate stage M1d (highest), reflecting their dismal prognosis. A suffix indicating a normal (0) or increased (1) LDH level is now assigned to each M1 subcategory eg M1a(1). For a comprehensive list of the changes the reader is referred to a table in the Manual.[1]

Controversies, Pitfalls and Recent Developments

A number of controversial issues raised in the previous edition of this chapter have been addressed with the updated AJCC staging system. The proximal extent of in-transit metastases in relation to the regional nodal basin was unclear and this has now been specified. In-transit metastases are located in-between the primary tumour and the nodal basin. Although lymph vessel metastases in the skin overlying the nodal basin or in the subcutaneous tissue underneath are thus classified as M1a, we recommend that such lesions be managed as in-transit disease.

A satellite metastasis is less than 2 cm away from the primary tumour and an in-transit metastasis is more than 2 cm away. Therefore, it is unclear how a (sub)cutaneous metastasis exactly 2 cm from the primary tumour should be called. In our view, it should be named a satellite, although the stage and management would be the same either way.

Surgeons engaging in regional limb perfusion and infusion often stick to the old MD Anderson staging classification adapted for stage II (Figure 10.4).

The survival rates of the UICC/AJCC- staging classification are based on the initial presentation of the patient. So, the survival rate for stage IV only applies to patients who present initially with stage

FIGURE 10.4 MD ANDERSON STAGING

Stage	Classification
I	Intact primary melanoma
IIA	Local recurrence in contact with scar or skin graft
IIB	Satellite lesion within 3 cm of the primary site
IIIA	Satellite (more than 3cm from primary site) or in transit metastases excluding regional nodes
IIIB	Positive regional lymph nodes
IIIAB	Satellite or in transit metastases with positive regional nodes
IV	Distant metastases

Modified MD Anderson staging classification that is often used for regional perfusion and infusion.

IV disease and not for a patient with stage II disease who develops a pulmonary metastasis a year later. This is why a local recurrence is the only melanoma manifestation that is not covered by the UICC/AJCC staging classification. Also, there is no consensus on what a local recurrence is, as definitions vary from "in contact with the scar or skin graft" to "within 5 cm of the scar". A local recurrence may represent regrowth after an incomplete excision of the primary tumour, but it may also result from a metastasis in a nearby lymph vessel, i.e. a satellite or even an in-transit metastasis. The former is associated with a better prognosis. In these instances pathology re-examination of the primary tumour re-excision specimen is recommended for clarification.

A tumour-negative sentinel node is assigned pN0, while pN1a is used for a positive sentinel node if completion node dissection either revealed no other nodal involvement or was not done.

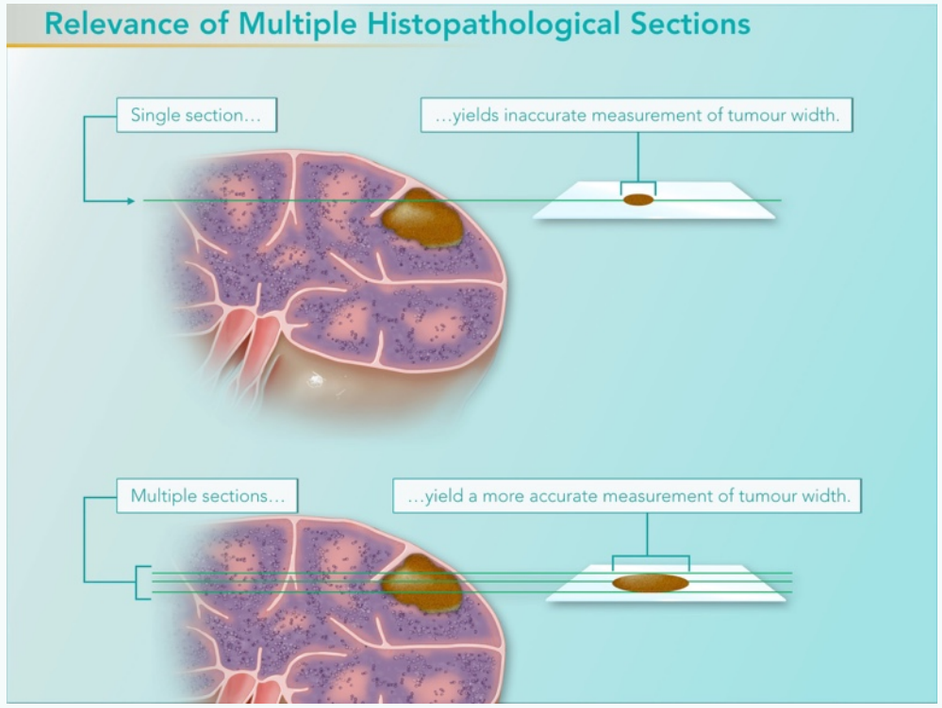
For breast cancer staging, the UICC/AJCC staging system includes a pN1mi category for microscopic metastases diameter of 0.2-2.0 mm. In contrast, the TNM system in melanoma does not contain the connotation 'mi'. One problem with such designation is that the metastasis is often found to

be substantially larger when adjacent slides are obtained (Figure 10.5). Therefore, the TNM system for melanoma qualifies a node as N1, even if just a single malignant cell is found.

Some pathologists and surgeons incorrectly classify a sentinel lymph node with a metastasis exceeding 2 mm as a macrometastasis. This connotation is again correct in breast cancer, but does not apply to melanoma. Although the tumour burden, the location of the metastasis and its growth pattern carry prognostic significance, these parameters are not used in the current classification.

The N stage is not directly based on tumour load. For instance, a sentinel node biopsy may reveal a metastasis (N1a) that is 5 mm in diameter, while an ultrasound may show a lymph node metastasis (N1b) that is 3 mm in diameter. So, an N1a metastasis may actually be larger than an N1b metastasis.

FIGURE 10.5 RELEVANCE OF MULTIPLE HISTOPATHOLOGICAL SECTIONS



The pathologist samples the lymph node looking for metastasis. If the pathology slide samples the metastasis at its edge, it will look smaller than it actually is. Multiple slides will generally give a better impression.

The ratio of the numbers of positive to examined lymph nodes (lymph node ratio) has recently been suggested as a useful and easy-to-calculate prognostic factor independent from the current TNM system. However, a subsequent study did not

confirm the ratio's prognostic value and it is not part of the current staging classification.

Some five per cent of patients present with a metastasis from an unknown primary site. Such a lesion is categorised as stage III when it concerns a lymph node, skin or subcutaneous metastasis and as stage IV when elsewhere.

Serum LDH concentration is an important parameter in stage IV disease, however, results may vary between labs.

Each new version of the staging classification differs from the previous version and these variances need to be taken into account when comparing study results from different eras.

The implementation of the 8th AJCC/UICC melanoma classification in the USA was deferred until January 1, 2018, to give physicians, software vendors, and all other interested parties time to adjust.

Cancers are staged based on the average prognosis of large categories of patients. One should be aware that each stage is the average of a substantial range and an individual patient may be at either end of the range. This is particularly true in a capricious disease like melanoma.

Looking ahead, the AJCC/UICC panel established a framework for developing robust prognostic models and clinical tools for stage IV disease that will generate staging information appropriate for contemporary clinical management with targeted therapy and immunotherapy.

FIGURE 10.6 T STAGING CATEGORIES FOR CUTANEOUS MELANOMA

T category		Thickness (mm)	Ulceration Status
TX:	cannot be assessed eg diagnosis by curettage	Not Applicable	Not Applicable
T0:	no evidence of primary tumour eg unknown primary or completely regressed	Not Applicable	Not Applicable
Tis:	melanoma in situ	Not Applicable	Not Applicable
T1		≤ 1.0	Unknown or unspecified
	T1a	< 0.8	Without ulceration
	T1b	<0.80	With ulceration
		0.8 -1.0	With or without ulceration
T2			Unknown or unspecified
	T2a	>1.0 - 2.0	Without ulceration
	T2b		With ulceration
T3			Unknown or unspecified
	T3a	>2.0 - 4.0	Without ulceration
	T3b		With ulceration
T4			Unknown or unspecified
	T4a	> 4.0	Without ulceration
	T4b		With ulceration

Used with permission of the American College of Surgeons, Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Figure 10.7 N Staging Categories for Cutaneous Melanoma

N Category		Number of tumour involved regional lymph nodes	Presence of in-transit, satellite and/or microsatellite metastases
NX		Regional nodes not assessed (eg SLN biopsy not performed or regional nodes previously removed for another reason) **Exception**: pathological N category is not required for T1 melanomas - use cN	No
N0		None	No
N1		One tumour-involved node **or** in-transit, satellite and/or microsatellite metastases with no tumour-involved nodes	
	N1a	One clinically occult	No
	N1b	One clinically detected	No
	N1c	None	Yes
N2		Two or three tumour-involved nodes **or** in-transit, satellite, and/or microsatellite metastases with one tumour-involved node	
	N2a	Two or three clinically occult	No
	N2b	Two or three (at least one of which clinically detected)	No
	N2c	One (clinically occult or detected)	No
N3		Four or more tumour-involved nodes **or** in-transit, satellite, and/or microsatellite metastases with two or more tumour-involved nodes **or** any number of matted nodes with or without in-transit, satellite and/or microsatellite metastases	
	N3a	Four or more clinically occult	No
	N3b	Four or more (at least one of which clinically detected) **or** any number of matted nodes	No
	N3c	Two or more (clinically occult or detected) and/or any number of matted nodes	Yes

Definitions: Clinically occult = detected by sentinel lymph node biopsy; Clinically detected = detected by imaging or physical examination

FIGURE 10.8 M STAGING CATEGORIES FOR CUTANEOUS MELANOMA

M Category		Anatomic Site	LDH level
M0		No evidence of distant metastasis	Not applicable
M1		Evidence of distant metastasis	See below
M1a		Distant metastasis to skin, soft tissue (including muscle and/or non-regional lymph node)	Not recorded or unspecified
	M1a(0)		Not elevated
	M1a(1)		Elevated
M1b		Distant metastasis to lung (+/- M1a sites of disease)	Not recorded or unspecified
	M1b(0)		Not elevated
	M1b(1)		Elevated
M1c		Distant metastasis to non-CNS visceral sites (+/- M1a or b sites of disease)	Not recorded or unspecified
	M1c(0)		Not elevated
	M1c(1)		Elevated
M1d		Distant metastasis to CNS (+/- M1a, b or c sites of disease)	Not recorded or unspecified
	M1d(0)		Not elevated
	M1d(1)		Elevated

Definitions: LDH = Lactate dehydrogenase serum concentration; CNS = central nervous system

Suffixes for M category: No suffix = LDH unrecorded or unspecified; (0) = LDH not elevated; (1) = LDH elevated

Citations and Further Reading

1. Gershenwald JE, Scolyer RA, Hess KR et al. AJCC Cancer Staging Manual. In Amin MB, Edge SB, Greene FL et al. (eds): 8th Edition. New York: Springer International Publishing 2017; 563-585.

2. Morton DL, Thompson JF, Cochran AJ et al. Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma. New England Journal of Medicine 2014; 370: 599-609.

3. Balch CM. Microscopic Satellites Around a Primary Melanoma: Another Piece of the Puzzle in Melanoma Staging. Annals of Surgical Oncology 2009; 16: 1092-1094.

4. Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: A Cancer Journal for Clinicians 2017; 67: 472-492.

5. Balch CM, Gershenwald JE, Soong S-j et al. Final Version of 2009 AJCC Melanoma Staging and Classification. Journal of Clinical Oncology 2009; 27: 6199-6206.

6. Breslow A. Thickness, Cross-Sectional Areas and Depth of Invasion in the Prognosis of Cutaneous Melanoma. Annals of Surgery 1970; 172: 902-908.

7. Gimotty PA, Elder DE, Fraker DL et al. Identification of High-Risk Patients Among Those Diagnosed With Thin Cutaneous Melanomas. Journal of Clinical Oncology 2007; 25: 1129-1134.

8. Green AC, Baade P, Coory M et al. Population-Based 20-Year Survival Among People Diagnosed With Thin Melanomas in Queensland, Australia. Journal of Clinical Oncology 2012; 30: 1462-1467.

11

Imaging

LOUISE EMMETT BAO HO OMGO E. NIEWEG
ROGER F. UREN ALEXANDER H.R. VAREY

Key Points

- Limited role for imaging in staging primary melanoma.
- PET-CT provides highly sensitive whole body surveillance with relatively low radiation exposure.
- MRI most sensitive for brain and liver metastases.
- USS most sensitive for in-transit and nodal disease and has no radiation.
- Early detection of low volume metastases affords better prognosis with new systemic therapies.

Introduction

The role of imaging in melanoma has several purposes, including:

- Staging at time of initial diagnosis
- Surveillance for regional or systemic metastases
- Monitoring of response to therapy
- Guiding biopsy of suspicious lesions

The goal of staging is to determine the presence and extent of any melanoma metastases at the time of primary tumour diagnosis. The optimal choice of imaging modality depends both upon the purpose and the balance of technical merits against the accessibility and the risks to the patient.

The modalities of imaging applicable for melanoma staging include:

- Ultrasound (lymph nodes, subcutaneous deposits and liver)
- PET-CT (systemic metastases)
- Diagnostic CT (systemic metastases, including guided core biopsies)
- MRI (brain and liver metastases)
- Lymphoscintigraphy (sentinel lymph node mapping)

Selection of imaging modality

For the purposes of selecting an appropriate modality, patients can be categorised according to whether they have clinical evidence of metastatic disease or not.

Primary melanoma

This section discusses imaging for patients with no evidence of metastatic disease.

Patients with low risk melanoma do not warrant radiological staging or surveillance by any modality. This is due to an exceptionally low yield of significant results, a high false positive rate, patient irradiation, and the costs to both the patient and health system.

Patients with intermediate risk melanoma have a well-documented role for sentinel lymph node mapping ± sentinel node biopsy or regional nodal surveillance with ultrasound. However, there is no role for radiological staging for systemic disease in this population, including those patients with a positive sentinel node biopsy, since the yield remains very low (≤1.8%). Despite this, there may be a role for surveillance imaging in patients with a positive sentinel node, as per other stage III patients. The optimal modality for this is discussed later in the chapter.

For patients with high-risk melanoma there is relatively little data describing the role of staging or surveillance imaging. Hence, some national guidelines advocate radiological staging and others do not. However, this group has around a 50% chance of developing metastatic disease. This is a similar risk to patients with stage IIIB/C disease, in whom roles for staging and surveillance do exist.

There is a well documented role for performing lymphoscintigraphy and sentinel node biopsy in these patients.

Metastatic melanoma

The management of patients with metastatic melanoma (AJCC stages III and IV), has changed with the advent of effective immuno and targeted therapies over the last 5 years. Accordingly, the benefit of early detection of metastatic disease has increased. Therefore, roles for surveillance and staging imaging of patients with oligo-metastatic or resected metastatic disease exist. Furthermore, frequent monitoring of those receiving treatment is indicated in order to detect disease progression and modify treatment accordingly.

Patients with microscopic sentinel node metastases alone (stage IIIA) arguably do not warrant staging imaging, due to very low metastasis detection and high false positive rates. However, it may still be

appropriate to perform surveillance imaging in these patients.

Imaging modalities

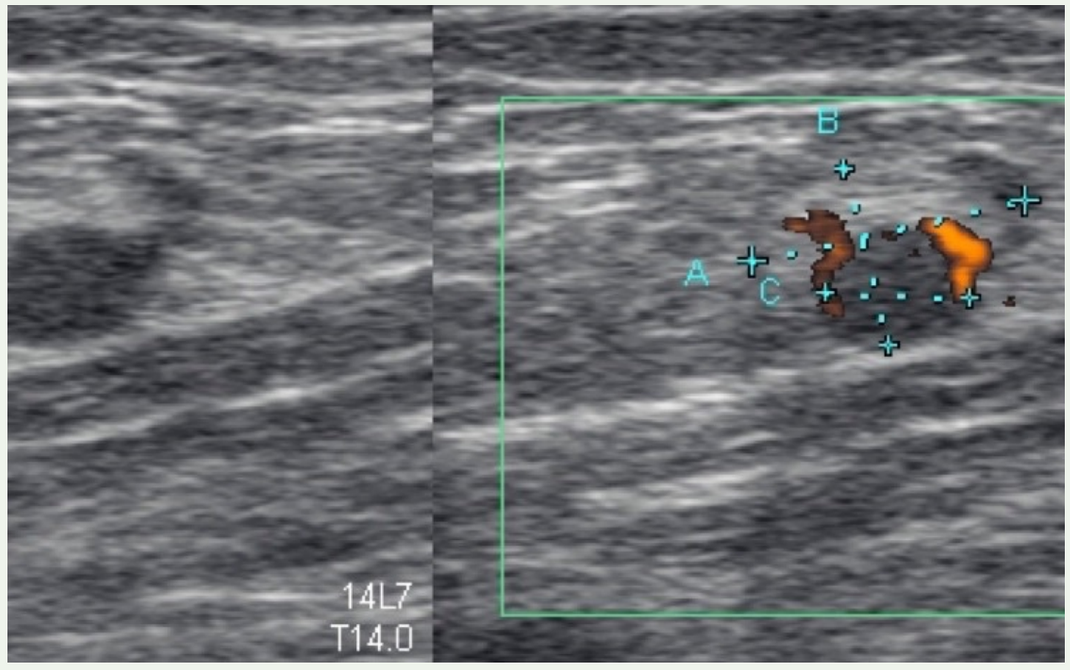
Ultrasound Scanning (USS)

Current generation ultrasound machines using high-resolution transducers can produce detailed images of the internal structure of lymph nodes at depths up to 4-5cms from the skin surface. Most of the lymph nodes to which melanoma may metastasise are within this range and USS now has an important role in detecting early metastatic disease within lymph nodes and small in-transit metastases in the subcutaneous tissues.

Sentinel node evaluation

After pre-operative lymphoscintigraphy to mark the precise location and number of SLNs, USS can be used to perform a targeted examination of the SLNs. If an early metastasis is detected, immediate

Figure 11.1 Ultrasound images of lymph nodes



Ultrasound imaging demonstrating a lymph node containing a metastatic melanoma tumour deposit, which was confirmed using a guided fine needle aspiration biopsy.

fine needle aspiration biopsy (FNAB) can be performed under USS guidance so that the exact part of the SLN showing the abnormality can be sampled. If melanoma metastasis is detected the patient can then be scheduled for a comprehensive therapeutic dissection of the node field rather than selective biopsy of the sentinel nodes identified by lymphatic mapping (lymphoscintigraphy).

At the time of surgery for primary melanoma, the size of any metastatic deposits is typically microscopic, far below the size detectable by USS. Consequently, USS misses around 77% of metastases found on SLN biopsy (ie has a sensitivity of 23% in our hands).

If SLN biopsy is not performed, USS can be used in clinical follow up to detect metastatic disease before lesions become palpable. Again, immediate FNAB under USS guidance is performed to confirm the diagnosis.

In-transit metastases

USS is very accurate and sensitive in detecting the presence and extent of in-transit melanoma metastasis. Detected lesions can be marked on the skin and their depth reported, to aid surgical removal.

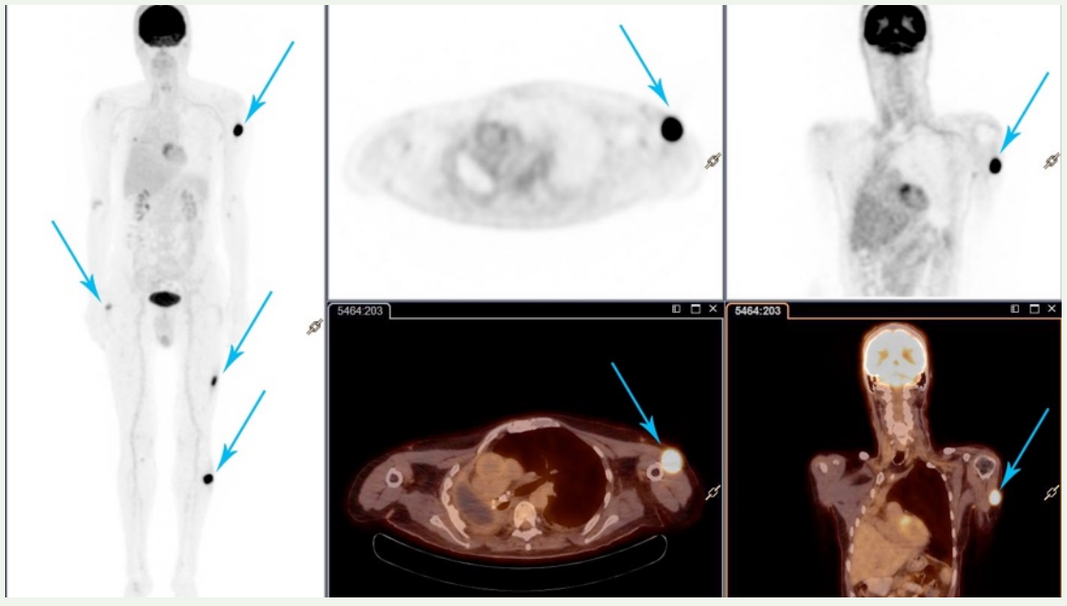
Positron Emission Tomography (PET)

PET imaging using ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is rapidly becoming the imaging modality of choice for the evaluation of patients with advanced melanoma. PET-CT using ^{18}F-FDG is sensitive for the detection of metastatic melanoma due to the high metabolic activity of melanoma cells, but has a number of limitations.

As ^{18}F-FDG competes with glucose for cell uptake, preparation of the patient by fasting prior to the procedure to reduce systemic insulin levels, and appropriate management of diabetes, is important to ensure maximal uptake within melanoma cells.

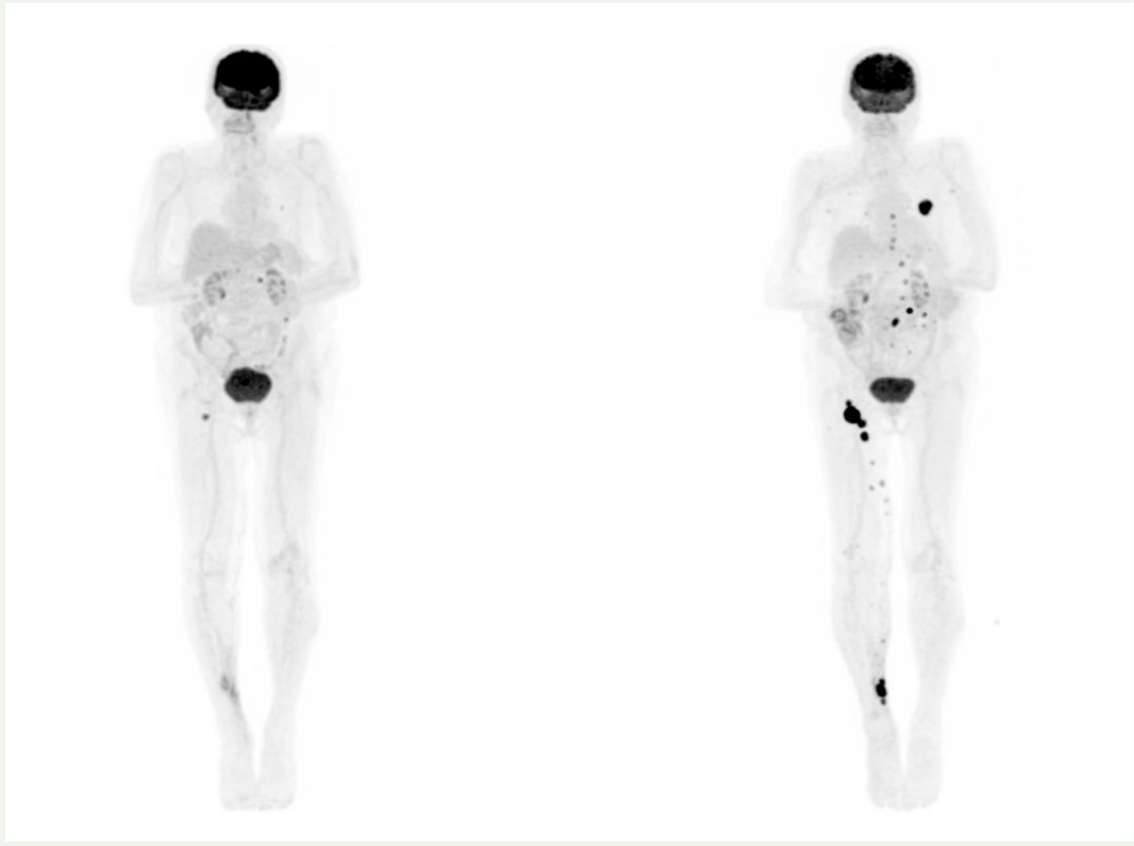
^{18}F-FDG also concentrates physiologically at sites of high glucose utilisation such as the heart and brain, and also in diabetic patients' bowels. Practically, this means that FDG-PET imaging of the brain has

Figure 11.2 PET-CT Detection of Asymptomatic Subcutaneous Metastases



Whole body imaging and high sensitivity of PET-CT (left & upper central/right panels) facilitated early detection of four melanoma metastases that would have been missed by diagnostic CT of chest, abdomen and pelvis. PET only images shown in lower central/right panels.

Figure 11.3 PET-CT Pre-Op for Right Groin Lymphadenectomy



This patient presented with a primary melanoma on the right leg, satellite lesions and a palpable right inguinal metastasis. PET-CT (left) demonstrated two small paraaortic FDG avid nodes and a possible left lung metastasis. Therapeutic nodal dissection was delayed pending a repeat scan at 3 months (right), confirming progressing widespread metastatic disease.

limited clinical utility because of the high background concentration in normally functioning brain cells, meaning small deposits of metastatic melanoma may be easily missed.

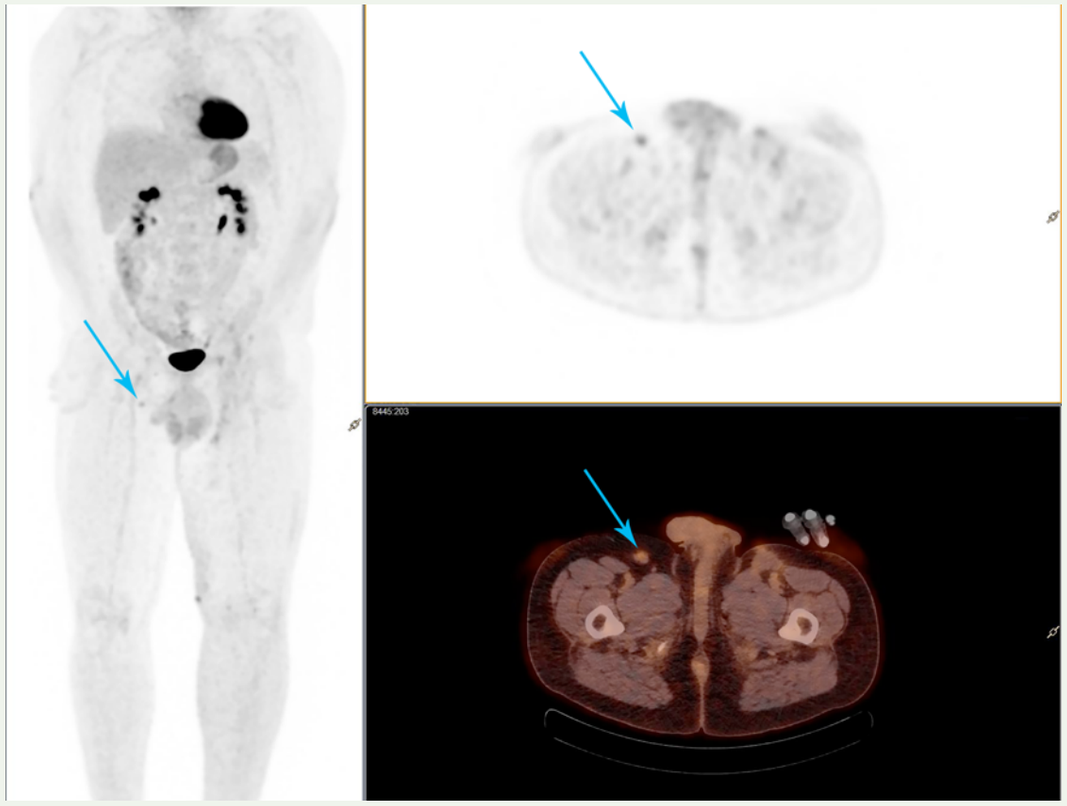
The intensity of ^{18}F-FDG concentration in cancer cells can be measured using a standardised uptake value (SUV). An increased SUV value raises the likelihood that a lesion will be malignant.

There are a number of limitations to PET imaging that should be taken into account in evaluating scan results. The volume of disease present limits the sensitivity of PET, which drops to less than 50% with tumour deposits of <4mm diameter.

As FDG-PET is a measure of cellular glucose uptake, a persistent low false positive rate due to scan findings related to inflammatory changes, sarcoidosis, and other unrelated tumours, is inevitable (Figure 11.4).

PET imaging is now always undertaken in conjunction with a low dose CT that is simultaneously acquired on the same camera, facilitating both anatomical information and localisation. The diagnostic accuracy of combined

FIGURE 11.4 PET-CT AND CT FALSE POSITIVITY



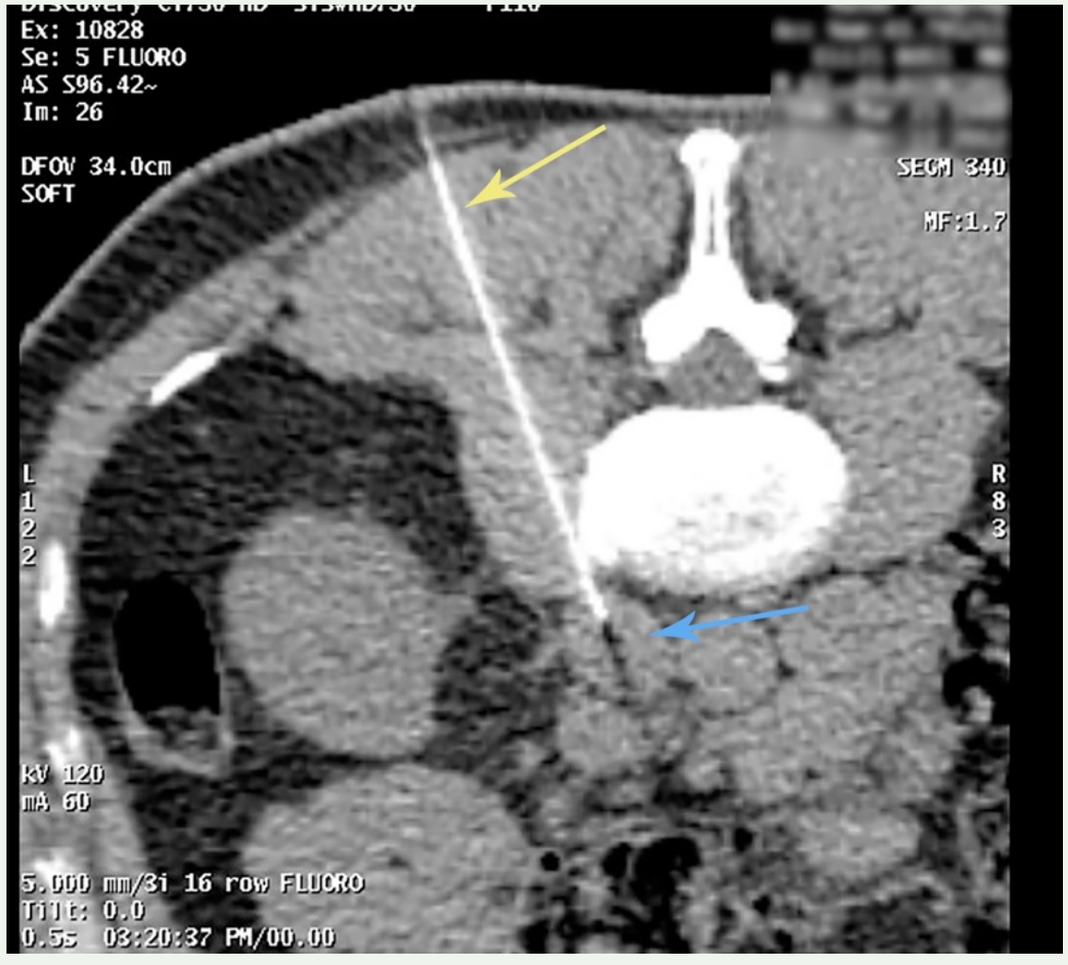
PET-CT FDG avid, enlarged lymph node in the right inguinal region, confirmed to be reactive on USS imaging.

PET-CT is significantly higher with fewer false positive and false negatives than PET alone. The CT component of a PET-CT scan can be either a multi-slice, contrast enhanced, or a low radiation dose CT. The CT and PET components have synergistic diagnostic value, hence the sensitivity and specificity for PET/Diagnostic contrast enhanced CT is very high. The CT is important for the detection of small lung nodules, often not present on PET imaging, and the PET imaging has a much higher sensitivity than CT alone for the detection of bone and subcutaneous lesions in metastatic melanoma (Figure 11.2).

Computed Tomography (CT)

Diagnostic CT has been widely used for routine surveillance of patients at high risk of melanoma recurrence, due to its availability and relatively low cost. However, the technique suffers the same limitations as FDG–PET in early stage melanoma, requiring abnormal anatomy or altered tissue density for detection. Small lesions or pathological changes in normal-sized tissues can be missed by CT imaging. A meta-analysis of diagnostic imaging

FIGURE 11.5 CT GUIDED BIOPSY



CT guidance of core biopsy needle (yellow arrow) into suspicious paraaortic lymph node (blue arrow) in a prone positioned patient.

modalities in later stage melanoma found a significantly higher diagnostic accuracy for PET-CT in disease surveillance (86% sensitivity, 91% specificity), than for contrast enhanced CT alone (sensitivity 63%, specificity 71%). In fact, no study has found the diagnostic accuracy of contrast enhanced CT to be higher than PET, or PET-CT for metastatic melanoma. Furthermore, PET-CT has a much lower radiation dose and is at least as accurate for whole body surveillance. The value of diagnostic CT alone in the assessment of melanoma is principally in its sensitivity for small pulmonary nodules; frequently missed on PET imaging alone, and not visible on MRI. CT also has a role in the characterisation of brain and liver lesions when MRI is unavailable.

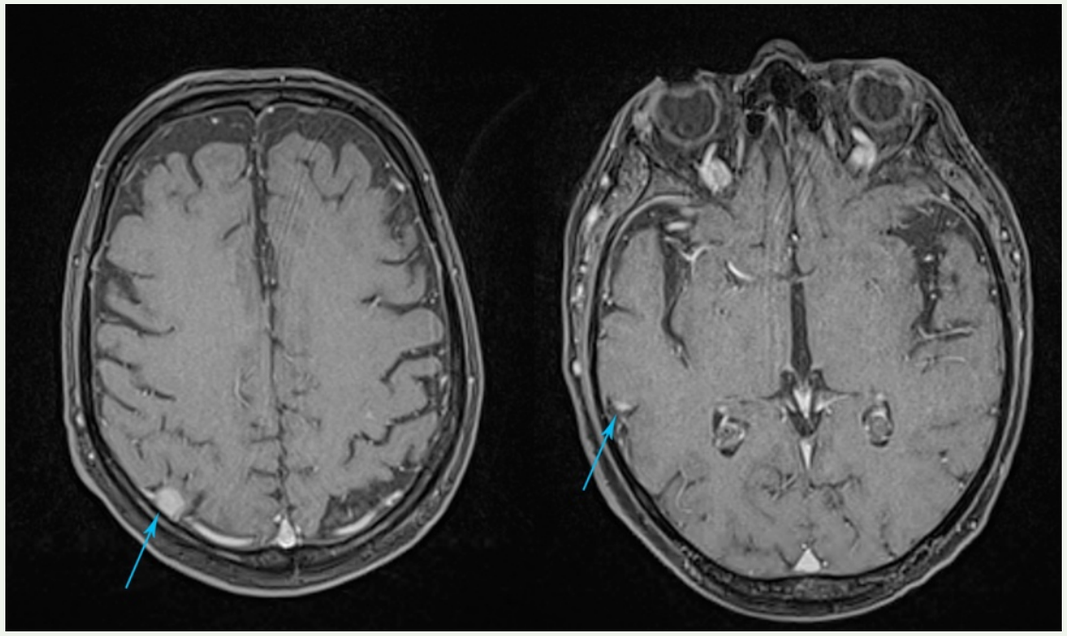
CT is the best modality for image-guided biopsies of suspicious lesions within the pelvis or abdomen. Since CT imaging is both fast and high resolution, it facilitates accurate procurement of relevant samples (Figure 11.5).

Magnetic Resonance Imaging (MRI)

Metastatic melanoma identified with MRI often displays typical appearances consisting of high intensity on T1-weighted images and low signal intensity on T2-weighted images. The characteristic signal intensities have been attributed to the paramagnetic effects of free radicals in melanin as well as products of haemorrhage. The greater the concentration of melanin, the greater the hyper-intensity on T1-weighted images.

MRI has been shown to be more sensitive than CT in the detection of metastatic melanoma that involves the brain, liver and bones (Figure 11.6). Numerous studies have demonstrated that contrast-enhanced MRI detects 2-3 times as many lesions as contrast-enhanced CT, especially lesions less than 5mm in diameter. In addition, approximately 20% of

FIGURE 11.6 MRI BRAIN MORE SENSITIVE THAN PET-CT FOR SMALL VOLUME METASTASES



MRI brain scans demonstrating 2 small brain metastases (blue arrows), not seen on PET-CT.

patients with solitary metastatic lesions on CT show multiple lesions on MRI. The sensitivity of detecting leptomeningeal disease is also higher with MRI.

The sensitivity of liver melanoma metastases detection with PET or MRI in a prospective study was 47% and 100% respectively. Lesion detectability by PET was related to lesion size. MRI is also superior to CT in detecting small and characterising small lesions, which may be indeterminate on CT.

MRI is highly sensitive to the presence of skeletal metastases within the bone marrow. In a large meta-analysis by Yang et al, MRI and PET were found to be comparable and both significantly more accurate than CT and bone scintigraphy for the diagnosis of bone metastases.

Plain Chest Radiography (CXR)

Routine surveillance of patients at higher risk of melanoma recurrence with plain CXR has been recommended in treatment guidelines until recently. However, a review of 1235 patients with > 1mm Breslow thickness followed for a median of 74 months found the sensitivity of surveillance CXR was 7.7% with a specificity of 96.5%. Of those who were diagnosed with metastatic disease on CXR (0.9%), only 0.2% had isolated pulmonary metastases

amenable to resection. Hence, CXR is no longer recommended for standard surveillance in melanoma patients.

Radiation Doses

Cumulative radiation doses need to be taken into account in patients undergoing frequent diagnostic procedures for cancer staging and surveillance. The diagnostic value of a procedure should be weighed against the patient's long-term prognosis, and risk of a second iatrogenically-induced primary malignancy. Patients undergoing an annual PET/ diagnostic contrast CT each year for 10 years have an estimated lifetime risk of a radiation-induced new primary cancer of 1.6% (male) and 1.9% (female).

^{18}F-FDG PET imaging now always incorporates a CT for the purposes of attenuation correction and anatomical detailing. This may be either a low dose CT, or a diagnostic contrast enhanced CT, dependent on clinician choice and the facility procedure. The radiation delivered from low dose CT is weight dependent, but averages 4mSv per patient in our institution (range 2.9-9.6mSv). The ^{18}F-FDG PET scan delivers 5-7mSv per patient, giving an average total radiation dose of 10mSv per patient for a PET/ low dose CT scan. A diagnostic CT scan adds an extra 14-19mSv to the procedure. Putting this in perspective, the average background radiation received per person worldwide is 3.0mSv/ year.

Ultrasound imaging, which has been shown to have a high diagnostic accuracy in surveillance for local melanoma recurrence, confers no extra radiation risk.

Citations and Further Reading

1. Belhocine, T.Z., et al., Role of nuclear medicine in the management of cutaneous malignant melanoma. J Nucl Med, 2006. 47(6): p. 957-67.

2. Ho Shon, I.A., et al., Imaging in cutaneous melanoma. Nucl Med Commun, 2008. 29(10): p. 847-76.

3. Sanki, A., et al., Targeted high-resolution ultrasound is not an effective substitute for sentinel lymph node biopsy in patients with primary cutaneous melanoma. J Clin Oncol, 2009. 27(33): p. 5614-9.

4. Mijnhout, G.S., et al., How morphometric analysis of metastatic load predicts the (un)usefulness of PET scanning: the case of lymph node staging in melanoma. J Clin Pathol, 2003. 56(4): p. 283-6.

5. Yancovitz, M., et al., Role of radiologic imaging at the time of initial diagnosis of stage T1b-T3b melanoma. Cancer, 2007. 110(5): p. 1107-14.

6. Xing, Y., K.D. Cromwell, and J.N. Cormier, Review of diagnostic imaging modalities for the surveillance of melanoma patients. Dermatol Res Pract, 2012. 2012: p. 941921.

7. Wagner, J.D., et al., FDG-PET sensitivity for melanoma lymph node metastases is dependent on tumor volume. J Surg Oncol, 2001. 77(4): p. 237-42.

8. Xing, Y., et al., Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. J Natl Cancer Inst, 2011. 103(2): p. 129-42.

9. Harris, M.T., et al., Impact of 2-deoxy-2[F-18]fluoro-D-glucose Positron Emission Tomography on the management of patients with advanced melanoma. Mol Imaging

12

Principles of Management

JONATHAN STRETCH ALEXANDER VAREY
ROBYN SAW SYDNEY CH'NG

Melanoma Institute Australia

General Concepts

Special Subtypes

Key Points

- Management strategy should consider individual patient's risks and benefits of any decision
- Histopathological confirmation and staging of the tumour are essential for correct primary treatment
- Predilection for lymphatic dissemination; hence the patterns of locoregional recurrence, including satellitosis, in transit and regional lymph node metastases
- Nodal drainage patterns are unpredictable for head and neck or truncal melanomas
- Consider sentinel node evaluation in frail patients, to optimise surveillance with ultrasound
- Structured surveillance plan required to monitor for recurrence or second primaries

SECTION 1

General Concepts

JONATHAN STRETCH ALEXANDER VAREY

INTRODUCTION

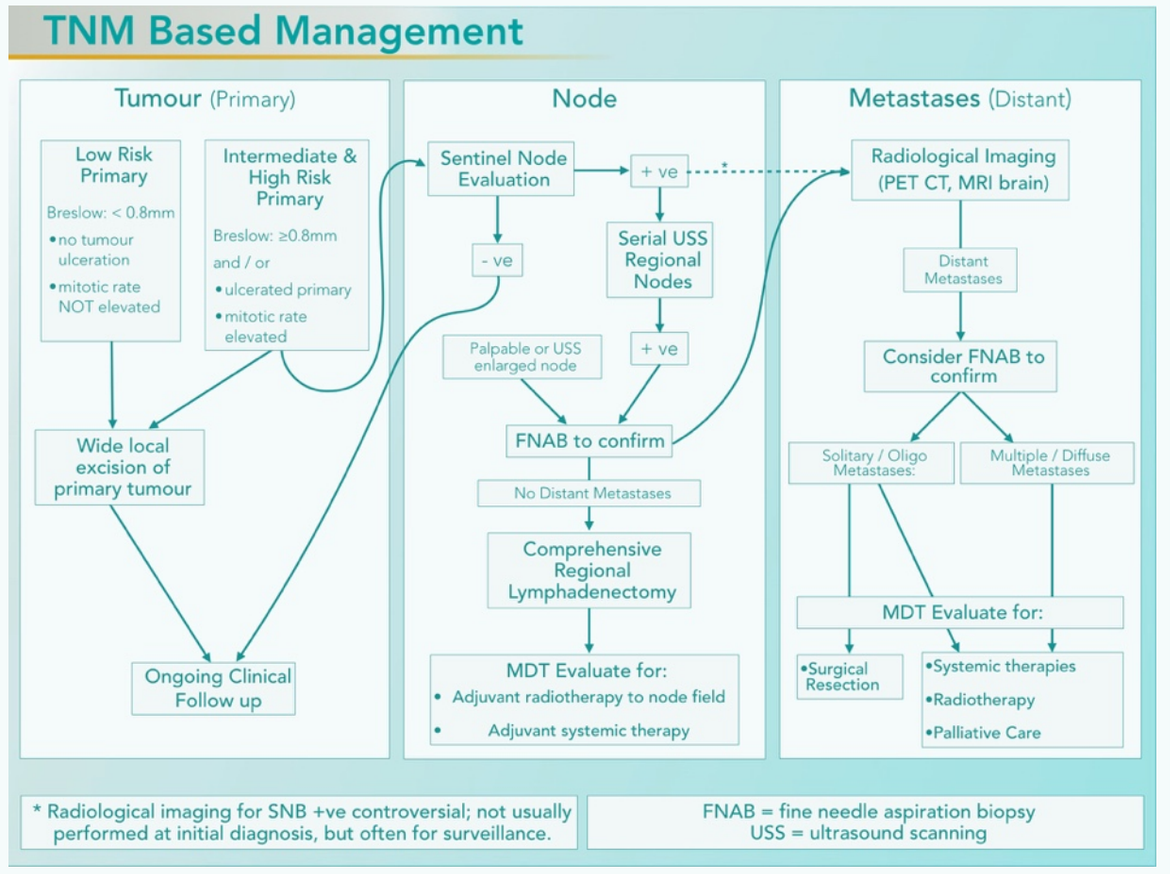
Caring for patients recently diagnosed with melanoma requires the following components to formulate an appropriate plan:

- accurate clinical history
- thorough examination
- histopathological tumour assessment
- clinical staging

The plan will combine the above assessments to determine the optimal treatment, given the probability of metastatic spread, anatomical location and patient suitability and wishes. This will include both the initial treatment and a structured approach to ongoing follow-up.

Ongoing patient follow-up serves to both monitor for local, regional, and distant metastases and to detect any further primary skin cancers. This latter aspect is particularly important, since melanoma

INTERACTIVE 12.1 MANAGEMENT WORKFLOW



patients have a five to ten fold elevation in the risk of developing a second primary melanoma compared to their background population risk.

History

The history should include details of the lesion and its evolution, the patient's risk factors for melanoma and their general health. Specifically relevant information includes:

- Site
- New or pre-existing lesion
- Change in colour, size, shape, timeframe
- Episodes of bleeding/ulceration/itch/trauma
- Previous skin cancers (melanoma or other)
- History of sunburn
- Use of sunbeds
- Family history of melanoma

The history of the primary tumour often aids both the clinician and the pathologist in establishing an accurate diagnosis.

Clinical Examination

The purposes of the clinical examination are to:

- determine the nature and extent of the primary tumour
- establish the options for reconstruction following removal of the tumour
- detect any palpable metastatic disease
- identify other primary skin cancers

Clinical identification of systemic metastases at the time of detecting a primary cutaneous melanoma is uncommon. However, synchronous multiple primary melanomas or other skin cancers are relatively common. Therefore, careful clinical examination of the primary tumour site, the regional lymph nodes, the abdomen (particularly the liver and spleen) and the entirety of the skin is required. This helps to

identify any metastases or second primary tumours, which may alter subsequent investigation and surgery plans.[1]

Primary Tumour

The primary tumour should be assessed as described in the Clinical Diagnosis chapter. Lesions that fulfil the ABCDE rule for the diagnosis of melanoma, are macular and do not display any evidence of ulceration are likely, but not invariably, to be low risk melanomas. Conversely, when the lesion has a palpable thickness or nodular component, clinical ulceration or local satellite lesions, it is indicative of an intermediate or high risk melanoma. However, the **clinical assessment of the lesion should not be relied upon** to implement a definitive management plan. Therefore, in all cases, a biopsy (preferably excisional) of the primary tumour remains a high priority. The rationale for this is that although a relatively confident clinical diagnosis of melanoma is often possible, pathological staging may identify adverse histological features that are not clinically apparent, including:

- Breslow thickness >1.0mm
- Ulceration
- Tumour Mitotic Rate >0/mm^2
- Microsatellitosis
- Lymphovascular invasion

If such features are detected, then further investigations and a more complex management plan may be required. This may include greater margins, sentinel node mapping ± biopsy and consideration for trials of adjuvant therapies. If an inappropriate procedure has already been performed, then the management options may be adversely restricted. Such restrictions may include limited reconstruction options and unreliable sentinel node identification, due to disturbance of

the lymphatics immediately around the primary tumour site.[1]

Excision Biopsy Site

The primary biopsy site should be assessed for any residual tumour or satellite lesions, the quality of wound healing and the availability of tissue for reconstruction.

All the melanoma management guidelines published throughout the world highlight the importance of an initial diagnostic biopsy to confirm the diagnosis and pathologically stage the tumour. For the reasons outlined in the Biopsy Techniques chapter, a narrow margin excision biopsy provides the optimal specimen for tumour characterisation.

Assessment of Regional Lymph Node Fields

Metastasis via lymphatics to regional lymph nodes is a classic feature of this melanoma. Consequently, careful clinical palpation of the anticipated relevant nodal fields is essential. However, lymphatic mapping with lymphoscintigraphy has demonstrated this to be unpredictable in around 10% of patients.

Primary tumours on the torso, especially at sites closer to the axial midline or the mid-abdomen, have notoriously unreliable drainage patterns. Therefore, in such patients, both groins, axillae and cervical nodal fields should be examined.

Primary tumours located on the limbs generally have predictable regional lymph node fields in the axilla and groin. However, 10% of patients have interval lymph nodes, located between the primary tumour and the regional nodal fields. Typical examples include the epitrochlear and mid brachial region of the upper limb and in the popliteal fossa of the lower limb. Accordingly, examination should include palpation for metastases to such nodes.

Lymphatic dispersal from primary cutaneous tumours in the head and neck can be diverse, necessitating a thorough examination of all nodes within this region, bilaterally.

High resolution ultrasonography (USS) now provides a method to assess lymph nodes for relatively subtle tumour burdens, that palpation would be unlikely to detect. The sensitivity of USS, coupled with the unpredictability of lymph node drainage patterns, justifies serious consideration of lymphatic mapping and USS assessment of the sentinel nodes for patients with intermediate and higher risk primary melanoma. The identified nodes can then be biopsied at the time of wide local excision, or serially monitored with USS for early signs of metastatic tumour. Thus if nodal recurrence does develop, it is likely to be a lower risk procedure to excise it than if detected when clinically palpable. This latter approach of close clinical observation, rather than biopsy of sentinel nodes, is of particular pertinence to elderly or frail patients.

Selecting Appropriate Treatment Strategies

Developing an appropriate melanoma treatment strategy requires evaluation of the patient's general health, identification of co-morbidities and life expectancy estimation, excluding melanoma. In particular, cardiovascular diseases and any anticoagulant therapy will influence the most appropriate surgical procedures. With this information, a risk-benefit calculation can be made for procedures that seek to reduce the risk from the melanoma. Thus in a frail patient, a simple wide local excision may be the preferred option, even though a healthier patient with a similar tumour would benefit from lymph node evaluation/biopsy.

Interactive 12.2 Primary Management Strategies

Management Strategies for Primary Melanoma

In Situ	Low Risk	Intermediate Risk	High Risk

Characterised by:
- In Situ
- Lentigo Maligna

Surgical Management:
- Excision with 5-10 mm clinical margins
- Sentinel Node Biopsy is NOT indicated for this pre-invasive tumour

Investigations:
- No radiological imaging is required
- Confocal microscopy may be useful in defining extent of lesion, especially Lentigo Maligna

Surveillance:
- Lifelong skin surveillance - new melanomas / other skin cancers
  - Family history melanoma or increased numbers of naevi - increased risk: more regular expert reviews ±TBP
- Review intervals for local recurrence
  - 6 monthly for 3 years then yearly

Excision Margins

Evidence for Radial Margins

Adequate local excision is an important component of managing both in situ and invasive melanoma, achieving around 90% cure. However, the optimal margins for primary melanoma excision have not been conclusively determined; the evidence includes several meta-analyses, five randomised trials and retrospective case series from both single and multiple institutions. These studies have generally demonstrated a trend towards improved locoregional recurrence and overall survival with wider margins, however, in most cases this has failed to reach statistical significance. This near homogeneity in outcomes would suggest that, if possible, a wider excision is recommended.

Many countries have developed guidelines on margins of excision, which are based on these studies, however, due to the gaps in the evidence, the final recommendations are in many cases a consensus agreement. There is no high level evidence for margin recommendations in patients with melanoma in situ or those with thick (Breslow >4mm) melanoma. The margins used by MIA surgeons (Interactive 12.2) are based upon the Clinical Practice Guidelines for the Management of Melanoma in Australia.

Evidence for Depth of Excision

There are few data to indicate guidelines on depth of excision of melanoma. Commonly the practice is to excise a melanoma to or through the deep fascia depending on tumour characteristics and local tissues available.

Situations for Deviation From Guidelines

There are limited data concerning margins for acral lentiginous and subungual melanoma. Functional amputation does not seem to have worse recurrence or overall survival than more radical amputation. For primary melanoma in the head and neck areas, anatomical constraints may make achieving wide margins difficult or impossible. Although at least a 1cm margin is ideal in this setting, occasionally more narrow margins may have to be accepted. Hutchinson's melanotic freckle is often part of a field change and in this situation it may be very difficult to achieve clear margins.

Clinical Practice

At Melanoma Institute Australia patients are managed in line with the following schema, according to the risk profile of their primary tumour:

- In Situ melanoma
- Low risk melanoma
- Intermediate risk melanoma
- High risk melanoma

In Situ Melanoma

Definition

Surgical Management

Complete local excision with approximately 5-10mm clinically normal skin surrounding the clinically apparent tumour. It should be recognised that the subsequent surgical specimen, particularly after fixation in formalin, may be reported as having been removed with narrower margins (3-4mm). This in

itself does not constitute an indication for further excision.

Investigations

None.

Surveillance

Multiple factors including the morphology of the original lesion, especially the definition of its margins, state of the surrounding skin, and the risk of further primary tumours all need to be evaluated carefully.

Low-Risk melanoma

Definition

Surgical Management

These tumours are typically excised to achieve 10mm clinical margins beyond the peripheral border of the tumour. In practical terms, an original excision biopsy utilising 2-3mm margins will have been performed initially to establish the diagnosis and micro-stage the tumour. Definitive re-excision of these tumours involves completely resecting the original biopsy wound and including all suture tracts. This generally involves approximately 10mm lateral cutaneous margins and excision to the next deep tissue plane, typically the deep fascia. Direct primary closure is frequently achieved.

Sentinel node biopsy is not performed for these prognostically favourable tumours.

Investigations

No imaging nor other forms of investigation aimed at detecting metastases are indicated. The yield from radiological imaging does not warrant the patient exposure to irradiation nor the expense to either the patient or the community health budget.

Surveillance

The risk of recurrence is low, but will occur in at least 5% of these patients. Additionally, patients diagnosed with melanoma are at a substantially increased (5-10 fold) risk of developing a subsequent new primary melanoma and therefore require lifelong general skin surveillance for further melanoma and indeed other forms of skin cancer. Simple clinical surveillance of the site of the primary tumour, regional lymph node field and skin generally at six monthly intervals in the first three years after diagnosis is strongly recommended. Thereafter, at least annual skin surveillance by a skilled clinician is appropriate. All patients should be instructed in how to monitor their skin for new and changing lesions.

The identification of a strong family history of melanoma (more than two first-degree family relatives) or increased numbers of naevi (banal or dysplastic) increases the risk of developing a subsequent melanoma and protocols of more regular expert skin surveillance are appropriate, potentially including total body photography.

Intermediate-Risk Melanoma

Definition

Surgical Management

These tumours are typically excised to achieve 10 - 20mm clinical margins beyond the peripheral border of the tumour. As with thin melanoma, an original excision biopsy utilising 2-3mm margins will have been performed initially to establish the diagnosis and micro-stage the tumour. Definitive re-excision of these tumours involves completely resecting the original biopsy wound in all dimensions and including all suture tracts. There is a paucity of evidence to guide selection of 20mm vs 10mm re-excision margins and clinical trials are still being undertaken to help resolve this matter. It is relevant to note that any margin of wider re-excision

beyond complete excision biopsy does not alter overall patient survival, but reduces the incidence of local recurrence. It is generally relatively easy to achieve 20mm excision margins on the torso and perform direct wound closure. However, in the head and neck region, virtually all international melanoma consensus guidelines accept 10mm excision margins. This smaller margin guideline is because larger margins would commonly require complex wound repairs, including grafts and also be associated with significant aesthetic and functional consequences. Similarly, the use of 10mm excision margins in the lower leg frequently facilitates direct primary closure.

Sentinel Node Biopsy should be considered for this patient group, as the rate of metastases in the regional node field steadily rises from approximately 6% (Breslow 1mm) with increasing tumour thickness. Patient age, sex and location (limb vs torso) are variables that are known to influence rates of sentinel node positivity.

Investigations

Apart from the imaging performed to determine the number and location of sentinel nodes, no additional imaging nor other forms of investigation aimed at detecting metastases are indicated preoperatively. If nodal metastases are identified as a result of sentinel node biopsy, radiological staging with CT or PET-CT is reasonable. MRI of the brain is the most sensitive imaging modality to screen for cerebral metastases.

Surveillance

Surveillance of these patients follows the principles described for patients with low risk melanoma. Patients with a confident negative sentinel node status have a substantially better overall prognosis than node positive patients.

High-Risk Melanoma

Definition

Surgical Management

Complete local excision of the primary tumour with a surgical margin that minimises the risk of local recurrence is a fundamental premise of managing this patient group. However, increasing margins beyond a generally accepted 2cm has not been shown to be of additional benefit.

This patient group is at high risk of both lymphatic borne metastases to the regional lymph node field and haematogenously disseminated tumour to distant sites. The high risk of systemic metastatic disease has been cited as a reason not to perform sentinel node biopsy in this patient group, despite its very low morbidity. However, clinical control of the regional node fields is critical to maintaining quality of life for patients, even if they develop systemic metastases. Since lymphadenectomy for microscopic disease has a lower complication and relapse rate than when performed for palpable disease, sentinel node biopsy should be seriously considered in this patient group.

Investigations

Apart from the imaging performed to determine the number and location of sentinel nodes, no additional imaging nor other forms of investigation aimed at detecting metastases are indicated preoperatively. If nodal metastases are identified as a result of sentinel node biopsy, radiological staging with CT or PET-CT is reasonable. MRI of the brain is the most sensitive imaging modality to screen for cerebral metastases.

Surveillance

Surveillance of these patients follows the principles described for patients with low and intermediate risk melanoma. Patients with a confident negative

sentinel node status have a substantially better overall prognosis than node positive patients.

Sentinel Lymph Node Metastases

Completion lymphadenectomy is no longer routinely recommended following a positive sentinel node biopsy, based on the results of the DeCOG-SLT and MSLT2 trials, which both failed to show any survival benefit from the procedure. Instead, it is recommended patients have regular (3-4 monthly) ultrasound surveillance of the regional lymph node basin with an experienced ultrasonographer for five years. However, there may be patient preferences or circumstances in which a completion lymphadenectomy is still performed.

Adjuvant Therapy

The role for adjuvant systemic therapy in completely resected melanoma is still being evaluated. Several studies have demonstrated that both immunotherapy and targeted therapy may be beneficial for high risk patients. However, ipilimumab has a high rate of serious toxicity and the clinical trial data on other therapies is promising but immature. Some centres may still offer either IL-2 or Interferon treatment.

Section 2

Special Subtypes

ROBYN SAW SYDNEY CH'NG
ALEXANDER VAREY

Introduction

There are particular nuances in the management strategies for the following situations:

- Lentigo maligna
- Lentigo maligna melanoma
- Acral lentiginous melanoma
- Subungual melanoma
- Desmoplastic melanoma
- Neurotropism
- Mucosal melanoma
- Anorectal melanoma
- Oropharyngeal melanoma

Lentigo maligna

Surgery is regarded the standard treatment of melanoma in situ (MIS), including lentigo maligna (LM). This usually consists of wide local excision (WLE) with a 5mm clinical margin. However, LM often presents therapeutic challenges because of large size, location in functionally and cosmetically sensitive areas with limited local tissue availability for flap reconstruction, as well as indistinct clinical and pathological margins. Consequently, a skin graft is often required. In addition, LM often occurs in elderly patients with significant co-morbidities that can further restrict therapeutic options.

LM has a propensity to recur locally, with reported rates after conventional WLE using a 5mm clinical margin ranging between 8 and 50%. The high recurrence rate has been attributed to failure to treat subclinical peripheral disease consisting of

atypical junctional melanocytes in the deep adnexal structures. Larger excision margins result in greater clearance rates, but also increase morbidity. Alternative surgical and non-surgical options have been suggested for LM to overcome the mentioned challenges:

Surgical

- Wide local excision
- Staged surgical excision

Non-surgical

- Radiotherapy
- Imiquimod
- Cryotherapy
- 5-flurouracil
- Electrocautery

Staged surgical excision (SSE) consists of preoperative delineation of the lesion using a Wood's lamp and thereafter excision of a marginal band surrounding the tumour at a 5-10mm margin, which is sent for permanent histology. The patient returns for subsequent excisions until negative margins are achieved. The tumour itself is excised last and the defect repaired. The advantages of this technique are sufficient marginal excision assessed by high quality permanent histopathological sections and avoidance of an open wound during the process.

Non-surgical therapies are increasingly used with varying success for patients with large LM, significant co-morbidities, or in patients preferring a more conservative approach. The main disadvantages include the absence of a surgical specimen for confirmation of clearance margins and the failure to treat deep peri-appendageal melanocytes.

Radiotherapy (RT) is an option for treatment of LM when surgical margins are inadequate, where surgery is not possible or not wanted and for

salvage in case of recurrence after surgery or other modalities. Advantages of RT are that it can be given to a large area with a generous margin and superiority to surgery in conservation of tissue. Late effects of RT are primarily fibrosis with hypopigmentation, telangiectasia, alopecia and decreased skin elasticity, which are determined mainly by total dose and fraction size. Ultra-soft x-ray/Grens-ray radiation, which only penetrates the epidermis, has often been used for LM. There is, however, no consensus about the optimum RT parameters to be used. A recent review showed a 5% progression to LMM with a median follow up of 3 years in 349 patients treated with RT as the primary modality. Based on this, a depth of 5mm of active treatment was recommended, to include appendages and decrease the risk of missing focally invasive areas. The efficacy for RT has been reported to be up to 88%.

Imiquimod is an immune response modifier that is licensed for the treatment of solar keratosis, superficial basal cell carcinoma and genital and perianal warts. It has been used to treat LM in several studies either as the primary modality or together with surgery. Clearance rates between 66-100% have been reported, however cases of invasive LMM have been reported during or after treatment. Imiquimod induces a number of pro-inflammatory cytokines within the skin, including interferon and tumour necrosis factor, which may potentiate immune responses. It also induces a cytotoxic T-cell mediated immune response in situ, which may account for the destruction of malignant melanocytes in LM. The Imiquimod cream is usually applied several times per week for 3 months and to be effective there needs to be a significant inflammation throughout this period. The main side effects are marked erythema, blisters, pain, influenza like symptoms, pruritus, keratitis and conjunctivitis.

Cryotherapy is not used at MIA, as to be effective it has to penetrate deeply into the skin, leading to wound healing problems. Similarly, LASER therapy is not used, due to high recurrence rates as a result of it's failure to penetrate deeply enough.

An alternative approach in an elderly patient with a large LM is to simply photograph and monitor the lesion carefully. Biopsies should be taken from any areas suspicious of invasive disease, however, transition to invasive melanoma is usually regarded as occurring slowly and being unlikely in these patients.

A Lentigo Maligna Clinic has been established at Melanoma Institute Australia. A multidisciplinary team consisting of plastic surgeons, radiation oncologists and dermatologists sees patients with difficult lesions. Patients typically have their lesion mapped with reflectance confocal microscopy (RCM) prior to attending the clinic, where the various treatment modalities are discussed in terms of oncological control, cosmesis and function, as well as logistics; principally surgery, radiotherapy, and topical therapy (imiquimod). A treatment plan is formulated in conjunction with the patient. Many patients also have RCM as part of their follow up, as detection of treatment failure is even more difficult than diagnosis, with frequent subtle non-specific pigmentation.

LENTIGO MALIGNA MELANOMA

Surgery is regarded the standard treatment of lentigo maligna melanoma (LMM), usually consisting of wide local excision (WLE) with a 10-20mm clinical margin, depending on the Breslow thickness and anatomical constraints. However, LMM poses therapeutic challenges because of the often large size, indistinct clinical and pathological margins and location in functionally and cosmetically sensitive areas with limited local tissue availability for flap

reconstruction. Consequently, a skin graft is often required. Furthermore, the LMM is often surrounded by much more extensive LM, the extent of which may be particularly difficult to determine pre-operatively. The surgical options are as follows:

- Wide local excision
- Staged surgical excision

Staged surgical excision (SSE) consists of preoperative delineation of the lesion using a Wood's lamp and thereafter excision of a marginal band surrounding the tumour at a 5-10mm margin, which is sent for permanent histology. The patient returns for subsequent excisions until negative margins are achieved. The tumour itself is excised last and the defect repaired. The advantages of this technique are sufficient marginal excision assessed by high quality permanent histopathological sections and avoidance of an open wound during the process.

Mohs micrographic surgery (MMS) is special form of SSE usually using frozen sections for histopathological evaluation of margins. Frozen sections offer convenience from a time conservation point of view but introduce up to a 50% risk of false negative results due to artefacts. Therefore some use permanent sections instead of frozen sections ("slow Mohs"). MMS initially uses narrower margins than SSE and WLE and generally results in smaller excisions that potentially decrease the functional and cosmetic impact of the treatment. The main disadvantages of both SSE and MMS are the cost and time consumption.

Acral Melanoma

The suspected diagnosis of Acral Melanoma (AM) should prompt referral to a specialist surgical oncologist. Treatment requires wide excision of the primary site with generous margins, as AM has been shown to harbour atypical cells far beyond the

clinical margins. Adequate surgical resection needs to be combined with suitable reconstruction to optimise the functional outcome of the limb. Most lesions, even in weight bearing areas, can be treated with excision and full thickness or split thickness skin grafting. Over time, grafts tend to partly fill out the contour defect, but are prone to desiccation and cracking. Grafts harvested from the instep of the contralateral foot may overcome some of these problems, but may have higher morbidity initially. Some local flap options are available for smaller defects in weight bearing areas, such as the medial plantar artery flap or the reverse sural flap for heel reconstruction. Thicker advanced lesions may require amputation. Free flaps are very rarely required.

Sentinel node evaluation should be offered to patients with intermediate and high risk melanomas without clinical regional node involvement. Lymphadenectomy is advocated for sentinel node positive patients with possible enrolment in adjuvant clinical trials. Multiple local treatment options besides surgery exist for patients with in transit metastases, such as injectables, ointments, radiotherapy, diathermy and isolated limb infusion or perfusion etc. depending on the extent and pace of the disease progression. Distant metastases are managed as for any other melanoma subtype.

Subungual Melanoma

The treatment of subungual melanoma is primarily surgical. However, there are no evidence based guidelines as to the level of resection, and the body of evidence in the literature is poor. Choice of level of resection and reconstruction method should take into account both the risk profile of the tumour and future limb function. Traditionally, digital amputation has been the recommendation, since the lack of subcutaneous fat results in a close proximity of the nail bed to the bone. Traditionally, many centres

performed proximal amputations at the metacarpo- or metatarsophalangeal level. However, there is now a trend towards more limited resections that preserve function. For invasive SUM, functional amputations are usually performed at the distal or proximal interphalangeal level or at the neck of the middle phalanx (proximal phalanx in the thumb/great toe). The local recurrence rate seems not to be decreased when a distal amputation is performed rather than a traditional proximal one.

It seems that in situ disease can safely be treated more conservatively than invasive disease. Options include excising the nail bed and skin grafting onto the underlying periosteum, or alternatively performing a minor amputation with preservation of the tendon insertions and a flap repair. This is in spite of the very small deep margins obtained.

Sentinel node biopsy should be discussed with and offered to patients with intermediate to high risk tumours, as for melanomas elsewhere. Patients with positive sentinel nodes are offered completion lymph nodes dissection and/or enrolment in trials. A staging PET-CT or CT should be performed if there is a suspicion of disease dissemination. Distant metastases are managed similarly to melanomas located elsewhere. ILI (isolated limb infusion) of ILP (isolated limb perfusion) may be offered in case of surgically non-resectable in transit metastasis.

Desmoplastic Melanoma & Neurotropism

The relatively uncommon nature of desmoplasia and neurotropism in melanoma and the significant overlap in their co-existence has resulted in a paucity of good quality prognostic studies on the two entities. However, a consistent observation is that the rates of sentinel lymph node metastasis are lower in pure desmoplastic tumours than is typical for other cutaneous melanomas, especially given the greater median Breslow thickness. In contrast,

neurotropism, probably has little effect on the rates of SLN metastasis. Although SLN metastases are less common in pure DM than non-DM, they are still present in around 6-8% cases and therefore SLNB is justified.

Surgical resection of DM follows the same principles as for melanoma in general, with margins based upon the pathological tumour stage. However, where neurotropism is present, several operations may be required in order to obtain adequate histologically confirmed margins. In some cases, such as when cranial nerves are involved, this may not be technically feasible. If there is doubt as to the adequacy of the margins, then radiotherapy should be administered to reduce the risk of recurrence. Due to the potential difficulties in obtaining adequate surgical resection in a single stage, complex reconstructions should be avoided until the results of histological assessment have been reviewed.

Citations and Further Reading

1. Australian Cancer Network Melanoma Guidelines Revision Working Group. Clinical Practice Guidelines for the Management of Cutaneous Melanoma in Australia and New Zealand. Sydney and Wellington: Australian Cancer Network and New Zealand Guidelines Group, 2008.

2. MacKenzie Ross AD, Haydu LE, Quinn MJ, et al. The Association Between Excision Margins and Local Recurrence in 11,290 Thin (T1) Primary Cutaneous Melanomas: A Case-Control Study. Ann Surg Oncol 2016; 23:1082-9.

3. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. Lancet 2005; 365:687-701.

4. Uren RF, Howman-Giles RB, Thompson JF, et al. Variability of cutaneous lymphatic flow rates in melanoma patients. Melanoma Res 1998; 8:279-82.

5. Lopez F, Rodrigo JP, Cardesa A, et al. Update on primary head and neck mucosal melanoma. Head Neck 2016; 38:147-55.

6. Edwards RH, Ward MR, Wu H, et al. Absence of BRAF mutations in UV-protected mucosal melanomas. J Med Genet 2004; 41:270-2.

7. Thompson JF, Uren RF, Shaw HM, et al. Location of sentinel lymph nodes in patients with cutaneous melanoma: new insights into lymphatic anatomy. J Am Coll Surg 1999; 189:195-204.

8. Uren RF, Sanki A, Thompson JF. The utility of ultrasound in patients with melanoma. Expert Rev Anticancer Ther 2007; 7:1633-42.

9. Thompson JF, Haydu LE, Sanki A, et al. Ultrasound assessment of lymph nodes in

13

Sentinel Lymph Node Evaluation

JONATHAN STRETCH OMGO E. NIEWEG
ANNETTE CHAKERA ALEXANDER H.R. VAREY

Melanoma Institute Australia

Key Points

- Sentinel lymph node biopsy (SLNB) provides the most accurate prognosis for melanoma.
- Patients with an intermediate thickness melanoma (1.2-3.5mm Breslow) and clinically occult nodal metastases may have a 44% survival benefit from SLNB.
- Sentinel lymph node mapping (lymphoscintigraphy) and frequent USS surveillance may be a good option for those patients not suitable for SLNB.
- Surgery for small volume nodal metastases has a better complication profile than for bulky disease.
- Adjuvant systemic therapy trial eligibility is usually based upon SLNB status - these drugs increase overall and disease free survival.

Background

Patients with invasive melanoma are at risk of developing metastases to the regional lymph nodes draining the melanoma site. This is the commonest site of first recurrence if sentinel lymph node biopsy (SLNB) is not performed. The risk of metastases to the regional lymph nodes is directly related to the thickness of the primary melanoma (Table 13.1). However, such metastases are not usually clinically apparent at the time of primary diagnosis.

Sentinel lymph nodes (SLNs) are those lymph nodes receiving direct lymphatic drainage from the primary tumour site and therefore at highest risk of harbouring metastases. Identification of SLNs can be most accurately achieved by a combination of pre-operative lymphoscintigraphy (LSG) with a radioactive colloid and intraoperative vital blue dye. Both the colloid and blue dye are injected within a few millimetres of the primary melanoma site to maximise the accuracy of node identification. LSG has resulted in a dramatic increase in knowledge of lymphatic anatomy and physiology. Consequently, previously unimagined patterns of lymphatic drainage and therefore potential tumour spread by

Table 13.1 Risk of regional lymph node metastases by primary melanoma thickness

Melanoma thickness (mm)	≤ 0.75	0.76 – 1	1.01 – 4	> 4
Risk of regional lymph node metastases at diagnosis (%)	≤ 2	5-10	10 – 30	>30
Should be offered sentinel lymph node biopsy *	If ulceration, and/or mitotic rate ≥ 3/mm^2 and age < 45 years	If ulceration, mitotic rate>1/ mm^2 or age <45 years	Yes	Yes

** No known dissemination*

lymphatics have been identified. This includes interval nodes such as in the popliteal fossa, epitrochlear region and triangular intermuscular space. Occasionally, drainage from the thorax and back has been observed flowing directly through to para-aortic and intra-abdominal nodes. In summary, we now know that lymphatic drainage patterns are not as predictable as previously thought.

Validation of The Sentinel Lymph Node Biopsy Concept

Several studies have validated that SLN status is a reliable and accurate indicator of the presence of metastatic melanoma in regional lymph nodes. SLN status is an important independent prognostic factor; patients with a negative SLN have a significantly better prognosis than patients with a positive SLN. Accordingly, SLNB has been incorporated into the AJCC melanoma staging system since 2002.

Multi-Center Selective Lymphadenectomy Trial 1 (MSLT-1) Summary

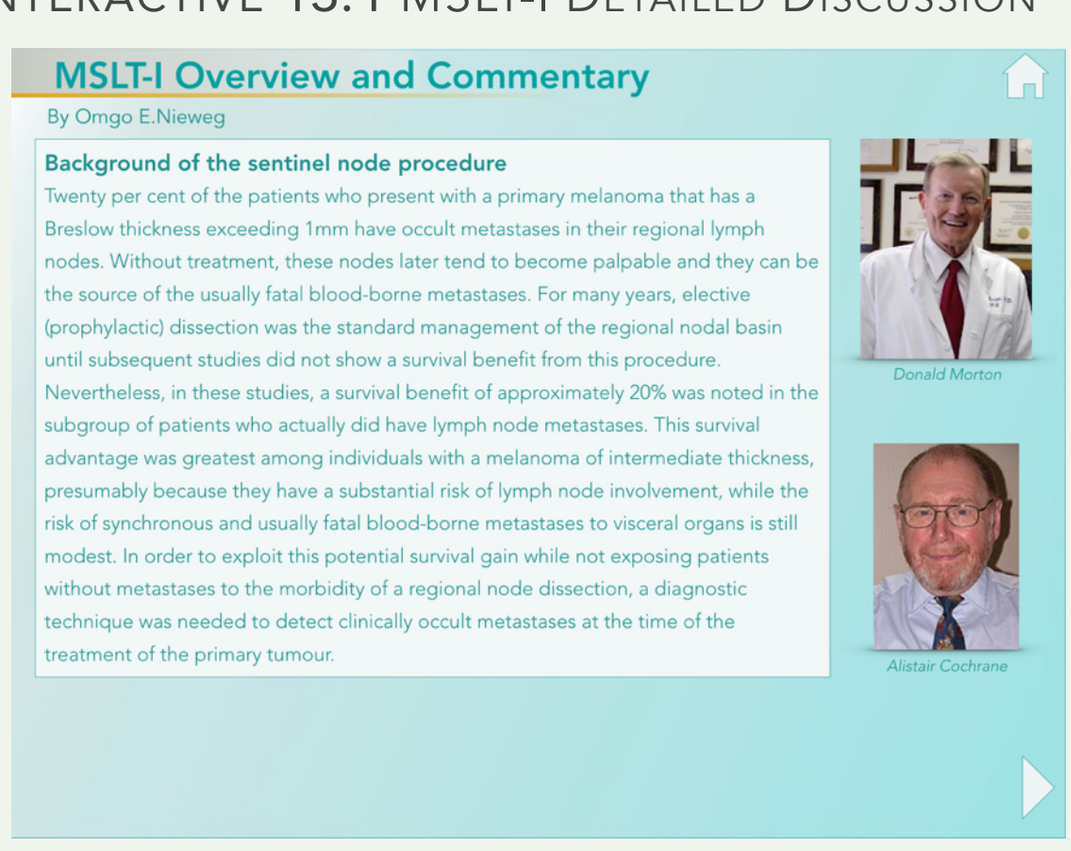
MSLT-1 , an international multicentre randomised controlled study, enrolled 1347 patients between January 1994 and March 2002, with an expected follow-up of 10 years. Its primary aim was to assess the outcome of patients with intermediate thickness melanomas (1.2–3.5mm) who were randomised to either wide local excision and sentinel node biopsy or wide local excision alone.

The final analysis of MSLT-1 demonstrated:

- SLNB negative patients had a significantly lower rate of distant metastasis and an excellent survival probability compared with SLNB positive patients.
- Sentinel node status was a better prognostic indicator than Breslow thickness, Clark level, ulceration or mitotic rate.

- CLND performed for patients with low volume metastatic disease detected by sentinel node biopsy was associated with less morbidity than TLND performed for patients with palpable nodal disease.
- There was no difference in the proportion of patients who had nodal metastases detected using SLNB compared with observation alone
- No overall survival benefit shown, but only ~20% of patients had metastases, therefore study was underpowered to detect this.

Interactive 13.1 MSLT-I Detailed Discussion



- Pre-determined subgroup analysis demonstrated a substantial improvement in 10 year survival: 62% for patients with intermediate thickness (1.2–3.5 mm) melanomas with positive SLNs who underwent immediate CLND, compared to 42% for patients in the observation arm who had TLND for nodal recurrence.
- False-negative rate was 20%.

SLNB may improve staging and regional disease control in thick melanomas, however the evidence is not strong. For thin melanomas there is insufficient evidence to support routine SLNB, although the procedure may be considered in patients with high risk features, especially in the subgroup with tumours between 0.75-0.99mm in thickness.

Contemporary Sentinel Node Evaluation

I. Pre-operative lymphoscintigraphy mapping of the lymphatic channels and SLNs that drain the primary tumour site

II. Pre-operative ultrasonography (US) of SLNs to identify metastatic disease foci >4-5mm in diameter
III. Careful evaluation of the information obtained by the above processes to determine the risk-benefit ratio of surgically procuring the identified SLNs

Surgical Procurement of Pre-operatively Mapped Sentinel Nodes

I. Intra-operative peri-tumoural injection of blue dye (eg, Patent Blue V)
II. Intra-operative use of a hand-held gamma probe to localise the isotope-labelled SLNs
III. Surgical removal of the SLNs
IV. Histological assessment of the SLNs using both conventional haematoxylin and eosin (HE) staining and immunohistochemistry. The role of polymerase chain reaction (PCR) analysis is currently under evaluation in MSLT-II

Benefits of Sentinel Node Biopsy

- Obtains the most accurate prognosis for an individual patient
- Provides reassurance for those patients with no metastases in the sentinel node
- Removes lymph node metastases early, reducing the morbidity and complication rate of removing the lymph nodes once clinically palpable
- Enables patients with nodal metastases to access adjuvant systemic therapy trials, which with the advent of new drugs such as the immunotherapies increases overall and disease free survival

Indications

Patients with the following characteristics should be provided with the opportunity to discuss the expected benefits of sentinel node biopsy:

- Primary melanoma Breslow thickness >1.0mm - 4.0mm. This group have around a 20% risk of sentinel node metastases.

- Primary melanoma thickness >4mm Breslow. Sentinel node status is still the most reliable prognostic indicator, despite these patients being at substantial risk of systemic metastatic disease. This is important information, especially for younger patients.
- Primary melanoma thickness 0.75-1mm Breslow if the melanoma is ulcerated or has a high mitotic rate (>1/mm^2). Sentinel node biopsy should also be discussed with younger patients (less than 45 years of age) who have primary melanomas in this thickness range, since the risk of a positive sentinel node is inversely related to a patient's age
- Sentinel node biopsy may also be offered to patients with tumours reported by the pathologist to be melanocytic lesions of uncertain metastatic potential (MUMP)

Indications (Special Considerations)

Pregnancy: sentinel node biopsy can be performed, but the imaging should be limited to standard lymphoscintigraphy and not include a SPECT/CT scan, so as to minimise radiation exposure to the foetus. Blue dye should not be used due to the risk of anaphylaxis and because its effects on foetal development are unknown.

Table 13.2 Indications For Sentinel Lymph Node Evaluation

- primary melanoma Breslow thickness 1.0-4mm
- primary melanoma Breslow thickness >4mm
- primary melanoma Breslow thickness 0.75-1mm **if**:
  - ulcerated tumour
  - high mitotic rate (>1/mm^2)
  - younger patient (<45 years of age)

Lactating women: sentinel node biopsy can be performed, but breastfeeding should be discontinued for 24 hours following the procedure.

Children: sentinel node biopsy can be performed.

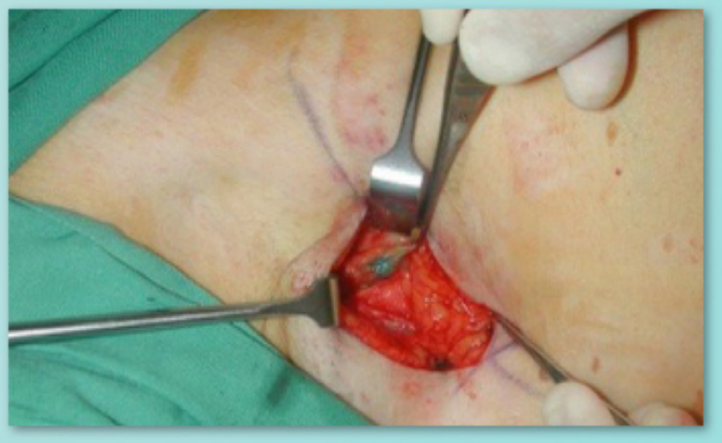
Interactive 13.2 Step-By-Step Guide to Understanding Sentinel Node Evaluation

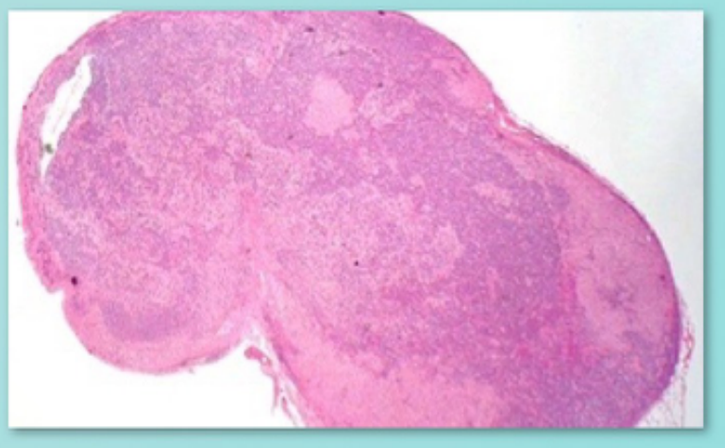
Sentinel Node Evaluation Process

Preoperative Imaging	Surgical Procurement	Histopathological Assessment

Sentinel Node Biopsy is a complex process that is comprised of:

- Pre-operative lymphatic mapping and ultrasound assessment of mapped sentinel lymph node
- Surgical procurement
- Histopathological assessment





Tap on the images or boxes to learn more about each scenario.

Contraindications

- known disseminated melanoma
- poor general health status / obesity / age over 75 years (relative contraindications - judge on individual patient basis)
- prior wide local excision (relative contraindication - this is likely to have disturbed the lymphatic drainage pathways that originally drained the melanoma site, and so could result in inaccurate sentinel node identification)

Morbidity

The complication rate from MSLT-1 was around 10%, however most of these were mild and temporary. General wound complications include haematoma, wound infection, seroma formation, nerve damage and hypertrophic or keloid scarring.

Lymphoedema occasionally occurs, typically following the harvesting of 4 or more SLNs from the groin. The risk is further increased if the primary tumour site is along the line of the long saphenous vein. However, the lymphoedema is usually mild in these situations. (Note that in MSLT-I some patients who had limb melanomas developed lymphoedema after wide excision only).

Citations and Further Reading

1. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992;127: 392-9.

2. Thompson JF, McCarthy WH, Bosch CM, O'Brien CJ, Quinn MJ, Paramaesvaran S, Crotty K, McCarthy SW, Uren RF, Howman-Giles R.Sentinel lymph node status as an indicator of the presence of metastatic melanoma in regional lymph nodes. Mel Research 1995; 5: 255-60.

3. Dessureault S, Soong SJ, Ross MI, Thompson JF, Kirkwood JM, Gershenwald JE, Coit DG, McMasters KM, Balch CM, Reintgen D; American Joint Committee on Cancer (AJCC) Melanoma Staging Committee. Improved staging of node-negative patients with intermediate to thick melanomas (>1 mm) with the use of lymphatic mapping and sentinel lymph node biopsy. Ann Surg Oncol. 2001; 8: 766-70.

4. Yee VS, Thompson JF, McKinnon JG, Scolyer RA, Li LX, McCarthy WH, O'Brien CJ, Quinn MJ, Saw RP, Shannon KF, Stretch JR, Uren RF. Outcome in 846 cutaneous melanoma patients from a single center after a negative sentinel node biopsy. Ann Surg Oncol. 2005; 12: 429-39.

5. Valsecchi ME, Silbermins D, de Rosa N, Wong SL, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: A meta-analysis. J Clin Oncol 2011: 29: 1479-87.

6. Li LX, Scolyer RA, Ka VS, McKinnon JG, Shaw HM, McCarthy SW, Thompson JF. Pathologic review of negative sentinel lymph nodes in melanoma patients with regional recurrence: a clinicopathologic study of 1152 patients undergoing

14

Surgery for Stage III and IV Disease

ALEXANDER H.R. VAREY JONATHAN STRETCH

Key Points

- Surgical resection is the mainstay of stage III disease management.
- Complete regional lymph node resection has lower morbidity and complication rate when performed for microscopic disease.
- Stage IV disease survival typically doubles with surgical resection of metastases, if patient is suitable.
- Intent of surgery for stage IV disease can be palliative or curative.
- Surgical resection has a role in combination with systemic therapies for resistant disease.

Stage III Disease

Patients are classified as having stage III melanoma due to the presence of lymph node metastases, microsatellites around the primary tumour or in-transit metastases (ITMs). Lymph node metastases can be detected either clinically (palpable) or histologically (microscopic) following sentinel node biopsy (SLNB). Therefore, the appropriate management of stage III disease depends on its site and extent.

Lymph node metastases

The current treatment for patients who have a positive SLNB is to recommend removal of the remaining lymph nodes in that same region, eg, groin, axilla, neck. This procedure is termed a completion lymphadenectomy (CLND). However, it has been proposed that these patients undergo serial ultrasound surveillance, reserving CLND for the ~20% of patients who subsequently develop a recurrence. This may be particularly pertinent for those patients with multiple co-morbidities. A randomised trial to answer this question (MSLT-II) recently closed to recruitment, but is unlikely to report before 2020.

Patients who have clinically palpable lymph node metastases, once confirmed on fine needle aspiration biopsy (FNAB), are then offered a therapeutic lymph node dissection (TLND), which removes all lymph nodes in the region, including the clinically palpable one(s).

Complications

Complications arising from CLND or TLND are typically greatest in the groin, followed by the axilla and then the head and neck region. Importantly, these are more frequent in TLND than CLND, further supporting the role of SLNB.

Table 14.1 Complications associated with Lymph Node Dissection

Early complications include:

- haematoma
- wound infection
- delayed healing
- skin necrosis of flaps (rare)

Late complications include:

- seroma / lymphocoele / abscess requiring aspiration or drainage
- shoulder dysfunction and stiffness (<10%)
- chronic pain (< 5 %)
- lymphoedema (upper limb ~5-15%; lower limb ~10-20%)

Microsatellites

The presence of microsatellites around a primary tumour represents a form of intra-lymphatic metastases, which are likely to be widespread and clinically occult. Consequently, the management remains wide local excision of the primary tumour, aiming to achieve clear margins. However, the patient should be closely monitored for the development of locoregional recurrences including in-transit and nodal metastases.

In-Transit Metastases

The management options for ITMs are broad and include surgical resection, electrosurgical fulgaration, intralesional injection, electrochemotherapy, topical therapy and isolated limb infusion/perfusion. Selection of the most appropriate strategy depends upon many factors, including anatomical site, extent of disease, rate of progression, presence of distant disease, co-morbidities, local expertise and availability. However, if surgery is performed, then wide margins are not required as these represent intra-lymphatic metastases that are likely to be widespread and initially clinically occult (Figure 14.1). Accordingly, close monitoring for further ITMs and regional nodal metastases is required.

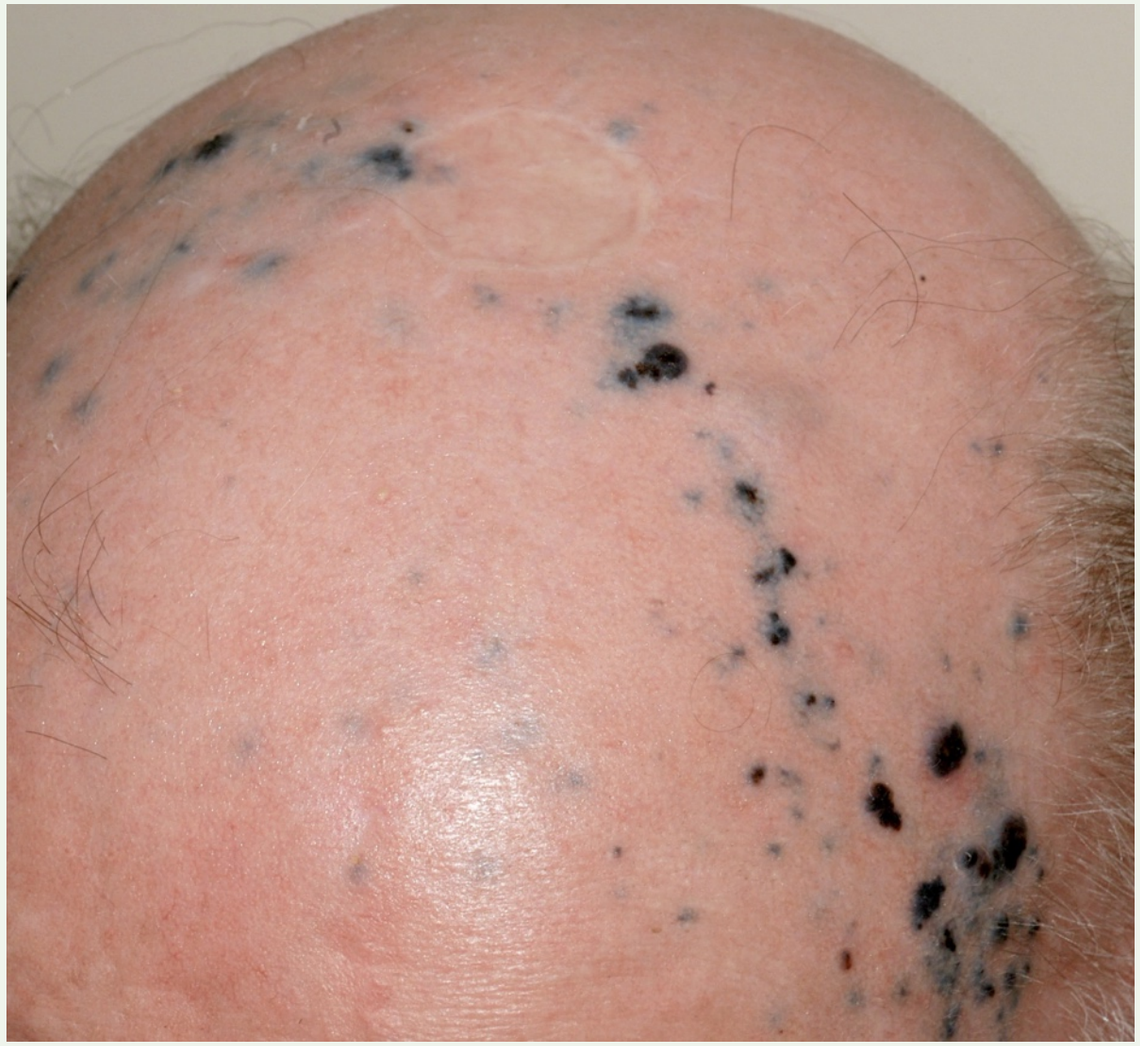
Stage IV disease

Stage IV disease encompasses a wide range of metastatic disease burden and prognosis, ranging from a solitary distant subcutaneous metastasis to multiple metastases in multiple organs. Accordingly, the management of such patients needs to be tailored according to the extent of disease burden, general health and performance status, symptoms and feasibility of surgical resection. The intent of surgery can be either curative or palliative.

Accurate assessment of the extent of disease burden is typically undertaken with PET-CT imaging. This may be supplemented with a high resolution CT or MRI of any potential sites of surgical resection in order to accurately determine the involvement of adjacent structures.

Where there are isolated metastases, such as in the peripheral lung or a para-aortic node, surgical resection may be feasible. Several metastectomy

Figure 14.1 In-Transit Metastases from a Scalp Primary Melanoma



Spread of ITMs to both sides of scalp and temples. Evidence of primary tumour site with skin graft reconstruction, overlying vertex of skull.

(7 months after initial treatment)

studies have demonstrated a 5 year survival of typically 20-30% (42% in one study), compared to 5-10% with standard medical therapy. Accordingly, patients in the MSLT-1 study demonstrated a 54% reduction in the risk of death when metastases were treated with surgery, using a multivariate analysis.

Patients presenting with widespread metastatic disease are often best managed with systemic therapy. However, there may be isolated disease that is resistant to this therapy, yet may be amenable to surgical resection.

Citations and Further Reading

1. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Puleo CA, Coventry BJ, Kashani-Sabet M, Smithers BM, Paul E, Kraybill WG, McKinnon JG, Wang HJ, Elashoff R, Faries MB; MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014 Feb 13;370(7):599-609.

2. Faries MB, Thompson JF, Cochran A, Elashoff R, Glass EC, Mozzillo N, et al; MSLT Cooperative Group. The impact on morbidity and length of stay of early versus delayed complete lymphadenectomy in melanoma: results of the Multicenter Selective Lymphadenectomy Trial (I). Ann Surg Oncol 2010;17:3324-9. Epub 2010 Jul 8.

3. Wei IH, Healy MA, Wong SL. Surgical treatment options for stage IV melanoma. Surg Clin North Am. 2014 Oct;94(5):1075-89, ix.

4. Howard JH, Thompson JF, Mozzillo N, Nieweg OE, Hoekstra HJ, Roses DF, Sondak VK, Reintgen DS, Kashani-Sabet M, Karakousis CP, Coventry BJ, Kraybill WG, Smithers BM, Elashoff R, Stern SL, Cochran AJ, Faries MB, Morton DL. Metastasectomy for distant metastatic melanoma: analysis of data from the first Multicenter Selective Lymphadenectomy Trial (MSLT-I). Ann Surg Oncol. 2012 Aug;19(8):2547-55.

5. Starritt EC, Joseph D, McKinnon JG, Lo SK, de Wilt JH, Thompson JF. Lymphedema after complete axillary node dissection for melanoma: assessment using a new, objective definition. Ann Surg. 2004 Nov;240(5):866-74. PubMed PMID: 15492570; PubMed Central PMCID: PMC1356494.

15

Systemic Therapies

ALEXANDER M. MENZIES GEORGINA V. LONG
PETER HERSEY CATRIONA McNEIL
RICHARD F. KEFFORD

Melanoma Institute Australia

Key Points

- Until recently, systemic therapies for melanoma were largely ineffective.
- Several new treatments for advanced disease that improve survival have become available; these either stimulate the immune system or inhibit the activity of specific mutated genes.
- Further trials are underway to improve the chances of cure for patients with early stage melanoma, and prolong survival in patients with advanced disease.

Introduction

Melanoma is curable via surgical techniques for the majority of patients with early stage melanoma, however, the risk of relapse at distant sites in patients with high-risk disease is approximately 50%. Once this occurs, the prognosis is extremely poor.

Systemic therapy is used in three settings in melanoma:

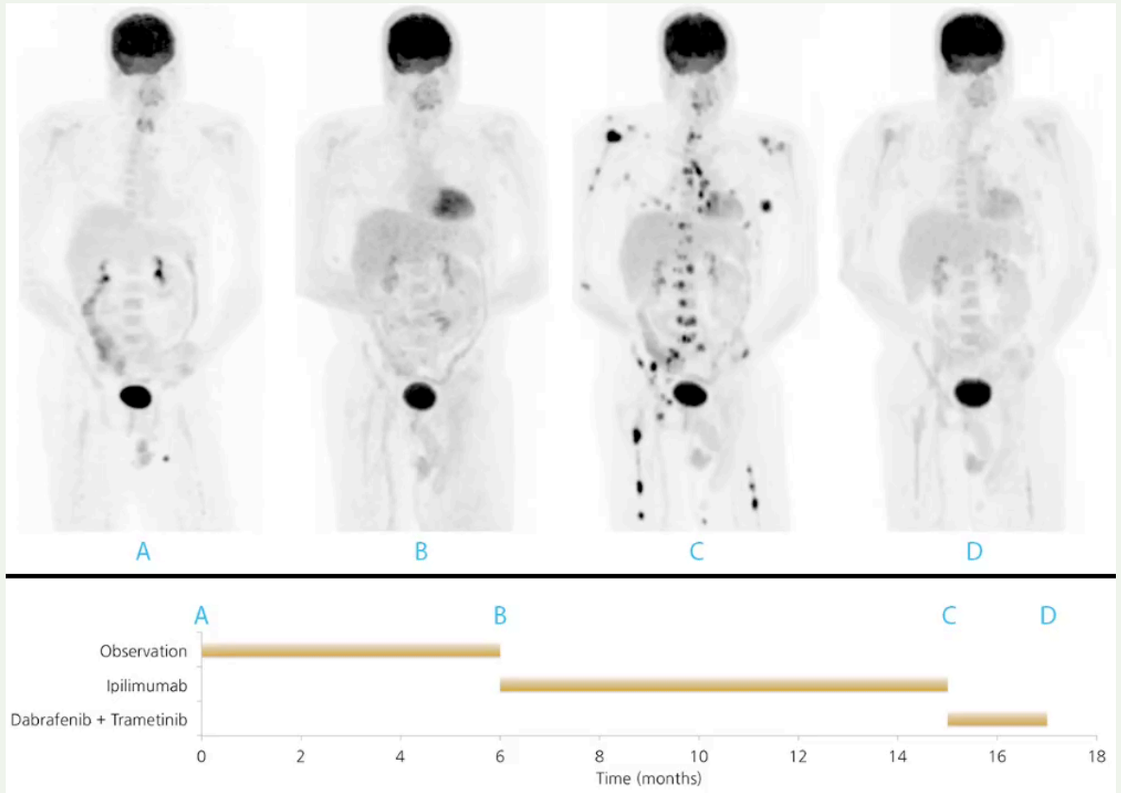
1. **Metastatic disease.**
   When the melanoma has spread to distant sites, for example the liver, lungs or brain (unresectable stage IIIC or stage IV melanoma), it is extremely difficult to eradicate all cancer cells in the body, such that cure is rare. The main goals of systemic therapy for metastatic melanoma are to prolong survival and improve symptoms and quality of life.
2. **Adjuvant**
   For patients with stage IIC/III disease (see Staging chapter), systemic therapy may be given after surgical removal of all apparent melanoma. The intent is to eradicate all potential remaining occult tumour cells in the body that may have spread from the primary tumour or draining lymph node prior to surgery. The goal of adjuvant therapy is to increase the likelihood of long-term cure.
3. **Neo-adjuvant**
   For patients with bulky, difficult to resect stage III disease, systemic therapy is given prior to surgery, with the aim of shrinking the tumour bulk in order to make surgery possible with less morbidity.

Until recently, almost all systemic therapies were ineffective in the metastatic setting, with response rates of less than 10% and a median survival of 6-9

months. The drug predominantly used was dacarbazine (DTIC), which has a progression free survival benefit ranging from 2-4 months, influenced by the prognostic characteristics of the group selected for study. DTIC is fairly well tolerated, requiring administration by short intravenous infusion once every 3 weeks. The side effects include fatigue, nausea and myelosuppression, but are generally mild and elderly patients with co-morbidities can often tolerate therapy. However, there are no randomised controlled trials comparing DTIC with placebo in metastatic melanoma.

The rapidly evolving understanding of tumour biology and immunity has provided the basis for the design of effective systemic therapies that have improved outcomes for patients with metastatic melanoma. In particular, the identification of immune checkpoints and specific driver oncogenes that are present in a large proportion of melanomas have been critical. While drugs targeting these have

VIDEO 15.1 RESPONSES TO SYSTEMIC THERAPIES



Sequential PET-CT scans showing disease progression at 6 months (medial left thigh - small) following the first routine surveillance scan and further progression despite systemic ipilimumab over the next 9 months. However, changing to targeted BRAF and MEK inhibitor therapy produced a rapid and dramatic reduction in disease volume over two months, correlating with improvement in symptoms.

entered routine clinical practice, a large number of trials are under way which are designed to build upon the early success of these therapies.

In the adjuvant setting, many systemic therapies are being evaluated in clinical trials to determine their effectiveness in preventing recurrence. This includes those novel therapies proven to be effective in metastatic melanoma and so far the results are promising. Neo-adjuvant trials are also in progress.

SECTION 1

Targeted Therapies

ALEXANDER M. MENZIES
GEORGINA V. LONG

Key Points

- Melanoma growth is driven by abnormalities of certain genes in the tumour.
- BRAF is an important gene that is mutated in ~40% of melanomas.
- Drugs that inhibit mutant BRAF (BRAF and MEK inhibitors) have high response rates, improve symptoms and prolong survival of patients with advanced melanoma. Toxicity with these treatments is usually mild.
- Drug trials are in progress for gene mutations other than BRAF.

Introduction

Systemic drug therapies for the treatment of patients with metastatic melanoma (stage IIIC unresectable or stage IV) were limited for decades. Very few patients had melanoma that was sensitive to chemotherapy, and until the advent of active immunotherapies and targeted therapies, the median survival for patients with metastatic melanoma was 6-9 months.

In this section called 'Targeted Therapies', we review the important cellular pathways in melanoma that are abnormal and how these aberrations may be targeted with drugs to improve the quality of life and extend the survival of patients with metastatic melanoma.

What is a Targeted therapy?

A targeted therapy is a drug that blocks the growth and spread of cancer by interfering with specific molecules involved in tumour growth and progression as opposed to simply blocking rapidly dividing cells (as with chemotherapy). Understanding the abnormal molecules and pathways in a melanoma cancer cell is how a 'target' is identified.

Important Cellular Pathways in Melanoma

There are many pathways in melanoma cancer cells that are abnormal and dysregulated. The pathway most frequently aberrantly activated in melanoma is the mitogen-activated protein kinase (MAPK) pathway. Normally, the MAPK pathway regulates cell proliferation, survival, migration and angiogenesis in a highly regulated and controlled manner (Figure 15.1). Molecular alterations in genes encoding key components of the pathway (e.g. RAF and RAS mutations) in melanoma result in uncontrolled tumour proliferation and survival.

BRAF Mutations in Melanoma

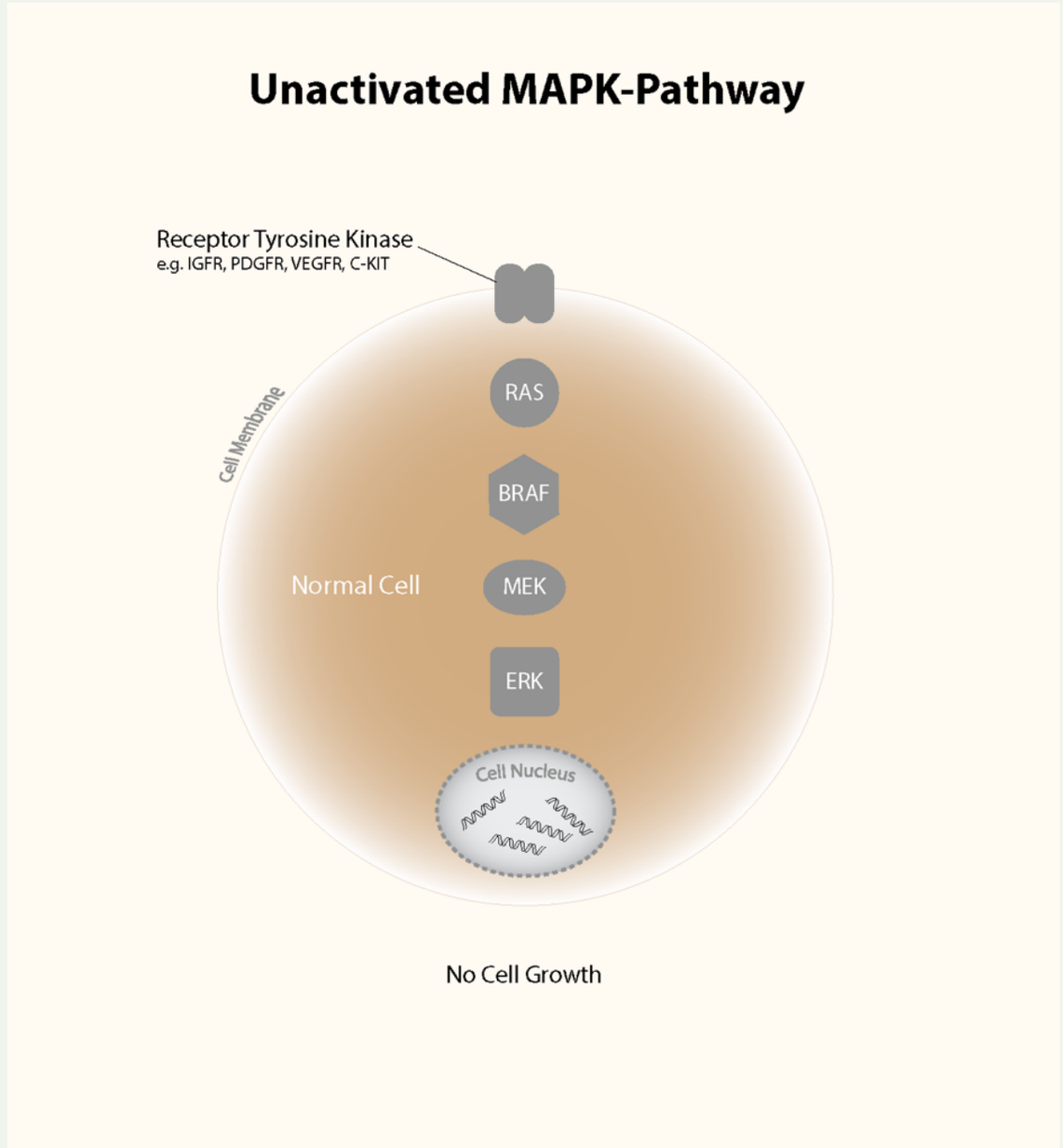
Approximately 40% of cutaneous melanomas have mutations in BRAF, and its prevalence is inversely proportional to patient age. Over 75% of these mutations are the V600E, but various others also occur, including V600K. Either the primary tumour or a metastasis can be tested, since the mutation status rarely, if ever, changes. However, it is preferable to use the most recently obtained tumour sample in case such a rare change has occurred.

Acral and mucosal melanomas have a lower frequency of BRAF mutations, and uveal melanomas do not have BRAF mutations. It is unclear if patients with BRAF-mutant melanoma have a poorer prognosis compared with BRAF wild-type disease.

BRAF and MEK Inhibitor Therapy

For patients with melanomas that have the V600 BRAF mutation, the median overall survival with

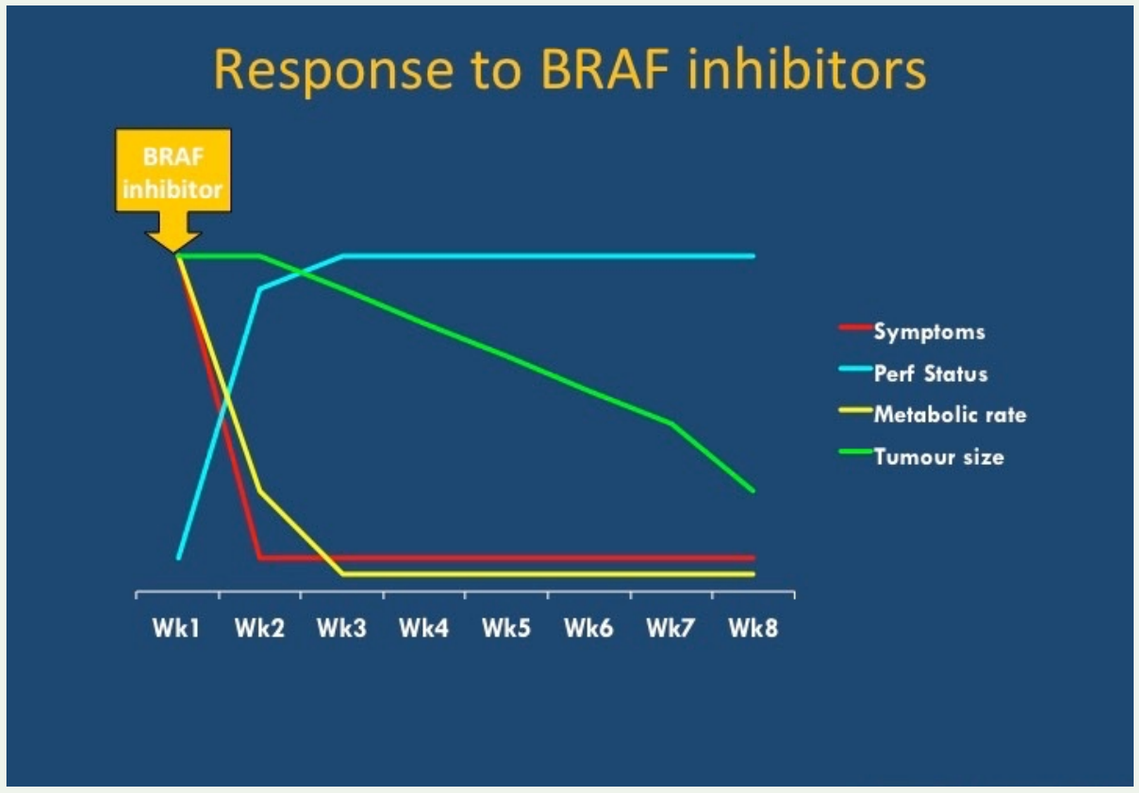
Figure 15.1 BRAF Pathway



No melanocyte multiplication in the absence of any growth factors to activate the MAPK pathway.

treatment using drugs that target the mutated BRAF protein (BRAF inhibitors) is extended to 15-18 months, and further progress has been made with combinations of therapies that target both BRAF and MEK, increasing overall survival to 24 months. Major shrinkage of tumours occurs in about 70% of patients with combination treatment, but nearly 95% of patients have some disease control.

FIGURE 15.2 TREATMENT RESPONSE TO BRAF AND MEK INHIBITION FOR METASTATIC MELANOMA



This chart demonstrates the very rapid improvement in symptoms and performance status, but slower reduction in tumour volume following commencement of BRAF inhibitor therapy.

Toxicity

In general, toxicities from BRAF and MEK inhibitors are mild. Cutaneous toxicities including rash, hyperkeratosis, low grade cutaneous SCC occur with BRAF inhibitor monotherapy, but are reduced when used in combination with MEK inhibitors. The combination of dabrafenib and trametinib can cause fever, while vemurafenib and cobimetinib can cause photosensitivity and hepatitis. Toxicities are common, often result in treatment interruption, but rarely result in permanent discontinuation.

SECTION 2

Immunotherapies

PETER HERSEY
ALEXANDER M. MENZIES
MATTEO CARLINO

Key Points

- Melanoma interacts with the immune system.
- Previous attempts to boost anti-tumour immunity with cytokines or vaccines were either toxic, ineffective, or both.
- New drugs (checkpoint inhibitors) act directly on cytotoxic T-cells to prevent inactivation, thus promoting anti-tumour immunity.
- Only a small subgroup of patients respond to ipilimumab, but in those that do, response is durable.
- PD-1 antibodies appear to have higher response rates, but also have durable survival.

INTRODUCTION

Primary melanoma is, in most instances, an immunogenic tumour, as evidenced by lymphocytic infiltration around and into the tumour (tumour infiltrating lymphocytes or TILs). This can be associated with varying degrees of regression of the tumour and complete regression is believed to be the basis of presentation of patients with metastatic melanoma, but no visible primary (occult melanoma). When melanoma progresses to the metastatic stage, lymphocytic infiltration is usually less, but spontaneous regressions may still occur. In patients with primary melanoma "brisk" TILs are associated with a lower rate of lymph node metastases, but have no effect on overall survival or disease free survival.

Targeting the CTLA4 Checkpoint

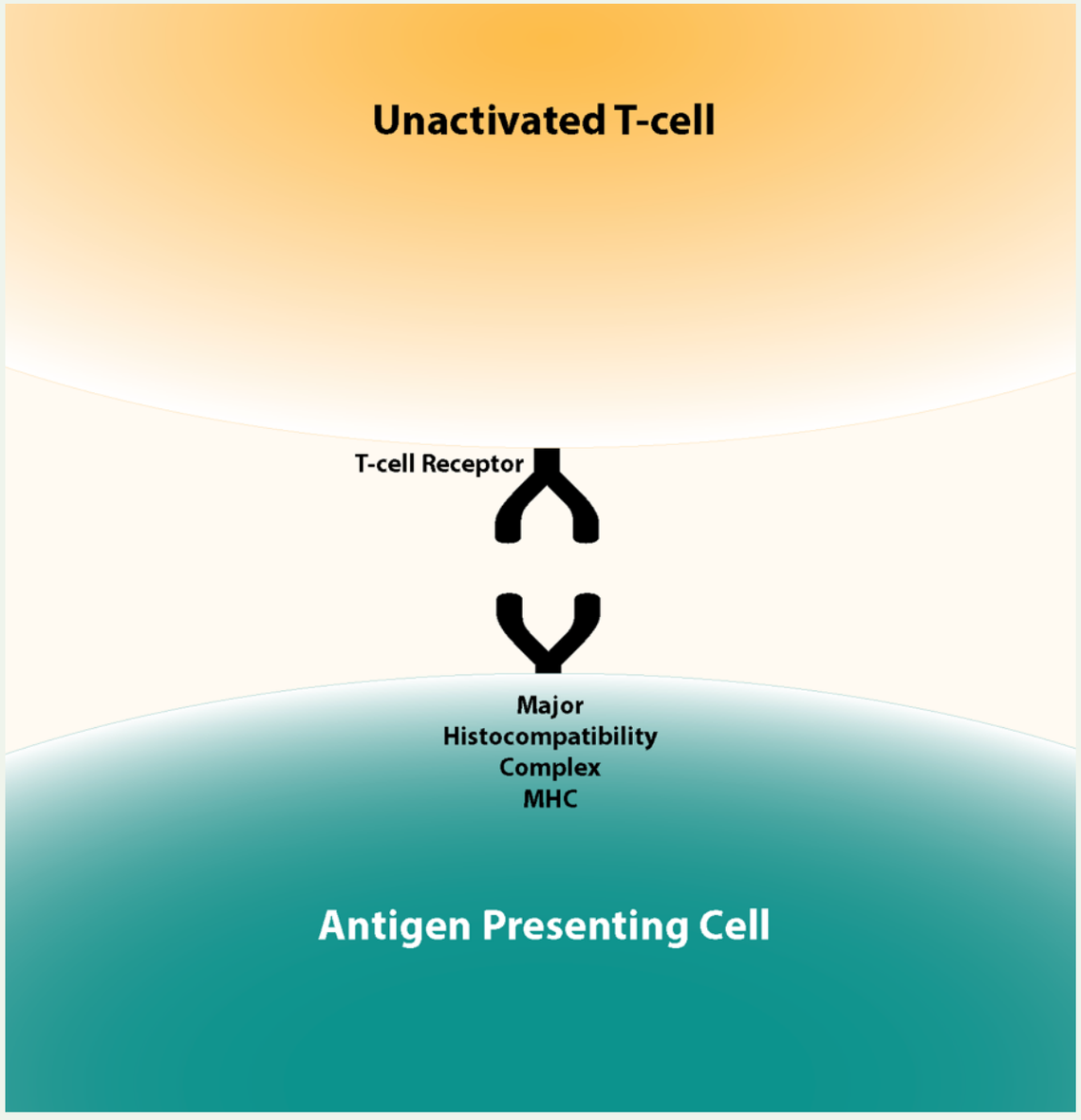
When T-lymphocytes are activated, physiological mechanisms restrict their division and return them to their resting state. One such mechanism is the appearance of a receptor on the surface of activated lymphocytes called Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4), which interacts with ligands on antigen presenting cells (APCs) or on tumour cells. This interaction of the ligand with CTLA-4 results in a negative signal in the lymphocyte that inhibits its division and cytotoxic activity (Figure 15.3).

Use of antibodies against CTLA-4 that block its ligand interaction result in continued activation of the lymphocyte. One such antibody, ipilimumab, is in clinical use.

Trial Data

Two large phase III randomised controlled trials have shown that ipilimumab treatment prolongs the overall survival of patients with unresectable Stage

Figure 15.3 Anti-CTLA-4 Immunotherapy



T-cell remains unactivated in the absence of tumour antigen coupled to the Major Histocompatibility Complex (MHC) of an APC binding to its receptor (TCR).

III or Stage IV metastatic melanoma, with approximately 10% of patients surviving each year. Overall five-year survival was 18.2%, compared to 8.8% in those treated with dacarbazine alone. However, only approximately 15% of patients have a significant response and as yet there are no validated biomarkers to determine who these patients are pre-treatment.

Toxicity

As expected, immune-stimulant medication can result in severe autoimmune side-effects in some patients, such as inflammatory colitis, hepatitis, hypopituitarism and dermatitis. Early recognition and the use of high dose steroids or other immunosuppressives such as mycophenolate are required.

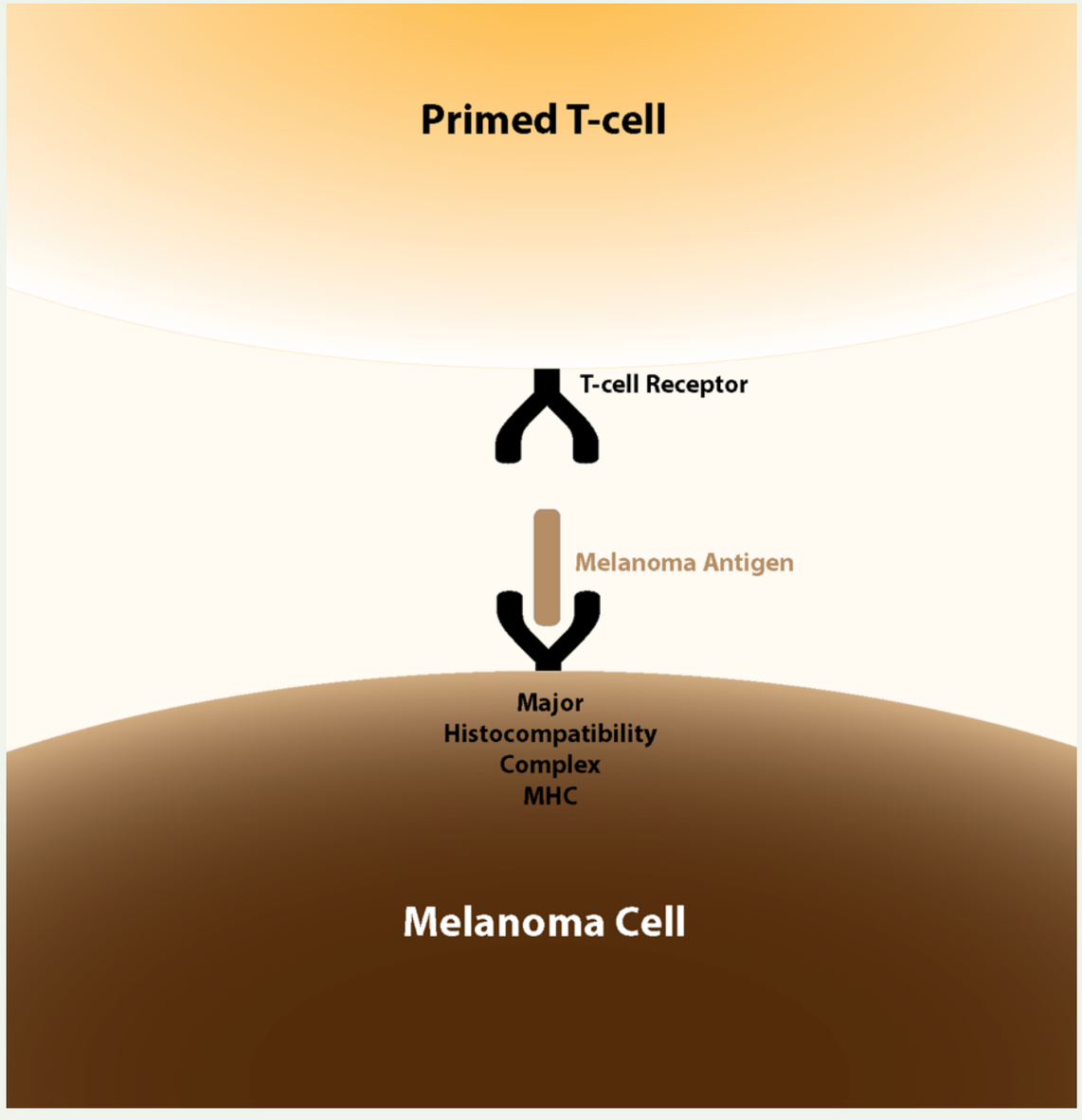
Targeting the PD-1 Checkpoint

Programmed Death-1 (PD-1) is another T-cell co-receptor that inhibits T-cell activity. When tumour cells express its ligand (PD-L1), PD-L1 binds to PD-1 on the T-cell, resulting in T-cell inactivation. Blocking this inhibitory interaction, by giving antibodies that bind to PD-1, results in increased T-cell activity against the tumour (Figure 15.4). Two such antibodies have been developed, known as pembrolizumab and nivolumab.

Trial Data

Several phase III trials have now been completed, demonstrating that anti-PD-1 antibodies have higher response rates than ipilimumab, can work in ipilimumab-resistant patients, and have less toxicity. Median overall survival is approximately 24 months, with overall survival at 1, 2, 3 and 5 years in the region of 70%, 55%, 40% and 35% respectively, and a plateau in the survival curve at 48 months. The use

FIGURE 15.4 ANTI-PD-1 IMMUNOTHERAPY



Primed T-cells traffic to melanoma cells in the periphery, ready for full activation by the target cells.

of anti-PD-1 and anti-CTLA-4 antibodies in combination achieves a response rate of around 60%, with a further 12% of patients achieving disease stabilisation, significantly greater than with ipilimumab alone. Three-year overall survival rates were 58% for the combination, 52% for nivolumab alone and 34% for ipilimumab alone.

Toxicity

The toxicities of anti-PD-1 therapy are similar to those of ipilimumab, but much less common and much less severe.

IMMUNOTHERAPY BASED ON INJECTION OF VACCINES OR CYTOKINES

Virtually all the vaccine studies have reported occasional clinical responses, which in some cases were durable. However, several large and well conducted randomised trials have failed to show clinical benefit in terms of progression free survival

(PFS) or overall survival (OS). Therefore, vaccine therapy remains confined to ongoing research only.

Various treatments involving cytokines to boost T-cell activation have been trialled, often in combination with chemotherapy (termed "biochemotherapy"). Most notably, high dose IL-2 has been shown to have high response rates and durable survival in carefully selected "fit" patients, but this comes at the cost of major toxicity. It is not a standard treatment in Australia and advances in checkpoint inhibitors have diminished its role in the treatment of metastatic melanoma.

SECTION 3

Adjuvant Therapies

CATRIONA MCNEIL
RICHARD F. KEFFORD
MATTEO CARLINO

Key Points

- Patients with high-risk surgically resected melanoma (AJCC stage IIB-III) should be considered for adjuvant systemic therapy.
- High dose ipilimumab improves overall and disease free survival, but is highly toxic and therefore not routinely used.
- Adjuvant nivolumab, pembrolizumab and for BRAF mutant melanomas combined dabrafenib/trametinib, increase disease free survival

The majority of resected thin melanomas are associated with an excellent prognosis, however, the risk of later distant metastatic spread increases dramatically with tumour depth, ulceration and locoregional nodal involvement. Stage IV melanoma (see Staging chapter) is an invariably fatal disease, and thus there has been a concerted effort to develop adjuvant treatment strategies to reduce the risk that an early-stage melanoma will ultimately manifest as distant metastatic disease.

Adjuvant Clinical Trials

The impressive activity of MAPK inhibitors and immune checkpoint blockade antibodies in the metastatic setting led to the hope that they may reduce the risk of recurrence and improve overall survival when given adjuvantly to patients with high-risk early stage melanoma. Ipilimumab has been shown to improve both disease-free and overall survival in the adjuvant treatment setting, but has a high risk of severe toxicity, including death and is therefore not TGA approved for this use in Australia.

At present three treatments, with an acceptable toxicity and safety profile, have been shown to significantly reduce the risk of relapse following one year of adjuvant systemic therapy. These are: Nivolumab; Pembrolizumab; and combination dabrafenib/trametinib (in patiens with BRAF mutant melanoma). Given the greater efficacy and more favourable safety profile these treatments have now replaced the historical adjuvant treatment options of interferon and high dose ipilimumab. In Australia, at present Nivolumab is the only option TGA approved for adjuvant treatment after resection of stage III melanoma, and none of these options is yet funded by the PBS (Pharmaceutical Benefits Scheme). However, enrolment in clinical trials remains a mechanism by which patients can access systemic adjuvant therapy.

Citations and Further Reading

1. American Joint Committee on Cancer (AJCC). Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. Cancer Staging Manual. 7th ed. New York: Springer-Verlag; 2010.

2. Thompson JF, Scolyer RA and Kefford RF. Cutaneous melanoma. Lancet 2005;365:687–701.

3. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 1996;14:7–17.

4. Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of Intergroup Trial E1690/S9111/C9190. J Clin Oncol 2000;18:2444–58.

5. Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS and Rao U. A pooled analysis of Eastern Cooperative Oncology Group and Intergroup trials of adjuvant high-dose interferon for melanoma. Clin Cancer Res 2004;10:1670–7.

6. Mocellin S, Pasquali S, Rossi CR and Nitti D. Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. J Natl Cancer Inst 2010;102:493–501.

7. Moschos SJ, Edington HD, Land SR, Rao UN, Jukic D, Shipe-Spotloe J, et al. Neoadjuvant treatment of regional stage IIIB melanoma with high-dose interferon alfa-2b induces objective tumor regression in association with modulation of tumor infiltrating host cellular immune responses. J Clin Oncol 2006;24:3164-71.

8. Eggermont AM, Suciu S, Santinami M, Testori A, Kruit WH, Marsden J, et al.

ACKNOWLEDGEMENTS

John K Dickson MB BChir MA FRCS(Plast)
Illustrations

Alexander HR Varey
Illustrations

16

Radiation Oncology

ANGELA HONG GERALD B FOGARTY

Key Points

- Adjuvant radiotherapy may be of benefit if surgical resection margins are close and further surgery is not feasible.
- Possible role in management of lentigo maligna.
- New randomised data suggest that adjuvant radiation therapy increases regional control after nodal dissection in stage III cutaneous melanomas.
- The role of radiotherapy in melanoma is being defined by high quality randomised trials.
- Radiotherapy has a significant role in the palliative setting.

Introduction

The aim of radiation therapy (RT) is to deliver a dose of radiation as specifically as possible to the target tumour volume, with minimal exposure of the surrounding normal tissue. This results in eradication of the tumour, improvement in quality of life and/or prolongation of survival.

RT produces its biological effects by causing DNA damage to cells. This damage is mediated either by direct ionisation of the DNA or indirectly via free radical formation due to intracellular water ionisation. The DNA damage leads to some early cell death through apoptosis. However, most cells only manifest the damage once they enter the mitotic phase of the cell cycle, and may undergo several divisions before cell death (mitotic cell death). For this reason, most tumours do not show a response to RT immediately, and instead may take weeks or longer. Normal cells can repair a significant proportion of radiation-induced DNA damage, whereas cancer cells have a poorer ability to repair. One of the reasons for splitting the total treatment dose into several smaller doses (fractionated treatment) is to allow for repair of the normal cell.

Radiation exposure is measured in Gray (Gy), which is defined as the absorption of 1 joule of energy per kilogram of matter. Radiation can be delivered by an external beam source or by an internal source (brachytherapy), using either interstitial implants or intracavitary techniques. The choice of technique depends upon the dose required and the tumour site and size.

Radiobiology

There is a perception that melanoma is radioresistant. However, more recent data supports a wide range of radiosensitivity in human melanoma cell lines, although it is generally lower than for the majority of other tumour types.

The question of the optimal dose fractionation schedule for melanoma remains unanswered. In general hypofractionated radiation therapy is associated with more severe late effects, but fewer visits to the radiotherapy department compared with hyperfractionated treatment.

Toxicity

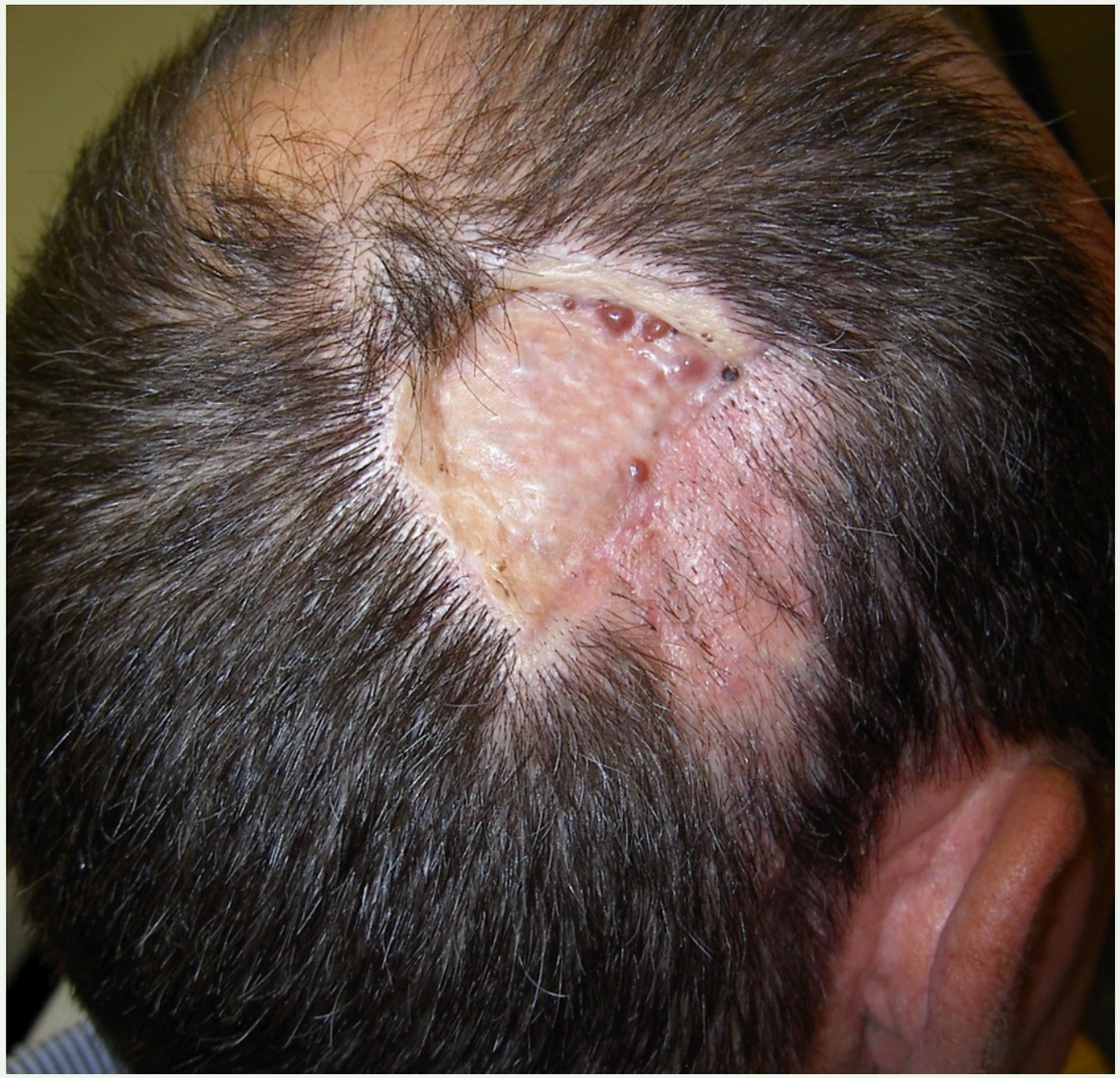
Acute effects arise because of the acute inflammatory response to RT in the local tissues that rely heavily on an ever-renewing cell population from a stem cell population. These tissues include skin, gut mucosa and bone marrow. Acute effects are related to anatomical site, total dose and overall treatment time. For example, in the neck region this is typically a self-limiting acute skin and mucosal reaction. These reactions should be managed conservatively with pain relief, mouth care, dressing management and nutritional support.

Late effects are related to dose per fraction (fraction size). Late effects usually start 6 months after RT and result from a chronic inflammation dominated by a fibrotic reaction in treated normal tissue. In the cervical region, the late consequences are mild subcutaneous fibrosis and alopecia within the treatment area. However, in the axilla and particularly the groin, there is an increased risk of lymphoedema and fibrosis if radiation is added to surgery for metastatic disease.

Radiotherapy To The Primary Site

Local disease control and cure are most likely to be achieved with surgical resection of the primary melanoma, hence it remains the standard of care. Furthermore, surgery enables histopathological assessment of the tumour, which provides prognostic data that can aid selection of adjuvant therapies, including RT. The role of such adjuvant RT to the primary site is empirical and has not been

FIGURE 16.1 ADJUVANT RADIOTHERAPY FOLLOWING LOCAL RECURRENCE



Multiple nodules of local recurrence after previous local excision and skin graft. This patient was treated with further local excision and adjuvant radiation therapy.

defined in clinical trials. Despite these limitations of evidence, indications for adjuvant RT to the primary site include:

- close or positive margins not amenable to further excision
- satellitosis
- recurrence after previous surgery
- desmoplastic or neurotropic features
- extensive lymphatic invasion

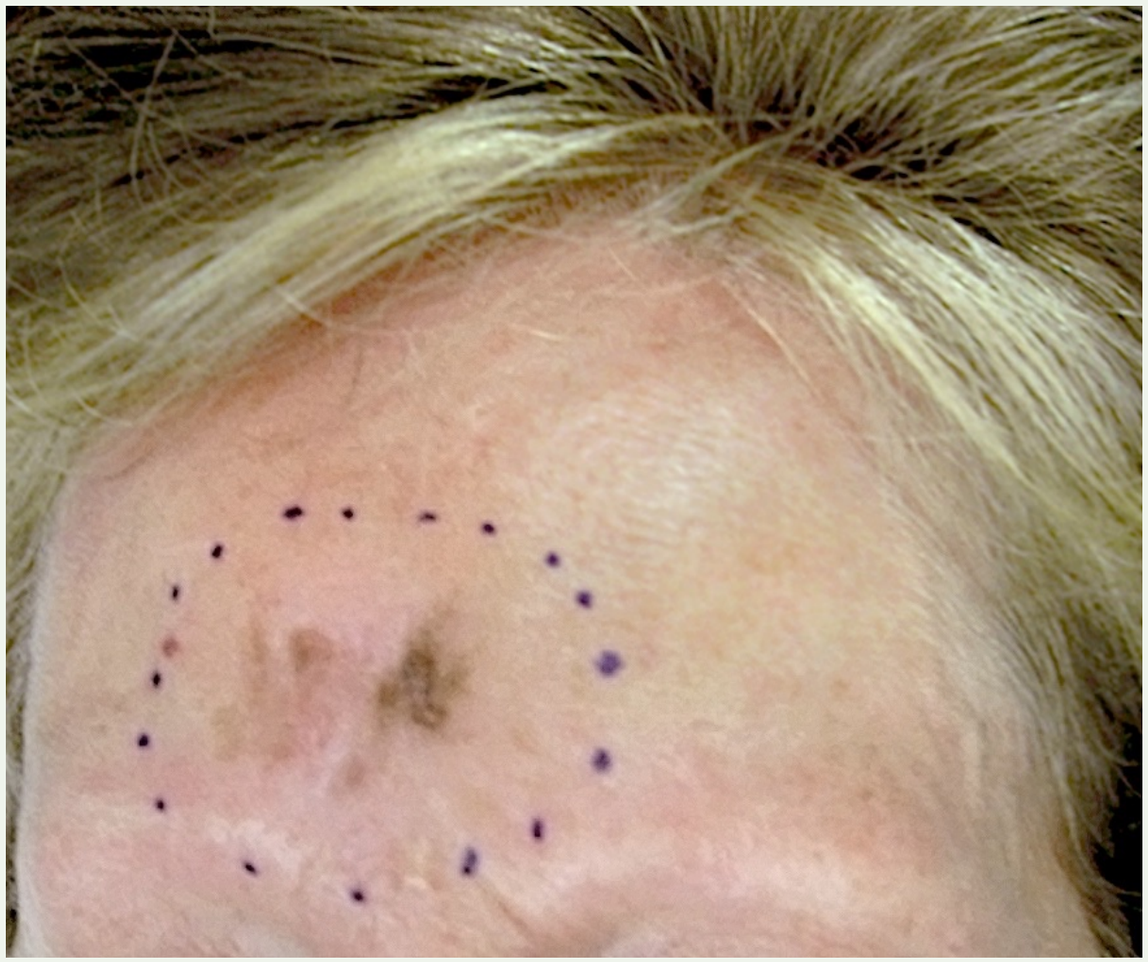
A range of fractionation patterns can be used depending on patient factors (age, co-morbidity, cosmetic outcome expectation) and tumour factors (location, target volume). Typical patterns range from 33Gy in 6 fractions over 3 weeks to 60Gy in 30 fractions over 6 weeks.

Lentigo Maligna

Surgery is considered the standard treatment for lentigo maligna (LM) and there is no high level of evidence for radiation therapy. RT is generally used when surgical excision is likely to cause significant

impact on cosmetic and functional outcomes or margins are likely to be involved. Large case series of RT in LM have demonstrated high cure rates of between 88% and 93%, whilst also achieving good local control and an acceptable aesthetic outcome.

Figure 16.2 Radiotherapy Treatment of Recurrent Lentigo Maligna



Prior to superficial radiation therapy to the marked area to the forehead for recurrent lentigo maligna, 3 years post surgical resection.

Table 16.1 Indications For Adjuvant Nodal Radiation Therapy

Patients with the following pathological feature should be referred to a radiation oncologist to discuss adjuvant radiation therapy:

- multiple nodal involvement:
    - one or more nodes in the parotid,
    - two or more nodes in the neck,
    - three or more nodes in the axilla and
    - four or more nodes in the groin
- nodal mass ≥ 3 cm in diameter in the neck or axilla
- nodal mass ≥4 cm in the groin
- presence of extranodal spread
- positive margin
- recurrence after previous dissection

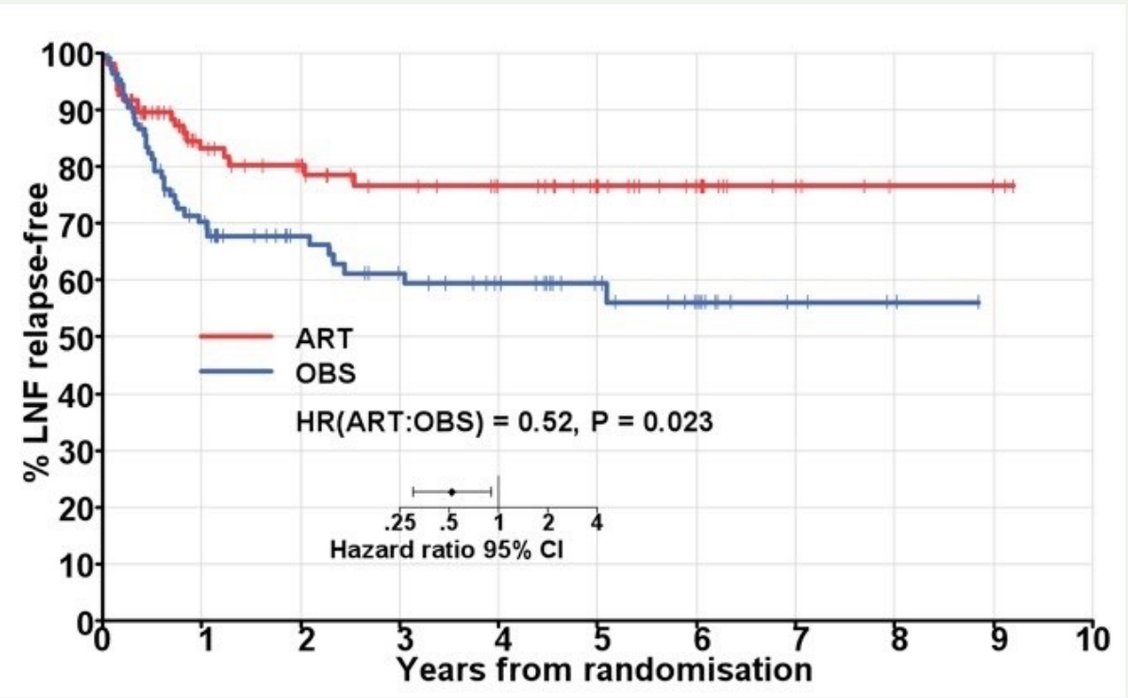
Adjuvant Nodal Radiation Therapy

Patients who have undergone a complete nodal dissection should be stratified according to their risk of relapse (Table 16.1) and adjuvant radiotherapy discussed with those at high risk. Several large retrospective studies support the use of adjuvant radiotherapy for an improvement in regional control. There is further support from the only randomised trial comparing observation with immediate nodal radiation therapy (48Gy in 20 fractions over 4 weeks) in patients with high risk nodal disease. The trial confirmed a significant improvement in nodal field control ([HR] 0.52, p=0.023). As expected for a local treatment modality, there was with no difference in relapse free survival at other sites, or overall survival (Figure 16.3).

Unresectable Nodal Disease

Occasionally, patients present with unresectable nodal disease without distant metastases. In our experience, pre-operative RT has been used to down-stage the disease. Standard fractionation (50Gy in 25 fractions over 5 weeks) is recommended to reduce the potential adverse effect of large

FIGURE 16.3 TIME TO NODAL FIELD RELAPSE WITH RADIOTHERAPY OR OBSERVATION



Kaplan-Meier curves demonstrating the 48% reduction in recurrence within the treated nodal field with radiotherapy compared to observation, post surgical resection of metastatic melanoma.

fraction size on wound healing. Operability of the disease can be re-assessed 4 to 6 weeks after completion of RT. Patients with this presentation should be discussed in the multidisciplinary team meeting to determine the relative merits of local radiation therapy and systemic therapy.

Palliative Radiation Therapy

Aims:

- symptom relief
- improved quality of the patient's remaining life
- may not extend survival

Palliative radiotherapy seeks to improve the quality of the patient's remaining life by both relieving and preventing the development of symptoms (e.g. in the setting of asymptomatic brain metastasis). The prescribed doses of RT to achieve this are generally lower than those used in the curative setting. Accordingly, palliative RT is considered successful if the symptoms have been relieved, even though there may still be measurable disease within the radiation therapy treatment volume. Furthermore, RT may or may not extend survival.

Table 16.2 Indications for palliative radiation therapy

- Brain metastasis
- Localised pain due to bony metastasis, subcutaneous metastasis
- Obstruction such as superior vena cava obstruction, orbital metastasis
- Diminish symptoms from tumour ulceration, e.g. odorous secretions, bleeding
- Decrease blood loss e.g. haemoptysis, GI bleeding
- Prolong local control following palliative surgery, even in advanced stage IV disease. For example, adjuvant radiotherapy may be given to an axilla after resection of bulky lymph node disease even in the setting of long-standing, asymptomatic lung metastasis

Brain Metastasis in Melanoma Patients

General Management

The management of brain metastases depends on the combination of patient, tumour and treatment factors. The main factor determining management has traditionally been the number of cerebral metastases. However, the recent advances in stereotactic radiosurgery techniques have enabled the effective treatment of multiple metastases in a single treatment session. Consequently, the total number of cerebral metastases is now less important than previously. Furthermore, recent data suggests that the total volume of metastases rather than their number is the stronger prognostic marker for survival after stereotactic radiosurgery.

Stereotactic Radiosurgery

Stereotactic radiosurgery is the delivery of a single ablative dose of radiation (16-22Gy) to an intracranial volume through the intact skull. This single fraction is biologically equivalent to at least 60Gy of standard external beam RT, depending on the target tissue and prescription point.

The potential morbidity of stereotactic radiosurgery includes worsening of symptomatic cerebral oedema in 4-6% of patients within 1-2 weeks of treatment, seizures within 1-2 days in 2-6% and delayed radiation necrosis in 2-11%. These risks increase with larger treatment volumes (larger lesions and/or more lesions), delivery of larger doses and prior treatment.

Skin and Subcutaneous Lesions

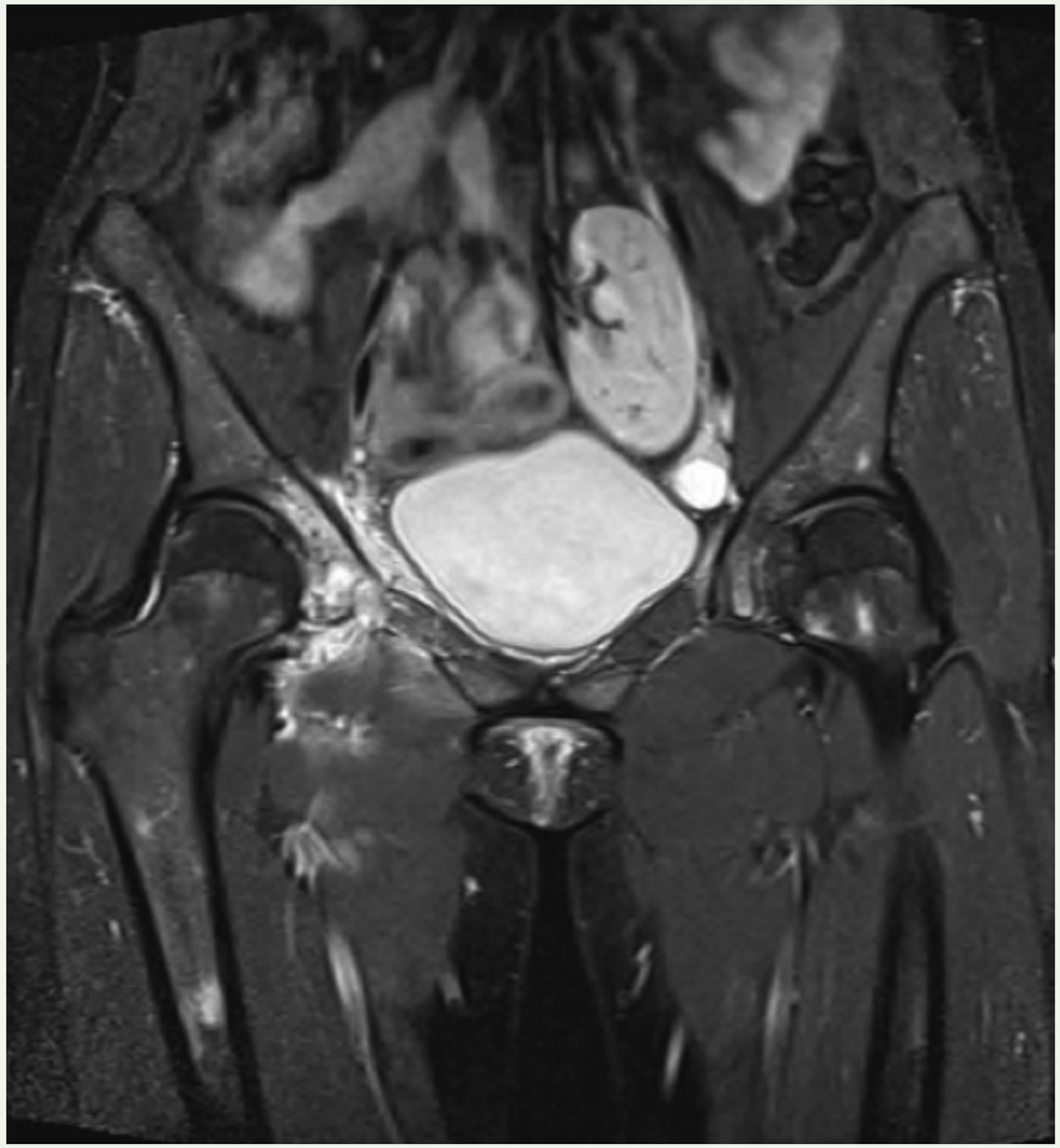
Skin is a common site of melanoma metastases, which can cause pain and ulceration with bleeding. Typical doses are 40Gy in 10 fractions, 20Gy in 5 fractions or 8Gy in a single fraction, the latter for field sizes less than 2cm in diameter. When prescribing to large areas (>5cm diameter), fraction size should be decreased in order to decrease the

acute skin reaction. Typical fractionation patterns are then 40Gy in 15 fractions or 30Gy in 10 fractions. The prescription depth is chosen to cover the clinically palpated depth.

Bone Metastasis

The most common palliative endpoint for bone metastasis is pain relief, which randomised studies have shown to be effective in about 80% patients. Palliative radiation therapy may also be administered as an adjuvant treatment after surgical fixation of unstable bony metastases.

Figure 16.4 Radiotherapy for bone metastases



Large metastasis in the right superior pubic ramus.

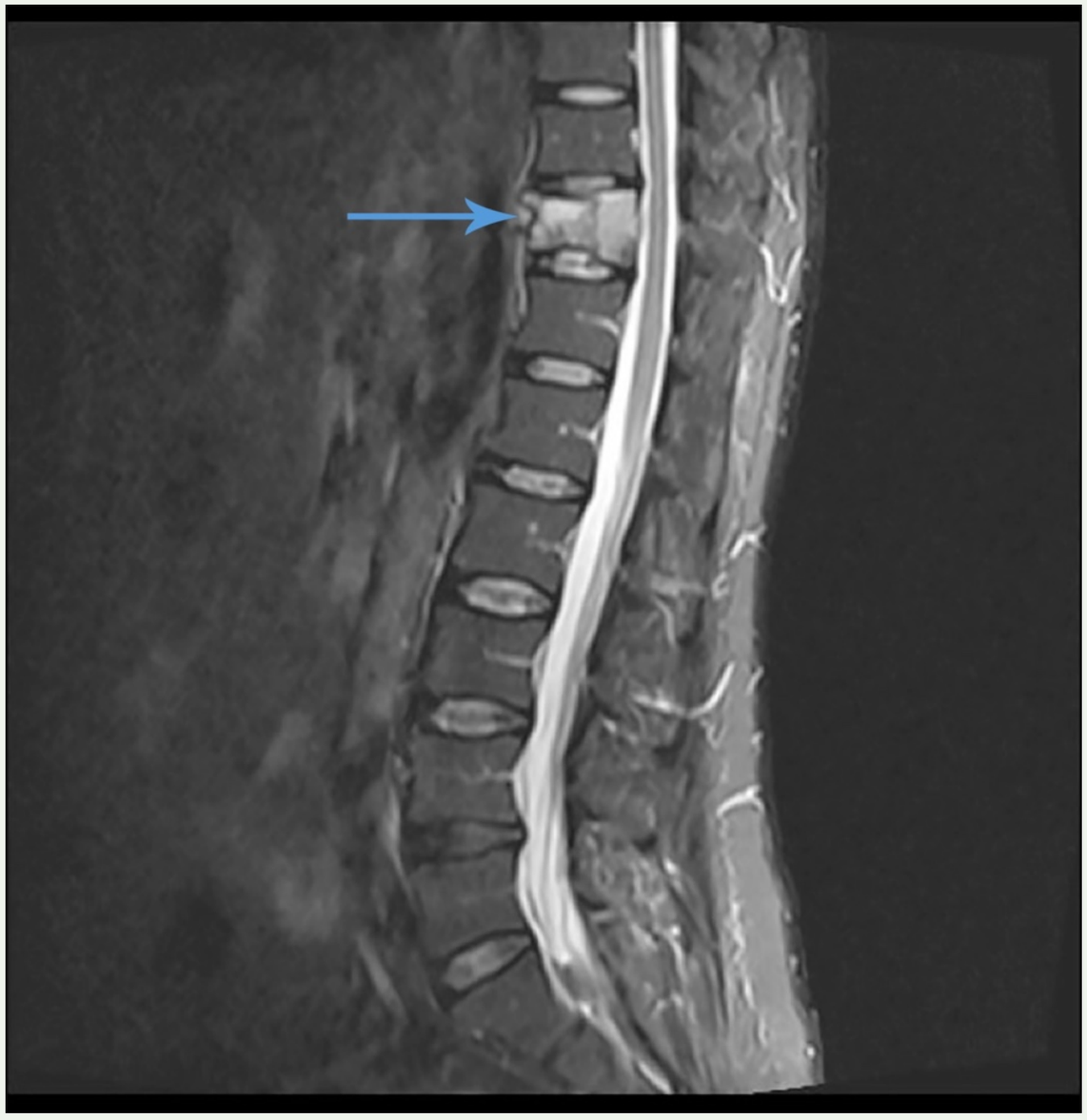
Spinal Cord Compression

Spinal cord compression can be due to bony metastasis, secondary epidural or intradural deposits. Neurosurgery is preferable for patients with:

- single level of compression with minimal disease burden elsewhere
- previous radiotherapy to that level
- bone fragment rather than tumour causing compression
- clinical deterioration during the course of radiotherapy

Patients fit for neurosurgery should have surgical decompression, followed by postoperative radiation therapy to maximise local control.

Figure 16.5 Spinal Cord Compression due to Melanoma Metastasis



MRI scan demonstrating spinal cord compression due to a metastasis in T11 vertebral body (blue arrow).

Citations and Further Reading

1. Barranco SC, Romsdahl MM, Humphrey RM. The radiation response of human malignant melanoma cells grown in vitro. Cancer Res 1971;31:830-3.

2. Thomson LF, Smith AR, Humphrey RM. The response of a human malignant melanoma cell line to high LET radiation. Radiology. 1975 Oct;117(1):155-8.

3. Dewey DL. The radiosensitivity of melanoma cells in culture. Br J Radiol 1971;44:816-7.

4. Elkind MM. The initial part of the survival curve: does it predict the outcome of fractionated radiotherapy? Radiat Res. 1988 Jun;114(3):425-36.

5. McKay MJ, Kefford RF. The spectrum of in vitro radiosensitivity in four human melanoma cell lines is not accounted for by differential induction or rejoining of DNA double strand breaks. Int J Radiat Oncol Biol Phys. 1995 Jan 15;31(2): 345-52.

6. Sause WT, Cooper JS, Rush S, Ago CT, Cosmatos D, Coughlin CT, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. Int J Radiat Oncol Biol Phys 1991;20(3):429-32.

7. Christie DR, Tiver KW. Radiotherapy for melanotic freckles. Australas Radiol. 1996 Aug;40(3):331-3.

8. Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. Br J Dermatol. 2002 Jun;146(6):1042-6.

9. Ang KK, Peters LJ, Weber RS, Morrison WH, Frankenthaler RA, Garden AS, et al.

17

The Psychosocial Impact of Cancer

KATHARINE HODGKINSON FRANCES BOYLE

Key Points

- Cancer stretches everyone's ability to cope.
- All health professionals have a role in, and responsibility for, assessing the psychosocial impact of cancer on patients and families.
- Support and information provided by the treatment team is greatly valued and effective in promoting adjustment.
- Depression and anxiety may need specialised treatment and referral networks of psychologists and psychiatrists skilled in the management of cancer patients must be developed and outcomes of treatment reviewed.
- Suicide rate is nearly doubled - all patients must be assessed.
- Self-care strategies for health professionals are vital.

Overview

Research indicates high psychological morbidity and unmet supportive care needs in patients with melanoma. High quality (levels I and II) research evidence supports the effectiveness of psychosocial interventions for people with cancer; specific benefits for melanoma patients include reduced distress, anxiety and fatigue, improved coping behaviours, improved physical wellbeing and cost-effectiveness. Accordingly, clinical care guidelines recommend the management of patients by multidisciplinary teams at specialist melanoma facilities, with psychosocial support available to all patients.

Psychosocial Impact on Cancer

The diagnosis of cancer is a significant life crisis for patients, their families, carers and friends. For each individual, the impact will be unique, although emotional responses may include: shock, disbelief, anger, confusion, depression, anxiety, hopelessness and grief. Physical and behavioural responses may include sleep and appetite disturbance, physical agitation, heart palpitations, headaches and withdrawal. Cognitive changes may include difficulty retaining new information, poor concentration and difficulty making decisions, even for those who may have previously functioned at a high level. Responses within couples and families may differ, resulting in increased distress and isolation at a time when support is most needed. Some patients, particularly those who are dealing with numerous other life stresses or have a psychiatric history, may have increases in maladaptive coping strategies, substance use, treatment non-adherence and responses such as anger, mistrust and dissatisfaction with care. Such behaviour may challenge the delivery of optimal care. Common concerns are presented in Table 17.1.

Table 17.1 Common Concerns

- dealing with a life-threatening diagnosis and uncertainty
- managing treatment demands
- managing emotional responses and adjustment in self and others
- communication with loved ones (especially children in the patient's life)
- communication with care teams, information processing and decision-making
- social, family and relationship issues (including the establishment of new relationships)
- ability to fulfill roles and responsibilities
- intimacy and sexuality (arising from general, medical, psychological and relationship issues, medication, cancer treatments, and/or disease variables)
- fertility, menopausal/hormonal changes, and body image concerns
- loss and grief
- spiritual and existential concerns
- physical symptoms from the disease and treatment (including fatigue)
- impairments in physical and cognitive functioning, lifestyle and quality of life (QOL)
- familial cancer risk for self and loved ones
- employment, housing, insurance, legal and financial issues
- access to health care services (eg, quality, location, availability, cost, etc.)

Adapted from Hodgkinson K. What is the psychosocial impact of cancer? In: Hodgkinson, Gilchrist (Eds), Psychosocial Care of Cancer Patients: A Health Professionals Guide to What to Say and Do, 2008

Emotional responses will be mediated by a number of factors related to:

- the disease (the site, stage, prognosis, etc)
- the treatment (modalities required, intensity and duration, side effects, etc.)
- personal characteristics (developmental stage in lifecycle, age, relationship status, other life stresses, loss history, psychiatric status/history, etc.)
- the availability of resources and supports (social support, financial resources, access to health care, etc.)

Sensitivity to the needs of individuals from culturally and linguistically diverse (CALD) backgrounds, indigenous peoples, lesbian and gay people, and those with psychiatric co-morbidities is critical to achieving best practice.

The uniqueness of each individual's circumstances means there is no "normal" adjustment trajectory, but most will adjust at some level within a number of weeks. Following this, distress will fluctuate depending upon the disease course. However, a significant minority will experience responses that require targeted professional psychological intervention. This may include a combination of peer support, cancer support groups/programs, social work, pastoral care and general practitioner, psychology/clinical psychology or psychiatry input. It is vital to identify those in need of more specialised care, as distress will often persist and requires psychosocial intervention.

Psychosocial Impact on Families, Carers and Loved Ones

Families, carers and loved ones are involved in the provision of physical, emotional, and practical support for the person with cancer and maybe profoundly affected by the cancer diagnosis. High levels of psychological and physical morbidity are reported: they may share the same concerns as

Table 17.2 The Challenges of Caring

- management of own and others' emotional responses
- communication of information to others and liaison with relevant organisations and care teams
- disruption to carer's lifestyle and plans
- financial constraints directly related to their caregiver role (eg, disrupted employment, travel/ accommodation costs, treatment related costs)
- physical "hands on" caring responsibilities for the patient/other family members
- limited social supports (formal and informal)
- poor self-esteem, reduced social interaction, and social isolation
- lack of knowledge about resources and sources of assistance
- concomitant health problem

Adapted from Hobbs K. Supporting families and carers. In: Hodgkinson, Gilchrist (Eds), Psychosocial Care of Cancer Patients: A Health Professionals Guide to What to Say and Do, 2008.

patients or may have unique concerns and unmet needs (Table 17.2). Family members, carers and loved ones are not merely providers of support but need support themselves.

Health professionals need to recognise, acknowledge, facilitate and support the vital contribution of carers in the patients' care. For example:

- *"I expect it is very tough going keeping up with your work commitments and managing the children while your wife is going through this"*
- *"We know how important it is to have support in these situations, but also hear how demanding it is on you as the carer".*

As part of the support system, health professionals can have a positive and meaningful influence; particular conversations and caring behaviours may be forever remembered even when outcomes were not as desired.

Families, carers and loved ones may be profoundly affected by the cancer diagnosis and their

responses are mediated by many of the same factors that affect patient responses (see above). Partners are particularly vulnerable to distress and have been called "second order patients" due to the high levels of psychological and physical morbidity they may experience. The witnessing of suffering in a loved one and the sense of helplessness accompanying this is typically identified as particularly traumatic. Significant others share many of the same concerns as patients, but also have unique concerns and unmet needs (Table 17.2). Family members, carers and loved ones are therefore not merely providers of support, but also need support themselves.

Social support is the only factor that has been consistently associated with psychological adjustment in cancer patients. Health professionals are part of the wider support system and can have a positive and meaningful influence on those for whom they care; particular conversations, kind acts and caring behaviours may be remembered forever with appreciation. Even when outcomes are not as hoped for, the perception of optimal and compassionate care can greatly relieve the burden of suffering.

Patients, carers and families frequently request guidance on supporting others, particularly young people. They may need information on how to communicate effectively; for example, how to communicate bad news, the provision of written resources on talking to children (such as those available through Australian state cancer councils), dealing with schools, and access to child/young adult focused support services. Trust and reassurance of ongoing love and care is to be encouraged and responses monitored, as a minority will require additional input from school counsellors, social workers or other specialist counsellors/ services.

TABLE 17.3 Common Concerns At The End Of Life

Emotional concerns

- increased uncertainty
- loss of independence/control
- dealing with others' requests to "keep positive"
- lack of understanding and support from loved ones
- loss of meaning/demoralisation
- intimacy and body image concerns
- process of death
- fear of pain
- grief about leaving family/loved ones
- loss of future, etc.

Concerns for loved ones

- concerns about being a burden to the family
- how to support children/others
- how loved ones will cope after death, etc.

Existential and spiritual concerns

- life meaning
- unfinished business
- afterlife, etc.

Physical and cognitive functioning

- loss of independence
- reduced mobility and activity levels
- decline in physical and cognitive functioning, etc.

Practical concerns

- how care will be delivered
- where to be cared for
- financial concerns
- legal issues
- funeral arrangements, etc.

Adapted from MacDonald M, Hobbs K. Grief, end of life and bereavement. In: Hodgkinson, Gilchrist (Eds), Psychosocial Care of Cancer Patients: A Health Professionals Guide to What to Say and Do, 2008.

Concerns across the Disease Continuum

Several periods across the disease continuum are often characterised by elevated distress: time of diagnosis, end of treatment, disease recurrence and end of life. The end of treatment is often associated with increased anxiety as close contact with the treatment team diminishes and social support declines. The adjustment process may be more challenging than expected, with difficulties often persisting in sexual functioning, fatigue and fear of disease recurrence.

Disease recurrence is often more distressing than the initial diagnosis (Table 17.3), and the support of symptom control teams needs to be sensitively integrated into ongoing care.

Common Psychological Symptoms

Given the far reaching impact of cancer, it is not surprising that approximately one third to half of patients and their loved ones develop symptoms of depression, anxiety or other psychological disorders (e.g. health anxiety, sleep disturbance, needle phobia, cognitive disorders and post-traumatic stress - see Table 17.4, Table 17.5). Passive suicidal

Table 17.4 Symptoms of Depression

- pervasive low mood and sadness
- loss of pleasure/joy and interest in usual activities
- feelings of worthlessness, hopelessness and/or guilt
- suicidal thoughts or plans, or thoughts of death*
- decreased concentration*
- insomnia/hypersomnia*
- weight loss or gain*
- fatigue*
- psychomotor agitation/retardation*

* Health professionals need to ascertain whether these symptoms are due to the disease in cancer patients.

Adapted from MacDonald M, Hobbs K. Grief, end of life and bereavement. In: Hodgkinson, Gilchrist (Eds), Psychosocial Care of Cancer Patients: A Health Professionals Guide to What to Say and Do, 2008.

Table 17.5 Symptoms of Stress and Anxiety

- excessive worry and concerns playing over and over in one's mind
- being snappy and irritable with others/being emotionally oversensitive
- poor concentration
- difficultly making decisions
- poor sleep (difficulty getting to sleep/staying asleep or waking early)
- fatigue and poor motivation
- experiencing a churning/upset stomach, feeling physically tense or "on edge"
- headaches
- loss of appetite or over-eating for "comfort" (possible weight loss/gain)
- abusing substances such as alcohol or drugs (prescribed or non-prescribed)

Adapted from MacDonald M, Hobbs K. Grief, end of life and bereavement. In: Hodgkinson, Gilchrist (Eds), Psychosocial Care of Cancer Patients: A Health Professionals Guide to What to Say and Do, 2008.

ideations are fairly common, but **suicidal risk must be assessed** in these patients, given they have rates nearly twice that of the general population.

Concerns Specific to Melanoma Patients

Patients newly diagnosed with melanoma and those who have stage III or IV disease, are particularly vulnerable to psychological distress. Risk factors identified include: female gender, younger age, lower level of education and lack of social support. Invasive surgical treatments, significant disfigurement, numbness, loss of functional capacities and scars that are deeply indented, or longer than anticipated, or more visible are associated with higher levels of distress. Furthermore, pain, lymphoedema or changes in function are challenging to manage and ongoing reminders of the disease.

Concerns about sun exposure or body image changes can result in significant lifestyle changes,

while the perception of preventability, guilt over past behaviours or a delay in presenting for treatment may compound emotional distress. Similarly, there may be a significant impact from knowledge of an inherited genetic susceptibility or a strong family history, topics which are currently under research. Additionally, although melanomas are not commonly diagnosed in body areas associated with sexual function, psychological, physical and treatment variables can all indirectly impact sexual functioning (e.g. lymphoedema affecting the limbs or pelvis).

Living with uncertainty is challenging psychologically; for those diagnosed with advanced disease, treatment options may be unclear, expensive or only available on a clinical trial and the disease path and prognosis uncertain or poor, with recurrence sites unpredictable. There may be a lot of waiting for tests and results, unknown efficacy and side effects for newer treatments and unpredictable shifts in decision-making. Furthermore, there may be ambiguity in medical information, statistics and timeframes, particularly in the current era of rapid progress with drugs for advanced disease. All these factors serve to maintain anxiety, yet fail to deliver guarantees of good health or survival.

Benefits of Psychosocial Care

Empirical evidence indicates that psychological interventions can improve psychosocial outcomes for melanoma patients. Accordingly, both national and international cancer care consensus based guidelines endorse co-ordinated and individualised psychosocial care as best practice. However, in reality, melanoma patients' psychosocial needs are often undetected and unmet, particularly those centred around emotional support and communication with team members. Consequently, routine screening of both patients and carers can

improve this support through improved clinical decision making, referral pathways and service delivery. Additionally, health professionals should convey a positive attitude towards psychosocial interventions, as there is level I and II evidence for psychological, physical, psychosexual and functional benefits.

Psychological interventions typically involve a number of individually tailored components, which are delivered over the short-term (6-12 sessions).

Interventions may target:

- depression
- anxiety/stress
- living with uncertainty
- communication
- lifestyle and functioning
- fatigue/pain/sleep management
- sexual/body image disturbance
- survivorship issues
- loss and grief
- dealing with the end of life concerns

Strategies typically involve Cognitive Behavioural Therapy (CBT) and Acceptance and Commitment Therapy (ACT) techniques, which may include:

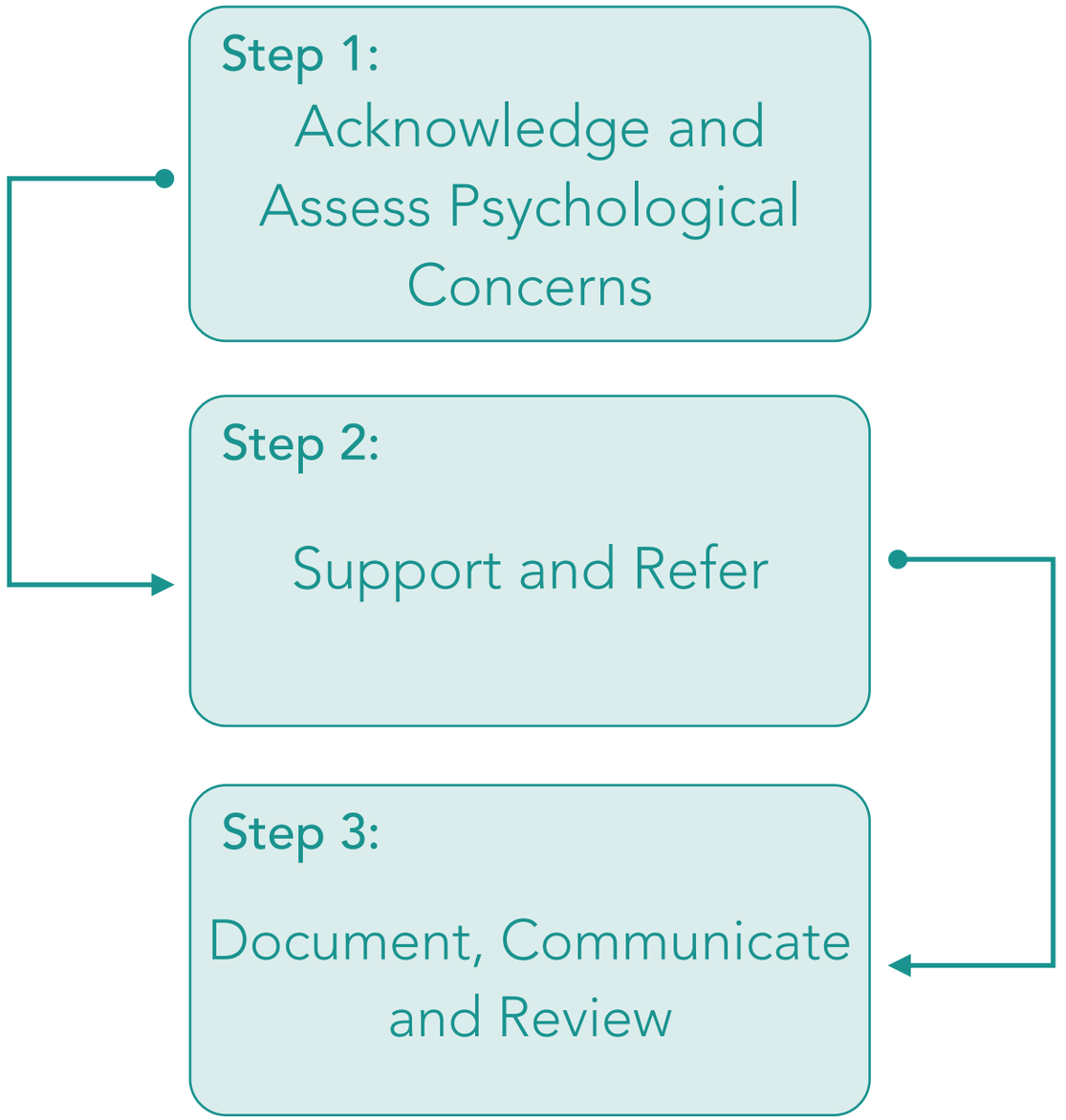
- psycho-education
- problem-solving
- stress management
- relaxation training
- behavioural treatments (e.g. desensitisation for conditioned nausea and vomiting)
- distress tolerance
- supportive counselling
- group psychosocial interventions *
- pharmacotherapy *

** either alone or as an adjunct to the other interventions*

How to help?

All health professionals have a role in the ongoing delivery of individualised psychosocial care to all patients. Accordingly, health professionals require

FIGURE 17.1 STEPS FOR HELP



- basic psychosocial assessment skills in order to offer support and referral. However, a lack of training, skills or time may be identified, or concerns expressed such as:

  - *"I might get out of my depth"*
  - *"Patients will mention it if it is a problem"*
  - *"It's not within the scope of my job"*
  - *"There's no services around here to help anyway"*

Reassuringly, skills can all be learnt and refined with practice and for most they are an extension of existing good communication skills. Delivery of psychosocial care can be achieved using a 3-step process (Figure 17.1):

Step 1: Acknowledge and Assess Psychosocial Concerns

All health professionals need to incorporate psychosocial support and basic assessment questions into every contact with patients and loved ones, across the care continuum. This will enable

TABLE 17.6 Risk Factors For Psychosocial Distress

Individual factors:

- living alone
- relationships status (single/divorced/widowed)
- female gender
- current mood/psychological status
- other current/past stressors (eg, financial difficulties)
- children younger than 21 years
- lack of perceived support
- history of psychiatric problems
- alcohol or other drug use

Disease/treatment factors:

- recent diagnosis or recurrence
- advanced disease
- poor prognosis
- treatment side effects (eg, lymphoedema)
- poorly controlled pain
- limited ability to perform daily living activities
- fatigue
- use of certain medications/treatments (e.g. steroids, Interferon)

Adapted from National Breast Cancer Centre (NBCC) and National Cancer Control Initiative (NCCI) 2003, Clinical practice guidelines for the psychosocial care of patients with cancer, NBCC, Camperdown, NSW, Australia.

identification of risk factors for poor adjustment, which will direct the need for a more thorough assessment (Table 17.6).

Opening a conversation with a simple acknowledgement of the emotional and social context of the cancer can help establish rapport, validate people's experiences and provide permission to express concerns. A normalising statement could be:

- *"It is often very difficult to take in this news having felt so well so I would like to talk at some point about how it affects other areas of your life and sense of wellbeing"*
- *"Many people find they get quite down in these situations and worried about how things are going to turn out."*

Follow this with simple questions about key areas of psychosocial functioning (Table -.-) and take opportunities when discussing treatment plans to enquire about whether anyone is available for support. Questions about treatment side effects can lead to questions about fatigue and mood, eg:

"You have told me you aren't able to get out much anymore, this often gets people pretty down – have you found you've been feeling depressed recently?"

Enquiring as to whether someone is still able to enjoy some aspects of life (eg, time with grandchildren, going to the movies, being in the natural environment, etc.) can help ascertain the extent and pervasiveness of mood disturbance. Questions about family and partners can lead to questions about the impact on relationships and intimacy, a neglected area of cancer care on which patients want more information. Similarly, questions about pain control can lead to questions about sleep patterns and anxiety, eg:

- *"You tell me it's hard to get back to sleep after 4am, do you find you start worrying about things then?"*
- *"Do these worries bother you a lot of the time?"*

Such enquiries are typically perceived to be supportive by patients and can help physicians direct care recommendations.

Table 17.7 Psychosocial Assessment Areas

- understanding of cancer and need for information
- current emotional well-being (eg, symptoms of depression, anxiety, etc.)
- physical well-being and functioning (eg, pain, fatigue, sleep disturbance, sexual functioning, etc.)
- relationship status and family functioning
- available supports and resources
- roles and responsibilities (eg, caring and work responsibilities)
- other background stressors (eg, finances/legal/housing, etc.)
- use of alcohol and other drugs

Adapted from Turner, J. Assessing concerns. In: Hodgkinson, Gilchrist (Eds), Psychosocial Care of Cancer Patients: A Health Professionals Guide to What to Say and Do, 2008.

Step 2: Support and Refer

The second step in providing psychosocial support includes the provision of emotional support and facilitation of coping skills, as well as access to information and referral to specialist services.

Listen carefully to patients' concerns, as this allows the health professional to assess the level of support required. Supplement this by identifying current and past coping strategies, for example:

- *"It sounds like keeping up with regular exercise and work really helped when your mother died."*
- *"Talking with your friends seemed to help with your depression in the past; do you think it would help now?"*

Validate current achievements, such as:

- *"You did very well getting through treatment, I hear from a lot of patients how tough going it can be."*
- *"It's great that you gave the support group a try."*
- *"It's helpful that you were able to tell me about the impact on your sexual functioning, so I can find out who can help."*

Offer patients and loved ones, with high levels of risk factors and/or indicators of distress, referral to specialist psychosocial services (referral is an indicator of best practice cancer care). There are multiple opportunities for referral over the course of the health professional relationship, so keep offering. Facilitating timely and appropriate psychosocial care can enhance job satisfaction, reduce the risk of burnout, and reduce the burden on the health care system.

Services vary greatly geographically and identifying your available referral options is critical. Psychiatry, clinical psychology/psychology, social work, pastoral care, sexual health services and the private sector may be able to assist. Furthermore, Australian state cancer councils have become increasingly innovative and are providing more web-based services to increase accessibility to support. Those with high levels of distress, psychiatric symptomatology or risk of harm to themselves/

TABLE 17.8 MAKING A REFERRAL

- Explain that stress in such extraordinary situations is very common: *"Cancer stretches everyone's ability to cope."*
- Suggest referral to help manage physical concerns eg, sleep: *"I notice you said you were not sleeping, we can help with that."*
- Present referral as routine: *"I mention seeing a psychologist to many other patients that I see, it's a way of looking after your health as a whole."*
- Explain that the psychologist will suggest specific strategies to help, it's not 'just talking'.
- Reassure that a referral does not make any judgement about how much support a carer can provide: *"Coping with cancer is hard work - in these situations it is helpful for everyone involved to have support."*
- Inform the patient about the benefits of psychological treatment (improved mood, increased quality of life, someone to problem-solve concerns, etc.) and suggest just giving one session a trial.

Adapted from National Breast Cancer Centre (NBCC) and National Cancer Control Initiative (NCCI) 2003, Clinical practice guidelines for the psychosocial care of adults with cancer, NBCC, Camperdown, NSW.

others will require direct referral or activation of services (see IPOS guidelines on management of suicidal risk, delirium, etc. in Holland, Greenberg & Hughes, 2006).

Effective referral is a skilled process; patients, family members and carers may be sensitive to perceptions they are not coping and they may be sceptical about whether *"anything can help"* or that it is legitimate if they *"aren't the one with cancer"*. Ways of overcoming barriers are listed in Table 17.8. The effectiveness and outcome of the referral needs to be reviewed and options for further support investigated if difficulties persist.

Step 3: Document, Communicate and Review

Document your psychosocial assessment data and plan in medical records and in your communications with the care team. Psychosocial needs should be regularly reviewed, particularity with changes in treatment plans, progressive disease, or referral to palliative care services.

Caring For Yourself

Health professionals should review their own professional development and well-being regularly; working in cancer care is particularly stressful and burnout rates are high. Providing care to melanoma patients and their families is a particularly high stress area, given the characteristics of both the patient population and treatment, plus the need for providing continuity of care for geographically rural and remote patients. Such demanding patient population characteristics include: young adults, metastatic disease, multiple health crises, high

disease burdens and providing end of life support. Demanding treatment characteristics include: a dynamic and medicalised process, disfiguring surgery, constantly evolving treatment opportunities, high levels of uncertainty, unpredictable care trajectories and high mortality rates. Variables related to the heterogeneity of patient and disease characteristics, high morbidity and mortality rates, as well as personal variables (eg, other stressors in our lives, self doubt, poor self-care etc.), all contribute to high burnout rates.

Caring for your own physical and emotional well-being is not an optional extra, but is essential to continued practice in cancer care. Learn and practice whatever works for you; have strategies that can be incorporated into daily practice, for example, regular exercise, good diet, accepting positive feedback, etc., as well as strategies that you may use less regularly, such as taking regular holidays, undergoing professional development/ communication training, and seeking mentoring/ professional support if either professional or personal difficulties arise. Recent evidence supports the practice of mindfulness-based techniques including meditation in managing stress in health care.

Key Resources

Australian Cancer Network Melanoma Revision Guidelines Working Party. 2008. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, Wellington.

K, Gilchrist G. (Eds) 2008. Psychosocial Care of Cancer Patients: A Health Professionals Guide to What to Say and Do. Ausmed Pub., Melbourne, Australia.

Holland, J.C., Greenberg, D.B. & Hughes, M.K. 2006, Quick Reference for Oncology Clinicians: The Psychiatric and Psychological Dimensions of Cancer Symptom Management, American Psychosocial Oncology Society (APOS) Press, Charlottesville.

National Breast Cancer Centre (NBCC) and National Cancer Control Initiative (NCCI) 2003, Clinical practice guidelines for the psychosocial care of adults with cancer, NBCC, Camperdown. Guidelines can be downloaded from National Health and Medical Research Council website: http://www.nhmrc.gov.au or copies ordered from NBCC on ph. 1800 624 973.

National Comprehensive Cancer Network (NCCN) 2007, NCCN practice guidelines in oncology. Distress management V.1.2008, www.nccn.org

Steensma DP, Jacobsen PB & Holland, JC Eds. 2012. Caring for the whole person The Science of Psychosocial Care. Special Series, Journal of Clinical Oncology, 30:11.

Tan JD, Butow PN, Boyle FM, Saw RPM, O'Reilly A. A Qualitative Assessment of Psychosocial Impact, Coping and Adjustment in High-Risk Melanoma Patients and Caregivers. Melanoma Research. 2014, 24:252-60

Citations and Further Reading

1. Beck, A.T., Rush, A.J., Shaw, B.F. & Emery, G. 1979, Cognitive Therapy of Depression, Guilford Press, New York.

2. Bonevski B, Sanson-Fisher R, Hersey P, Paul C, Foot G. 1999, Assessing the perceived needs of patients attending an outpatient melanoma clinic. Journal of Psychosocial Oncology 1999; 17:101–118.

3. Butow P. 2008, Psychosocial issues in melanoma. In: ACN Clinical Practice Guidelines for Management of Melanoma.

4. Carlson, L.E., & Bultz, B.D. 2004, 'Efficacy and medical cost offset of psychosocial interventions in cancer care: making the case for economic analyses', Psycho-Oncology, 13(12): 837-49.

5. Cassileth BR, Lusk EJ, Tenaglia AN. Patients' perceptions of the cosmetic impact of melanoma resection. Plast Reconstr Surg 1983; 71(1):73–75.

6. Dunn, S. 2004. The doctor suffers too. Paper presented at the Leura International Breast Cancer Conference, Leura, Australia.

7. Fang CY, Manne SL, Pape SJ. Functional impairment, marital quality, and patient psychological distress as predictors of psychological distress among cancer patients' spouses. Health Psychology 2001; 20(6):452-457.

8. Gamel, C., Hengeveld, M., Bryn, D. 2000, 'Information needs about the effects of gynecological care on sexuality: A review of the literature', Journal of Clinical Nursing, 9(5):678-88.

9. Girgis A, Hansen V, Goldstein D. 2008. Are Australian oncology health professionals

18 Optimising Communication

FRANCES BOYLE KATHARINE HODGKINSON

Key Points

- There is evidence that the way the treatment team communicates with patients with melanoma to provide information, empathy and support can influence patient satisfaction in the long term.
- Informed decision making can be assisted by use of avoidance / explanation of jargon, making opportunities for patients and families to ask questions and clarify values, question prompt lists and written notes and flow charts, and summarising the take home message.
- When breaking bad news, ensure time to explore emotional reactions and offer support before moving on to treatment planning.
- When discussing prognosis, ask patients what they wish to know, and if time frames are requested, use typical, best and worst case rather than a single time frame.

Difficult Conversations

In an average work day, oncology professionals will explore sensitive subjects with patients that most people avoid in all but the most intimate of conversations – death, disfigurement, sexual functioning, finances, spirituality, and hopes and fears for loved ones. At the same time they will deliver complex test results, consult with busy colleagues, and consent patients for procedures that may be life saving or life threatening. Time constraints, missing results and interruptions will add to their stress.

Effective and empathic communication will be vital to the survival, safety and satisfaction of melanoma patients, and the wellbeing of oncology professionals. Good communication is the foundation of strong trusting relationships between patients, families and those who care for them.

Addressing patient concerns shortens consultations and reduces the risk of error, litigation and burnout.

Randomised trials demonstrate that communication skills of clinicians at all levels can be learnt, e.g. in workshop settings with actors playing the role of patients (see pammcleancentre.org and cognitiveinstitute.org).

What Increases the Degree of Difficulty in Communicating?

Patients come to a cancer consultation with a wide range of information and understanding of their condition. Potential obstacles to communication include:

- prior health care experiences that may have engendered mistrust
- pre-existing coping skills (active, passive, information seeking or avoidant)
- co-morbidities including pain, depression, cognitive dysfunction

- sensory impairment including deafness and impaired vision
- cultural backgrounds that emphasise stoicism and avoidance of bad news
- psychiatric and personality disorders

Health professionals need to be aware of how their own thoughts, feelings, past experiences, work environment, and personal wellbeing can influence the flexibility of their interactions.

General Communication Strategies in Cancer Consultations

Preparation

A difficult conversation can be made easier if some of the problem solving is done beforehand, and uncertainties and surprises are minimised. This preparation is not always possible, as an unexpected symptom or sign may be revealed during the consultation. In that case, acknowledge the anxiety of the moment (at least to yourself) and slow down the interaction to allow some thinking time. The situation does not need to be fixed immediately, but a plan to address the difficulty should be discussed, e.g. *"I am glad you have raised this; I will try and find out and get back to you."*.

Ensuring access to the referral letter, scan and pathology results ahead of the consultation allows an opportunity to chase missing information, to consult with colleagues in the multidisciplinary team and to do some background research if necessary.

Opening the Conversation

- Set protocols with support staff for ensuring privacy and minimising interruptions
- Have a box of tissues accessible (although not necessarily centre stage)
- Create a collaborative environment by:
  - addressing the patient by name
  - inviting him or her to include others if desired

- introducing yourself and your role:

  "I am Dr X. I am a surgical trainee working on Professor Y's team and will speak with him after I have checked on your progress."
- positioning your chair where you can see the patient and family members at eye level
- positioning the desk or bed table so that you can share written information with them
- acknowledging the patient's difficult circumstances:

  "Sounds like you've had a tough few weeks. I hope we can help sort things out today for you."

In a hospital setting, research shows that patients are more satisfied with health professionals who sit down to speak to them; patients tend to overestimate the time these health professionals spend with them, compared with those who stand at the end of the bed.

Agenda Setting

As with any meeting, knowing an outline of the topics to be covered can assist in time management.

Doctor: *"I was planning to check today how you are doing and discuss your test results. Are there other issues you want to cover, or questions you have? "*

Patient: *"I want to hear the results and I am also worried about how my son will manage bringing me in for treatment every day. Is there any transport available?"*

Question prompt lists can increase the range of questions asked, particularly about prognosis, and shorten consultations if health professionals endorse their use.

Hearing the Patient's Story

Critical diagnostic clues can be gleaned from listening to the patient tell his or her story, e.g.

"Your local doctor has sent me your scans and pathology results, but I don't have a good feel for how fast this has happened. Would you mind telling me the story…"

In addition, it allows the health professional to understand something of the patient's style, background and emotional state, which can help in tailoring information. Research shows that this aspect of the consultation is commonly completed in 1 minute. Health professionals who frequently interrupt this exposition of the plot are more prone to patient complaints and litigation; if something goes wrong, the patient remembers that the doctor did not listen.

Minimal verbal encouragers (*"Uh Huh….and then….?"*) and appropriate non-verbal behaviour (e.g. learning forward, nodding, maintaining eye contact) demonstrate attention and help the flow of information. Note taking or turning away to the computer keyboard should be unobtrusive and not interfere with eye contact.

Asking Questions With an Emotional Focus

The old saying 'Shoot first, ask questions later' characterises the communication style of health professionals most at risk of litigation. Failure to clarify a patient's view of his or her circumstances and information preferences before launching into delivering difficult news is risky. Open questions yield more accurate and full information particularly when emotional content is likely:

"Can you tell me how things are at home at present?"

compared with closed and leading questions:

"Your husband is giving you plenty of backup, right?"

If the patient is angry or distressed, supplementary probing (acknowledging, then asking a second question about the same topic) to open up the subject before moving on to solutions is vital. For the patient, having the opportunity to be heard may be sufficient in itself, though apologies are sometimes required; the health professional should make sure to ask what course of action the patient requires rather than incorrectly assuming what it is. The old surgical adage "If there is pus, let it out" pertains in this situation, particularly if an adverse event has occurred – premature closure can be dangerous.

"That must have been alarming for you. Was there anything else that happened that complicated things?"

Language

The training undertaken by health professionals includes learning a language which is efficient in shortcutting communication with one another; unfortunately, this also it difficult for patients to understand. As with other bilingual communication settings, remembering to use the correct language is important. Here are some communication tips to help in the patient consultation:

- Beware of obvious medical jargon and acronyms, and ordinary words that have different meanings in medical contexts
    - Positive nodes, positive margins, progressive cancer – these are not good things!
- Avoid unintended negative attributions:
    - *"The patient has failed treatment"*: this sentence does not reflect the reality that our treatment has failed the patient.
- Use analogies, as long as they are likely to be understood by patients from diverse cultural backgrounds (be careful about football analogies unless you know which code the patient follows!):

- *"The lymphatic channels in your arm are like a six lane highway, they can get congested at peak hour…"*

- Relate the experiences of other patients to normalise the difficulty of the cancer journey and to help open up emotional aspects of the discussion:
  - *"Many patients have told me how helpful it was to have someone outside of the family to talk to. Would that be useful for you?"*
- Actively encourage questions to check the patient's understanding:
  - *"I've covered a lot of ground with you today, and I expect it will have triggered off some questions in your mind? Would you like to ask them now?"*
  - *"Most people say that they think of questions between consultations. It's a good idea to write them down, so that you remember to ask them next time."*

Routines

Experienced health professionals develop little routines or speeches to describe common issues that arise in everyday practice. While these may be effective tools, they tend to lose their freshness (to the speaker) with frequent repeat performances, so there is a tendency to speed up. It is then very difficult for patients to interject and ask questions. A good communication tip is when delivering a tried and tested line or story to a patient, try to imagine you are thinking it through for the first time. Remember to breathe at the end of each sentence to allow the patient to engage in the conversation.

"The pain is like a sponge; it soaks up the morphine, which reduces the likelihood of side-effects and addiction. If the pain increases, the morphine can be safely increased and when the pain improves, the sponge gets smaller and the dose is reduced to match it. Does that make sense?"

Information Tools

Understanding can be improved by writing down information during the consultation:

- key points around treatment choices (including pros and cons)
- timelines that show the order and scheduling of therapy and timing of side-effects (Figure 18.1)
- flow diagrams showing the decision points around investigation results (Figure 18.2)
- diagrams that demonstrate key concepts
- lists of tasks to be done (preferably in chronological order) or medication to be taken

Carbonised paper can be helpful, allowing a copy to be kept for the professional's records.

Generic preprinted information, consent forms and decision aids can be a useful supplement to give the patient to look at later and to discuss with family members, but personal, handwritten notes are recommended. These notes allow the patient an opportunity to comment favourably on the legibility of your writing, another sign of your professionalism.

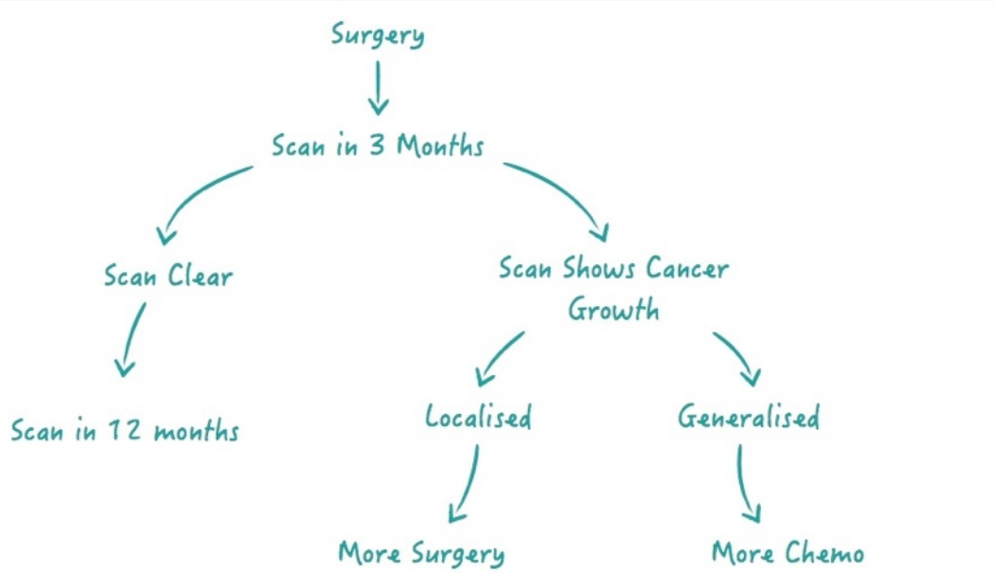
Acknowledging Emotion

Anxiety is a component of almost all medical interactions, including even the most routine of follow-up appointments. It is amplified by delays, missing or ambiguous information, the perception

FIGURE 18.1 THERAPY & SIDE-EFFECT SEQUENCE MAPPING

Timelines which show the order and scheduling of therapy and timing of side-effects and how they should be managed.

FIGURE 18.2 DECISION POINT MAPPING



Flow diagrams showing the decision points around investigation results and therapy choices.

that the health professional is too busy or distracted and in some cases the patient's own predisposition. Research has shown that acknowledging emotion and expressing compassion can assist in reducing anxiety while adding less that a minute to the length of consultations. Anxiety that is not managed impairs recall and decision-making.

- Patients will frequently give cues that they have an emotional concern, rather than openly stating it. If these cues are not recognised and explored, they are unlikely to be raised again, and opportunities will be missed.

Patient: *"The chemotherapy is going well, so I tell my daughter that everything will be OK."*

Doctor: *"I know you rely on her for support during the treatment and it's a tough road for carers as well as patients. How is she managing with things at present?"*

Empathy can be expressed by eye contact and appropriate touch as well as by words. The opportunity to examine the patient permits changes in dynamics which can facilitate a difficult conversation, e.g. standing beside a patient who is sitting on an examination couch may allow a

reassuring touch on the shoulder that would be difficult at a desk.

Breaking Bad News

If the news is bad (e.g. cancer diagnosis or recurrence, failure of treatment), undue delay or obfuscation in delivering it can waste time in the consultation, and increase anxiety in both the doctor and the patient. A useful approach is to warn that bad news is coming, to allow patients to brace themselves, and then to tell the news clearly and succinctly.

"I think you knew that I was worried last week when you told me about the pain in your hip. We did the scan because I was concerned the cancer might have recurred. Unfortunately, the scan does show the cancer has come back in the hip bone. I'm sorry."

- After telling the news, stop and wait for the reaction to clarify. Do not move on to discussing treatment until the patient signals they are ready for more information. Common reactions include anxiety, disbelief, anger and distress. Ask an open question with an emotional focus to clarify the nature of the reaction.

"It would help me to know what you are thinking just now?"

Discussing Prognosis

A key concern for cancer patients is the natural history of their condition and the likely outcome of their treatment. Despite this concern, questions about prognosis can be difficult for patients to raise. Avoidance of the issue can increase distress and anxiety (*"It must be bad, he has not said anything about the future…"*). Insensitive disclosure on the other hand, particularly of a poor prognosis, can

extinguish hope (*"They told me nothing could be done, I'm a goner…"*).

Research indicates the following steps may be useful in discussing the prognosis of a disease with patients:

- Ask patients what they would like to know about the likely course of their illness:
  - Needs may change over time, so renegotiation at key decision points will be required
  - Needs of the patient and family may differ, but remember the patient needs to control the flow of information to others
- If a timeframe is requested, then an honest answer is best couched in terms of:
  - acknowledging uncertainty and the potential impact of future treatment advances
  - the average (median) from the literature
  - the best case if treatment is effective
  - the worst case if treatment is ineffective
- Avoid using statistics that rely on an understanding of relative risk reduction with treatment. Use a best estimate of survival and absolute percentage improvements and remember, many patients fail to understand complex statistical concepts.
  - *"For melanomas like yours, around 60% of patients will be free of recurrence 5 years on. Interferon would increase that to around 65%"*
- Forecasting can assist in preparing patients for future bad news:
  - *"There may come a time when the current chemotherapy is no longer helping, and we can talk again then about how you would like to proceed…"*

Promoting hope and a sense of control is a key responsibility of health-care professionals working with cancer patients. This responsibility was highlighted by head and neck surgeon Professor Chris O'Brien in his 2008 account of his diagnosis of glioblastoma multiforme:

> *"Patients need to be embraced by a sympathetic supportive doctor or team who*

can demonstrate their willingness and ability to put into action a plan…to get matters sorted out. Patients with poor prognosis diseases will never do well if they are treated by individuals or teams who nihilistically believe they have no chance of success."

In a study undertaken at the Melanoma Institute Australia, it was found that patients with metastatic melanoma who expressed a more optimistic outlook had better survival. The mechanisms underpinning this finding remain unclear, and optimism may well be a character trait predating the diagnosis. Nevertheless, Australian research in patients with advanced cancer endorsed the following ways in which health professionals might foster hope:

- Reassure patients that pain will be controlled (Table 18.1).
- Appear to know all about the particular cancer and the particular patient.
- Offer the most up-to-date treatment.
- Discuss all treatment options.
- Interject some humour into the consultation.
- Suggest working as a team with the patient and family.
- Offer to answer all questions and answer them honestly.

Table 18.1 Key Messages For Patients With Cancer Regarding Pain Management

- Relief of pain is important and there is no benefit in suffering.
- Pain can usually be well controlled with medications taken by mouth.
  - If these medications do not work, many other options are available.
- Morphine and morphine-like medications are often used to relieve pain.
  - When these drugs are used to treat cancer pain, addiction is rarely a problem.
  - These are controlled substances that need to be properly safe-guarded in the home.
  - These medications must be used with caution and should not be mixed with alcohol or illicit substances.
  - If you take these medications now, they will still work later.
- Communication with doctors and nurses is critical.
  - Patients must tell doctors and nurses how much pain they have.
  - Patients must tell doctors and nurses about any problems the pain medications may be causing, as there are probably ways to improve these problems.
  - Patients should tell doctors and nurses if they have difficulties getting the medication or concerns about taking them.
  - Patients should be told to expect optimal treatment of pain and side-effects.

Finishing Well

At the conclusion of a consultation, summarising the discussion can assist all parties to remember what has been decided and what is planned. Recall can be improved by:

- Checking understanding:
  - *"We've discussed the results in detail today, and some options for treatment. I'm wondering what message you will take away with you?"*
- Agreeing on a what the patient wants to tell everyone:
  - Patient: *"So what will I tell my family?"*
  - Doctor: *"The key message is that the scans have not worsened, and that the treatment appears to be working. We will continue with this treatment and reassess it in 6 weeks. Have I missed anything?"*
- Making a 'To do' list for the patient (and yourself)
- Jotting responses down on a question prompt list if it has been used to serve as a summary
- Tape recording the consultation if the patient requests it

In closing the consultation, an expression of support, a plan for action and endorsement of questions will help patients to cope with the many challenges that melanoma presents. Ensure patients are clear about when and how they can contact members of the treatment team if concerns or questions arise between consultations.

Citations and Further Reading

1. Dimoska A, Girgis A, Hansen V, Butow PN, Tattersall MN. Perceived difficulties in consulting with patients and families: a survey of Australian cancer specialists. Med J Aust 2008;189:612-5.

2. Schofield PE, Butow PN, Thompson JF, Tattersall MH, Beeney LJ, Dunn SM. Psychological responses of patients receiving a diagnosis of cancer. Ann Oncol 2003;14:48-56.

3. Buckman R. Breaking bad news: why is it still so difficult? Br Med J 1984;288:1597-9.

4. Ptacek JT, Fries EA, Eberhardt TL, Ptacek JJ. Breaking bad news to patient's: physicians perceptions of the process. Support Care Cancer 1999;7:113-20.

5. Hodgkinson K, Gilchirst J. Psychosocial care of cancer patients: a health professional's guide to what to say and do. Melbourne: Ausmed; 2008.

6. Brown RF, Butow PN, Dunn SM, Tattersall MH. Promoting patient participation and shortening cancer consultations: a randomized trial. Br J Cancer 2001;85:1273-9.

7. Fallowfield L, Jenkins V, Farewell V, Saul J, Duffy A, Eves R. Efficacy of a Cancer Research UK communication skills training model for oncologists: a randomised controlled trial. Lancet 2002;359:650-6.

8. Fogarty La, Curbow BA, Wingard JR, McDonnell K, Somerfield MR. Can 40 seconds of compassion reduce patient anxiety? J Clin Oncol 1999;17:371-9.

9. National Breast Cancer Centre and National Cancer Control Initiative. Clinical practice guidelines for the psychosocial care of adults with cancer. Camperdown:

Addenda

Melanoma Institute Australia

The Poche Centre

- Design
- Layout
- Gallery

Fellowships

- Surgical Oncology
- Medical Oncology
- Pathology

Sabbaticals

Publications

Watercolour sketch of the Poche Centre by a patient

ADDENDUM 1

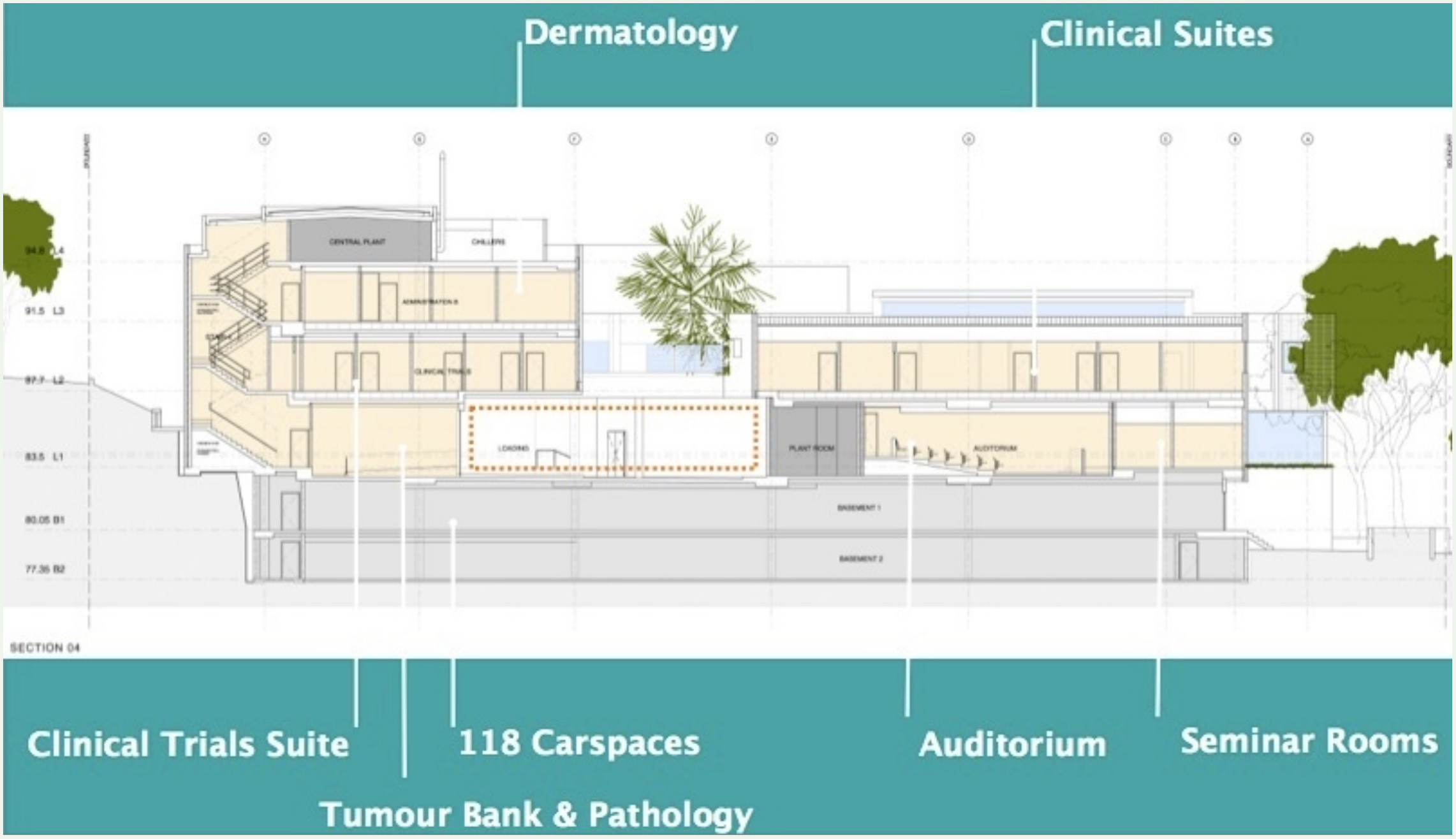
The Poche Centre

The Poche Centre forms the core of the Institute's activities. It was entirely funded by Mr Greg Poche AO and opened in 2010 by the Governor of NSW, Professor Marie Bashir AC

A majority of our clinicians conduct outpatient care at the Centre which houses the core administrative activities, informatics and database, clinical trials unit, and biospecimen bank coordination.

The building is also equipped with outstanding meeting and conference facilities, including a 100 seat auditorium. The weekly multidisciplinary meeting is hosted there every Friday morning.

The Poche Centre Layout Drawings



General schema of building

The Poche Centre Architectural Folio

Main entrance to the Poche Centre

1 of 13

The Poche Centre was designed for the single purpose of serving as the hub of the Melanoma Institute's activities and the project scoped with a brief of creating the optimal facility for patient care, research and education.

A further intent was to create a welcoming and pleasant environment for both patients and staff, acknowledging that the diagnosis and ongoing care of patients diagnosed with melanoma can be a stressful experience for them.

Architect **Alex Kibble** was commissioned to design the building. He enthusiastically embraced the brief, to create a uniquely engaging and highly functional built environment for patients confronting Australia's national cancer.

A concept of combining Australian hardwood timber finishes, ochre tones and contemporary styling progressively evolved, fulfilling the original concepts for the centre.

In parallel, the technical specifications for the centre were defined, including a high level of communication and informatics resources, perhaps not surprising for an organisation renowned for its world leading melanoma database.

Throughout the design and construction of the Poche Centre, the project was enthusiastically supported without question by the benefactor.

Alex Kibble

ADDENDUM 2

Fellowships at MIA

Melanoma Institute Australia offers a range of clinical and research Fellowships across the broad range of multidisciplinary melanoma care and research. The Fellowships include:

Poche Fellowships (Surgical Oncology)

These Fellowships, named in honour of our generous benefactor, are highly sought-after by young surgeons from all over the world who seek vocational experience in melanoma and surgical oncology.

Fellows work under the supervision of the specialist surgeons and engage with the broad range of their activities. Opportunities exist to align with general surgical oncology, reconstructive plastic surgery and Head & Neck specialist subgroups. Fellowships involve a substantial clinical workload in dedicated outpatient clinics, operating sessions and weekly multi-disciplinary meetings. Fellows are also required to participate in Melanoma Institute Australia's clinical research programs. They are required to undertake research projects in the fields of melanoma and skin oncology.

Applicants for Poche Fellowships are required to hold a FRACS or equivalent and be eligible for registration with the Medical Board of New South Wales. They will have recently completed advanced training in plastic or general surgery and be seeking further experience in melanoma and surgical oncology. Applications are accepted from non-Australian candidates.

Cameron Fellowship in Molecular Pathology

This is a one year Fellowship for newly qualified pathologists or final year anatomical pathology trainees. The Fellow will provide assistance to the anatomical pathology team and participate in clinical trials and research programs. The program is mentored by Professor Richard Scolyer. The caseload at Melanoma Institute Australia, together with the expert consulting service that MIA pathologists provide to external pathology practices both nationally and internationally, provide a unique opportunity to gain experience in both histological pathology and melanoma molecular biology.

Melanoma Medical Oncology Fellowships

This Fellowship position is open to third year advanced medical oncology trainees or those who have recently qualified as a Medical Oncologist. The Fellow provides assistance to a team of medical oncologists and will participate in clinical trials and clinical research programs. The Fellowship offers an excellent opportunity for training in the care of melanoma patients as well as exposure to world leading clinical and translational research in a multidisciplinary setting. This fellowship is supervised by Georgina Long and Alex Guminski.

Melanoma & Breast Surgical Oncology Fellowships

Young surgeons seeking further training within a high volume breast cancer multidisciplinary team together with melanoma practice within the Melanoma Institute Australia can gain substantial experience in this fellowship. There is also exposure to multidisciplinary soft tissue sarcoma care and other aspects of surgical oncology. Applicants need to hold a FRACS or equivalent, be eligible for registration with the Medical Board of Australia; have completed (or will have done by commencement of the Fellowship) advanced training in general surgery.

Table 1 Poche Surgical Fellows have included:

- Richard Martin (New Zealand)
- Marc Moncrieff (United Kingdom)
- Will McMillan (New Zealand)
- Susan Gollop (New Zealand)
- Phillip Brackley (United Kingdom)
- Jeremy Bond (United Kingdom)
- Deborah Bourke (United Kingdom)
- Jonathan Duncan (United Kingdom)
- Alastair MacKenzie Ross (United Kingdom)
- Kieran Power (United Kingdom)
- Annette Chakera (Denmark)
- Alexander Varey (United Kingdom)

Professorial & Senior Academic Sabbaticals

MIA (and previously SMU) has been privileged to host sabbaticals for many eminent melanoma clinicians and researchers. These have included:

Jeffrey Gershenwald
M.D.Anderson Cancer Center, Texas, USA

David Ollila
Chapel Hill, University North Carolina, USA

Michael Atkins
Boston, USA

Kristoffer Drzewiecki
Copenhagen University Hospital Rigshospitalet, Denmark

Seng-Jaw Soong
University of Alabama, USA

Charles Balch
Johns Hopkins Hospital, USA

Stephan Ariyan
Yale Melanoma Unit, USA

The Institute welcomes enquiries regarding sabbaticals.

Most cited MIA Publications from last 10 years

1. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, McArthur GA, Hutson TE, Moschos SJ, Flaherty KT, Hersey P, Kefford R, Lawrence D, Puzanov I, Lewis KD, Amaravadi RK, Chmielowski B, Lawrence HJ, Shyr Y, Ye F, Li J, Nolop KB, Lee RJ, Joe AK, Ribas A. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;366:707-714
   PubMed Link

2. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, Hamid O, Schuchter L, Cebon J, Ibrahim N, Kudchadkar R, Burris HA, 3rd, Falchook G, Algazi A, Lewis K, Long GV, Puzanov I, Lebowitz P, Singh A, Little S, Sun P, Allred A, Ouellet D, Kim KB, Patel K, Weber J. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694-1703
   PubMed Link

3. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, Wolchok JD, Hersey P, Joseph RW, Weber JS, Dronca R, Gangadhar TC, Patnaik A, Zarour H, Joshua AM, Gergich K, Elassaiss-Schaap J, Algazi A, Mateus C, Boasberg P, Tumeh PC, Chmielowski B, Ebbinghaus SW, Li XN, Kang SP, Ribas A. Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. N Engl J Med 2013
PubMed Link

4. Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, Mann GJ, Hughes TM, Thompson JF, Scolyer RA, Kefford RF. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol 2011;29:1239-1246
PubMed Link

5. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, Hamid O, Infante JR, Millward M, Pavlick AC, O'Day SJ, Blackman SC, Curtis CM, Lebowitz P, Ma B, Ouellet D, Kefford RF. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet 2012;379:1893-1901
PubMed Link

6. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, Puzanov I, Hauschild A, Robert C, Algazi A, Mortier L, Tawbi H, Wilhelm T, Zimmer L, Switzky J, Swann S, Martin AM, Guckert M, Goodman V, Streit M, Kirkwood JM, Schadendorf D. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:1087-1095
PubMed Link

7. Barrett JH, Iles MM, Harland M, Taylor JC, Aitken JF, Andresen PA, Akslen LA, Armstrong BK, Avril MF, Azizi E, Bakker B, Bergman W, Bianchi-Scarra G, Bressac-de Paillerets B, Calista D, Cannon-Albright LA, Corda E, Cust AE, Debniak T, Duffy D, Dunning AM, Easton DF, Friedman E, Galan P, Ghiorzo P, Giles GG, Hansson J, Hocevar M, Hoiom V, Hopper JL, Ingvar C, Janssen B, Jenkins MA, Jonsson G, Kefford RF, Landi G, Landi MT, Lang J, Lubinski J, Mackie R, Malvehy J, Martin NG, Molven A, Montgomery GW, van Nieuwpoort FA, Novakovic S, Olsson H, Pastorino L, Puig S, Puig-Butille JA, Randerson-Moor J, Snowden H, Tuominen R, Van Belle P, van der Stoep N, Whiteman DC, Zelenika D, Han J, Fang S, Lee JE, Wei Q, Lathrop GM, Gillanders EM, Brown KM, Goldstein AM, Kanetsky PA, Mann GJ, Macgregor S, Elder DE, Amos CI, Hayward NK, Gruis NA, Demenais F, Bishop JA, Bishop DT. Genome-wide association study identifies three new melanoma susceptibility loci. Nat Genet 2011;43:1108-1113
PubMed Link

8. Wilmott JS, Long GV, Howle JR, Haydu LE, Sharma RN, Thompson JF, Kefford RF, Hersey P, Scolyer RA. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res 2012;18:1386-1394
PubMed Link

9. Lian CG, Xu Y, Ceol C, Wu F, Larson A, Dresser K, Xu W, Tan L, Hu Y, Zhan Q, Lee CW, Hu D, Lian BQ, Kleffel S, Yang Y, Neiswender J, Khorasani AJ, Fang R, Lezcano C, Duncan LM, Scolyer RA, Thompson JF, Kakavand H, Houvras Y, Zon LI, Mihm MC, Jr., Kaiser UB, Schatton T, Woda BA, Murphy GF, Shi YG. Loss of 5-hydroxymethylcytosine is an epigenetic hallmark of melanoma. Cell 2012;150:1135-1146
PubMed Link

10. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, Weber JS, Joshua AM, Hwu WJ, Gangadhar TC, Patnaik A, Dronca R, Zarour H, Joseph RW, Boasberg P, Chmielowski B, Mateus C, Postow MA, Gergich K, Elassaiss-Schaap J, Li XN, Iannone R, Ebbinghaus SW, Kang SP, Daud A. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014;384:1109-1117
PubMed Link

ABCDE rule

The ABCDE rule is a mnemonic based system to describe concerning skin lesions as follows:

A: Asymmetry
of shape or pattern

B: Border
irregularity or 'geographical edge'

C: Colour
variability with shades of brown to black, sometimes including red, white or blue

D: Diameter
over 6mm maximal dimension, or growing

E: Evolution
changing appearance with time, or other suspicious feature developing eg, bleeding, crusting, itching

---

Related Glossary Terms

Geographical edge

Index Find Term

Chapter 2 - Benign Melanocytic Lesions
Chapter 4 - Primary Melanoma Subtypes
Chapter 4 - Primary Melanoma Subtypes
Chapter 4 - Primary Melanoma Subtypes
Chapter 4 - Primary Melanoma Subtypes
Chapter 4 - Primary Melanoma Subtypes
Chapter 6 - Clinical and Instrument-Aided Diagnosis
Chapter 6 - Clinical and Instrument-Aided Diagnosis

Afferent lymphatics

lymphatic vessels that drain lymph from the primary melanoma site to the lymph nodes, where it is filtered in the subcapsular sinuses.

Related Glossary Terms

Efferent lymphatics, Lymph

Index Find Term

AJCC staging system

This system of staging, last revised in 2009, gives an overall stage based on 3 component parts.

- Stages I and II: no evidence of metastatic disease
- Stage III: microsatellite, in transit or nodal metastases
- Stage IV: other metastatic disease

Components:

- pathological Tumour (pT) stage 1-4
- nodal status (N)1-3
- metastatic disease status (M) 0-1

Clinical Staging*				Pathological Staging†			
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0	IB	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0	IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0	IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N > N0	M0	IIIA	T1-4a T1-4a T1-4b T1-4b	N1a N2a N1a N2a	M0 M0 M0 M0
				IIIB	T1-4a T1-4a T1-4a	N1b N2b N2c	M0 M0 M0
				IIIC	T1-4b T1-4b T1-4b Any T	N1b N2b N2c M3	M0 M0 M0 M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

Related Glossary Terms

Breslow thickness, In-transit metastases (ITMs), Intermediate-risk melanoma, Microsatellites, Sentinel Node, Tumour Mitotic Rate, Ulceration

Index Find Term

Banal naevi

Banal naevi are melanocytic naevi that lack any atypical features.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 6 - Clinical and Instrument-Aided Diagnosis

Basal cell naevus syndrome

This rare syndrome, also known as Gorlin's, is characterised by the presence of:

- Multiple BCCs, with early onset
- Tendency to develop other tumours including: medulloblastoma, melanoma, meningioma, breast carcinoma and non-Hodgkin's lymphoma
- Broad nasal root
- Borderline intelligence
- Jaw cysts
- Palmar pits
- Skeletal abnormalities

Mutation lies in the PTCH (Patched) tumour suppressor gene; 50% offspring will be affected (autosomal dominant).

Related Glossary Terms

Bazex syndrome, Rombo syndrome

Index Find Term

Chapter 5 - Melanoma Mimics

Bazex syndrome

Similar to Basal Cell Naevus syndrome, but without the skeletal abnormalities or other features.

- Multiple BCCs
- Follicular atrophoderma
- Hypotrichosis
- Hypohidrosis

Rare, X-linked dominant inheritance pattern.

Related Glossary Terms

Basal cell naevus syndrome, Rombo syndrome

Index Find Term

Chapter 5 - Melanoma Mimics

bFGF

The full name for bFGF is basic fibroblast growth factor. This family of growth factors are involved in limb and nervous system development, wound healing, blood vessel and tumour growth.

Related Glossary Terms

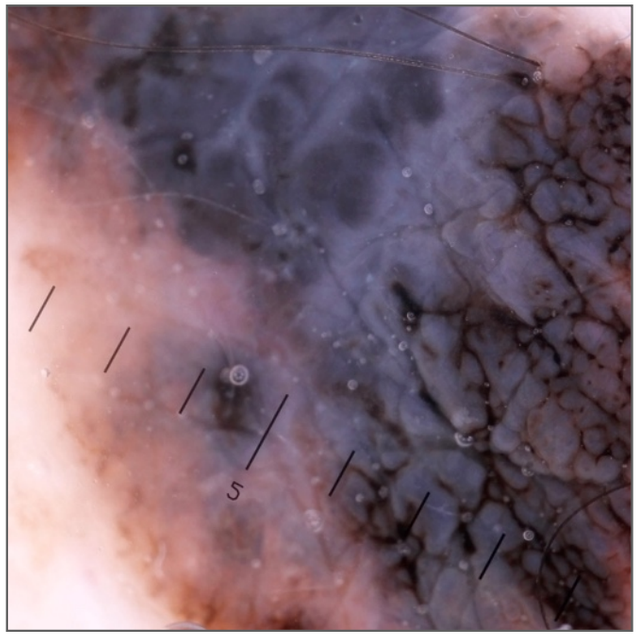
Drag related terms here

Index Find Term

Chapter 7 - Biopsy Techniques

Blue-white veil

The presence of a white ‘ground-glass’ appearance overlying an area of blue, structureless pigmentation.



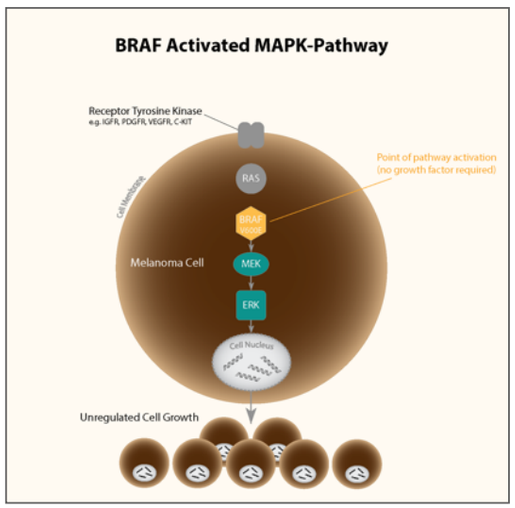
Related Glossary Terms

Drag related terms here

Index Find Term

BRAF

BRAF is an intracellular protein that forms part of the MAPK signalling pathway to conduct growth signals from cell surface receptors to the cell nucleus. Activating mutations of this protein are found in approximately 50% of cutaneous melanomas, leading to uncontrolled growth.



Related Glossary Terms

Mitogen-activated protein kinase (MAPK) pathway, Targeted therapy

Index Find Term

Breslow thickness

The Breslow thickness of a melanoma is measured from the granular layer of the epidermis to the deepest part of the tumour. This represents the most important prognostic histopathological feature in the current staging system.

Related Glossary Terms

AJCC staging system, Epidermal granular layer, High-risk melanoma, Intermediate-risk melanoma, Low-risk melanoma

---

Index Find Term

Carcinoma

a malignant tumour originating from epithelium.

Related Glossary Terms

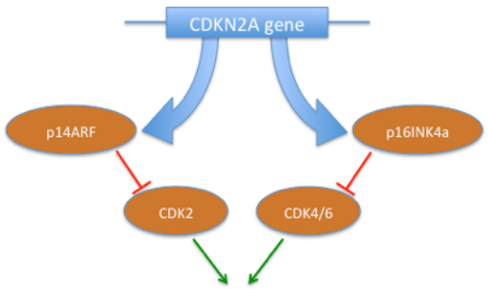
Melanoma

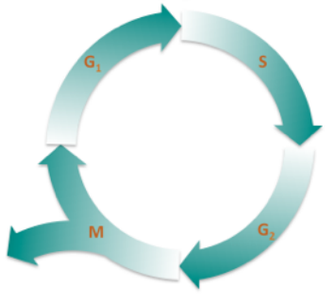
Index Find Term

Chapter 1 - Epidemiology

CDKN2A

This gene encodes two proteins, known as p14ARF and p16INK4A, which inhibit cyclins (CDK2 and CDK4/6). Since cyclins promote cell cycle progression from G1 to S phase, p14ARF/p16INK4A are inhibitors of this. Mutations of these genes can result in loss of this cell cycle regulation and promote tumour growth.





Related Glossary Terms

Cell cycle, High-penetrance mutation

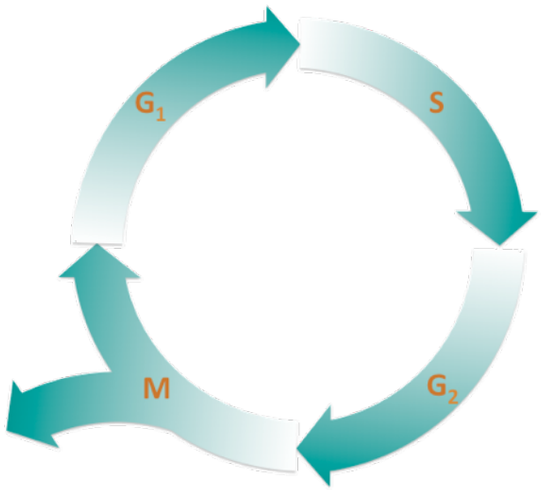
Index Find Term

Chapter 1 - Epidemiology

Cell cycle

The cell cycle comprises 4 phases:

- G1 - Growth and normal metabolism
- S - Synthesis/DNA replication
- G2 - Growth and preparation for mitosis
- M - Mitosis (separation into 2 cells)



Related Glossary Terms

CDKN2A

Index Find Term

Completion lymphadenectomy (CLND)

Completion lymphadenectomy is the process of removing all remaining lymph nodes within a nodal ‘basin’. This is performed following diagnosis of melanoma within one or more excision biopsied nodes, typically the sentinel node(s). Typically around 20% of patients will have further metastatic deposits of melanoma within these other nodes.

Related Glossary Terms

Therapeutic lymph node dissection (TLND)

Index Find Term

Chapter 13 - Sentinel Lymph Node Evaluation

Chapter 14 - Surgery for Stage III and IV Disease

Cytological atypia

Changes in the structure of the nucleus and/or cytoplasm conferring an abnormal appearance to a cell. While it is commonly attributable to neoplasia, it can also be the result of cellular injury and degeneration.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 2 - Benign Melanocytic Lesions

Chapter 9 - Histopathological Assessment & Synoptic Reporting

Efferent lymphatics

Efferent lymphatic vessels drain lymph away from lymph nodes to either veins or downstream nodes.

Related Glossary Terms

Afferent lymphatics, Lymph

Index Find Term

Epidermal granular layer

The epidermis is comprised of four or five layers, depending on the anatomical site. These layers are as follows from superficial to deep:

- Cornified
- Lucidum (glabrous skin of hands and feet)
- Granular
- Spinous
- Basal

The granular layer is the most superficial layer of live cells and is the reference point for determining Breslow thickness. Normal melanocytes lie sparsely interspersed between the keratinocytes of the basal layer.

Related Glossary Terms

Breslow thickness

Index Find Term

Chapter 9 - Histopathological Assessment & Synoptic Reporting

Epithelioid

Displaying cell shape features reminiscent of epithelium, namely a cuboidal cellular appearance. Such melanocytes lack their usual prominent dendritic processes.

Related Glossary Terms

Drag related terms here

Index Find Term

Fibroplasia

The formation of new collagen tissue beneath and adjacent to epidermal ridges. The thin collagen fibres within papillary dermis are replaced by thickened fibrous tissue.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 9 - Histopathological Assessment & Synoptic Reporting

Fine needle aspiration biopsy (FNAB)

Fine needle aspiration biopsy is the process of obtaining a tissue biopsy using a hypodermic needle (typically 22 gauge) and syringe. The resultant biopsy sample provides cells and fluid, but typically no solid tissue mass. Analysis is therefore termed cytology.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 11 - Imaging

Chapter 14 - Surgery for Stage III and IV Disease

Fitzpatrick skin phototype

The Fitzpatrick skin phototype classification is a widely used system to determine people's tendency to sunburn.

Skin Type	Skin Colour	Sun Exposure Reaction
I	Pale White	Always burns, never tans
II	White	Usually burns, sometimes tans
III	White	Sometimes burns, usually tans
IV	Light brown/ Olive	Rarely burns, always tans
V	Brown	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Related Glossary Terms

Drag related terms here

Index Find Term

Geographical edge

The term refers to a sharply demarcated edge, such as is seen on a map, a feature associated with melanoma. In contrast, benign lesions tend to gradually fade into adjacent normal skin.

Related Glossary Terms

ABCDE rule

Index Find Term

Gray (Gy)

A Gray (Gy) is a measurement of radiation exposure, defined as the absorption of 1 joule of energy per kilogram of matter (water or human tissue).

Related Glossary Terms

Hypofractionated radiotherapy

Index Find Term

Chapter 16 - Radiation Oncology

High-penetrance mutation

a gene that, when mutated, frequently results in an alteration in the expressed protein function, affecting the phenotype of the person.

Related Glossary Terms

CDKN2A

Index Find Term

Chapter 1 - Epidemiology

High-risk melanoma

Three categories (AJCC Stages IIB/IIC or III due to microsatellites)

a).
Breslow: >2.0 - 4.0mm
Ulceration: yes
TMR: any
Microsatellites: any

b).
Breslow: >4.0mm
Ulceration: any
TMR: any
Microsatellites: any

c).
Breslow: any
Ulceration: any
TMR: any
Microsatellites: yes

Related Glossary Terms

Breslow thickness, Intermediate-risk melanoma, Low-risk melanoma, Microsatellites, Tumour Mitotic Rate, Ulceration

---

Index Find Term

Hypofractionated radiotherapy

Hypofractionation is the process of delivering radiotherapy in a higher dose per fraction and typically in fewer fractions.

Related Glossary Terms

Gray (Gy), Stereotactic Radiosurgery (SRS)

Index Find Term

Chapter 16 - Radiation Oncology

Immunohistochemistry

identifies the presence and location of proteins in pathology slides by using specific antibodies that stain the tissue (usually brown or red). In melanoma, these typically include HMB45, MelanA and S100. However, individually they are neither 100% specific or sensitive for melanoma and thus a combination is usually used.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 13 - Sentinel Lymph Node Evaluation

Immunotherapy

Immunotherapy refers to any treatment that modulates the immune system. Significant recent progress has been made using this approach in melanoma, with antibodies against T-cell inhibitory co-receptors, such as PD-1 and CTLA-4.

Related Glossary Terms

Systemic therapy

Index Find Term

Chapter 13 - Sentinel Lymph Node Evaluation

In situ melanoma

Growth of melanoma cells through the epidermis, without invasion of the underlying dermis.

Related Glossary Terms

Melanoma, Pagetoid spread

Index Find Term

In-transit metastases (ITMs)

In Transit metastases are those occurring in the skin or subcutaneous tissues within the same lymphatic drainage region as the primary melanoma, eg, an ITM from a left leg primary could be anywhere on the left lower limb. ITMs may be pigmented or non-pigmented. The presence of ITMs classifies the disease as at least stage III.

Related Glossary Terms

AJCC staging system

Index Find Term

Chapter 9 - Histopathological Assessment & Synoptic Reporting
Chapter 9 - Histopathological Assessment & Synoptic Reporting
Chapter 12 - Special Subtypes
Chapter 14 - Surgery for Stage III and IV Disease

Interferon alpha

Interferon alpha is a member of a family of naturally occurring proteins produced by the body in response to viral infections. When administered in a therapeutic context it induces a complex series of intracellular events that result in anti-proliferative, antiviral and immunomodulating effects.

Related Glossary Terms

Drag related terms here

Index Find Term

Intermediate-risk melanoma

Several categories (AJCC Stages IB to IIA)

a).
Breslow: ≤1.0mm
Ulceration: yes
and/or
TMR: ≥1/mm^2
Microsatellites: nil

b).
Breslow: >1.0mm - 2.0mm
Ulceration: any
TMR: any
Microsatellites: nil

c).
Breslow: >2.0 - 4.0mm
Ulceration: nil
TMR: any
Microsatellites: nil

Related Glossary Terms

AJCC staging system, Breslow thickness, High-risk melanoma, Low-risk melanoma, Microsatellites, Tumour Mitotic Rate, Ulceration

---

Index Find Term

Chapter 12 - General Concepts

Chapter 12 - General Concepts

Interval node

A node identified along the course of a lymphatic vessel between a primary melanoma site and a recognised node field. Approximately 10% of primary tumour sites on the limbs drain to interval nodes including the epitrochlear and popliteal areas. On the upper back, Interval nodes in the Triangular Intermuscular Space (TIS) are also frequently identified. If drainage to such interval nodes is ignored by the surgeon during sentinel node biopsy, metastatic melanoma will be missed in some patients

---

Related Glossary Terms

Lymph, Lymphoscintigraphy, Sentinel lymph node biopsy (SLNB)

Index Find Term

Chapter 13 - Sentinel Lymph Node Evaluation

Low-risk melanoma

Breslow: ≤1.0mm

Ulceration: nil

TMR: <1/mm^2

Microsatellites: nil

Related Glossary Terms

Breslow thickness, High-risk melanoma, Intermediate-risk melanoma, Microsatellites, Tumour Mitotic Rate, Ulceration

---

Index Find Term

Chapter 12 - General Concepts

Lymph

Lymph is a clear/white fluid that is similar to plasma, containing white blood cells, especially lymphocytes, and no platelets or red blood cells.

Related Glossary Terms

Afferent lymphatics, Efferent lymphatics, Interval node, Lymphovascular Invasion, Sentinel lymph node biopsy (SLNB), Sentinel Node, Therapeutic lymph node dissection (TLND)

Index Find Term

Lymphoscintigraphy

A clinical imaging technique whereby a radioactive mapping agent is used to identify the lymphatic channels that drain from the site of a primary tumour and the sentinel nodes located at the ends of these vessels. In Australia, the agent used is antinomy sulphate colloid, complexed to technicium-99 (^{99}Tc).

Lymphoscintigraphy can be combined with single photon emission computed tomography (SPECT-CT) to provide improved anatomical localisation.

Related Glossary Terms

Interval node, Patent Blue V, Sentinel lymph node biopsy (SLNB), Sentinel Node, Vital Blue Dye

---

Index Find Term

Lymphovascular Invasion

The presence of tumour cells within lymphatic or vascular structures, abbreviated to LVI.

Related Glossary Terms

Lymph

Index Find Term

Chapter 12 - General Concepts

Macular

A term used to describe a lesion that is not raised above the surrounding skin surface.

Related Glossary Terms

Drag related terms here

Index Find Term

Melanocyte nests

Cohesive aggregates of melanocytes, occurring within the epidermis (junctional nests) or dermis (dermal nests).

Related Glossary Terms

Drag related terms here

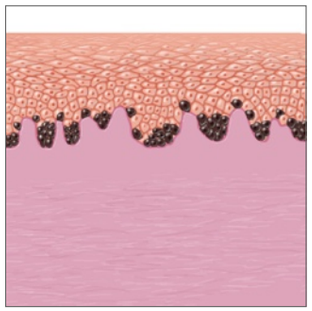
Index Find Term

Chapter 9 - Histopathological Assessment & Synoptic Reporting

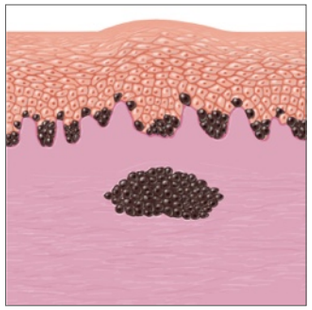
Melanocytic naevi

Melanocytic naevi are benign tumours of melanocytes, that can arise during embryonic development (congenital) or after birth (acquired). Acquired naevi have a very low individual risk of malignant transformation (~1/100,000), though this is higher than normal single melanocytes. Acquired naevi can be classified according to their location in the skin as junctional, compound or intra-dermal.

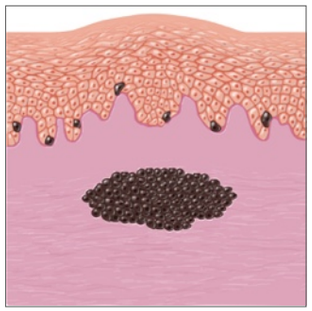
Junctional:



Compound:



Intradermal:



Related Glossary Terms

Drag related terms here

Index Find Term

Melanoma

Melanoma is a malignant tumour of melanocytes. Most commonly it arises from the skin (cutaneous), but can occur in any epithelial site, including the gastro-intestinal tract (mucosal) and eye (uveal). The typical route of spread is by lymphatics, but haematogenous also occurs. Overall, approximately 10% of patients develop metastases of their melanoma and die as a result.

ORIGIN mid 19th cent.: from Greek melas, melan- ‘black’ + -oma.

Related Glossary Terms

Carcinoma, In situ melanoma, Pleomorphic melanocytes

Index Find Term

Using This Book - Using This Book

Melanophages

Melanophages are macrophages (immune cells) that have internalised melanin by the process of phagocytosis. These cells are typically found in the presence of melanoma regression.

Related Glossary Terms

Regression, Tumour Infiltrating Lymphocytes (TILs)

Index Find Term

Microsatellites

Microsatellites are now defined by the AJCC as being the presence of any nests of intralymphatic melanoma metastases of >0.05mm diameter and separated from the primary tumour by at least 0.3mm of **normal** dermis (no inflammation or regression). Since microsatellites are metastases, they have a poor prognosis.

Related Glossary Terms

AJCC staging system, High-risk melanoma, Intermediate-risk melanoma, Low-risk melanoma, Regression

---

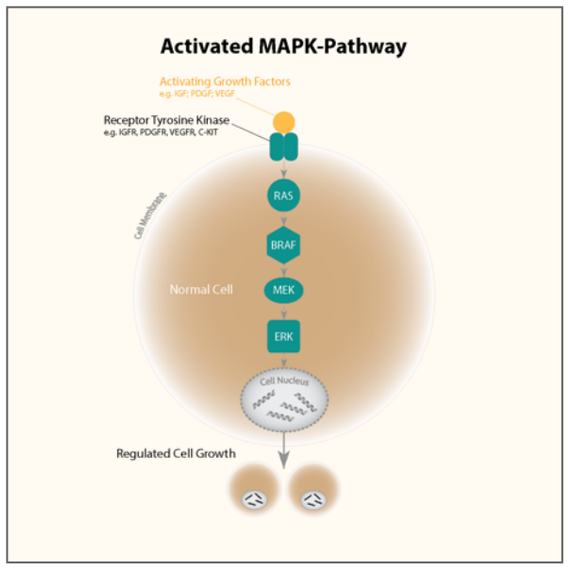
Index Find Term

Chapter 12 - General Concepts

Chapter 14 - Surgery for Stage III and IV Disease

Mitogen-activated protein kinase (MAPK) pathway

The MAPK pathway is a cascade of signalling proteins that transfer a pro-growth signal from receptors on the cell surface to the nucleus. Mutations of this pathway can result in auto-activation in the absence of external growth factors, leading to unregulated cell growth. A common such mutation in melanoma is of the BRAF protein in the cascade. Various drugs that target the proteins in the pathway have been shown to be effective in melanoma patients with specific mutations of its proteins.



Related Glossary Terms

BRAF, Targeted therapy

Index Find Term

Chapter 15 - Systemic Therapies

Pagetoid spread

Pagetoid spread represents the upward migration of abnormal melanocytes within the epidermis, away from their usual location in the basal layer, a feature of in situ melanoma.

Related Glossary Terms

In situ melanoma

Index Find Term

Patent Blue V

Patent Blue V dye is used by Melanoma Institute Australia clinicians for visual verification of the lymphoscintigraphy findings when performing SLNB. This dual localisation technique has been shown to be the most reliable, although there is a less than 1% risk of anaphylactic reaction to the dye.

Related Glossary Terms

Lymphoscintigraphy, Sentinel lymph node biopsy (SLNB), Vital Blue Dye

---

Index Find Term

Chapter 13 - Sentinel Lymph Node Evaluation

PDGF

The full name of PDGF is platelet derived growth factor. This family of growth factors are important in wound healing and cancer growth, due to their effects on connective tissue cell proliferation and migration.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 7 - Biopsy Techniques

Pleomorphic melanocytes

Melanocytes that have a variety of appearances on histology are deemed pleomorphic.

Related Glossary Terms

Melanoma

Index Find Term

Reflectance confocal microscopy (RCM)

this imaging method uses a LASER beam to illuminate the skin at depths of up to 0.2mm and the reflected light passes through a pinhole aperture to be captured by a digital camera. The very high resolution (<0.002mm or <2µm) of this technique allows visualisation of the skin cells, such that individual atypical melanocytes can be seen. However, in thick skin, such as the palms and soles, the melanocytes are usually too deep for visualisation.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 3 - Pre-Invasive Melanoma

Chapter 12 - Special Subtypes

Regression

Regression is the presence of scar tissue, known as fibrosis, thought to represent the clearance of melanoma from that area by the immune system. However, it's prognostic significance is unclear.

Related Glossary Terms

Melanophages, Microsatellites

Index Find Term

Rete ridges

The rete ridges are the downward projections of the epidermis between the upward projecting dermal papillae.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 3 - Pre-Invasive Melanoma

Chapter 9 - Histopathological Assessment & Synoptic Reporting

Rombo syndrome

Rare syndrome, with some similarities to Bazex syndrome, with the following characteristics:

- Multiple BCCs
- Vermiculate atrophoderma
- Milia
- Hypertrichosis
- Trichepitheliomas
- Peripheral vasodilation

Transmitted in an autosomal dominant fashion.

Related Glossary Terms

Basal cell naevus syndrome, Bazex syndrome

Index Find Term

Chapter 5 - Melanoma Mimics

Sentinel lymph node biopsy (SLNB)

SLNB is the process of surgically excising lymph node(s) identified as sentinel nodes, for the purpose of histologically detecting any metastatic melanoma deposit. This can detect even a single cell (~0.015mm diameter), whereas the best imaging (ultrasound) can detect a deposit of 4mm or greater. SLN status is therefore the most accurate determinant of prognosis for melanoma patients.

Related Glossary Terms

Interval node, Lymph, Lymphoscintigraphy, Patent Blue V, Sentinel Node

---

Index Find Term

Sentinel Node

Any lymph node that receives lymph directly from a primary tumour, which can be several in number and in several nodal basins.

Related Glossary Terms

AJCC staging system, Lymph, Lymphoscintigraphy, Sentinel lymph node biopsy (SLNB)

Index Find Term

Stereotactic Radiosurgery (SRS)

SRS and Stereotactic Body Radiation Therapy (SBRT) are forms of radiation therapy that focus high-power energy on a small area of the body.

Related Glossary Terms

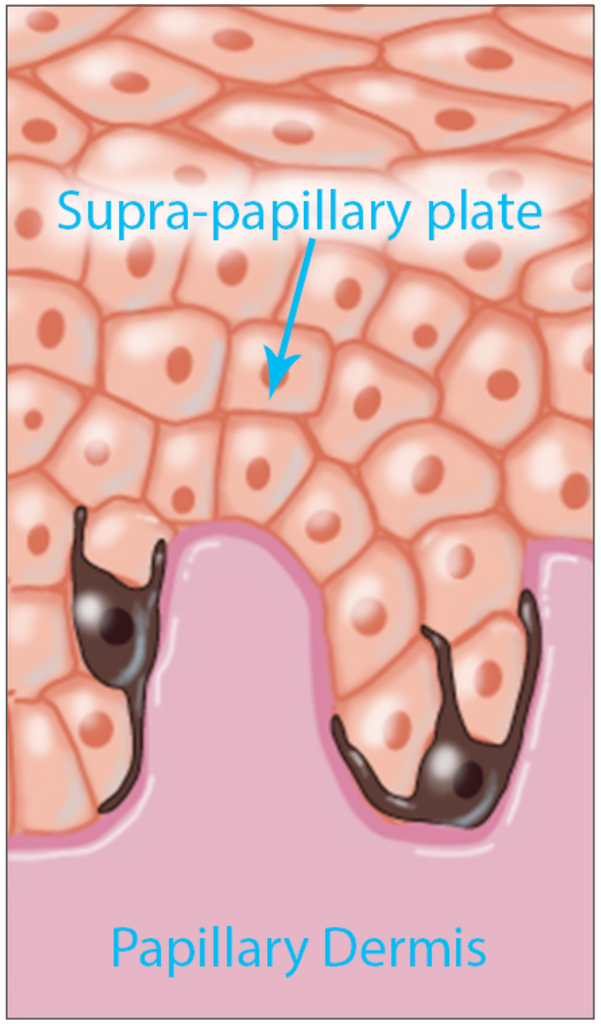
Hypofractionated radiotherapy

Index Find Term

Chapter 16 - Radiation Oncology

Supra-papillary plate

The section of epidermis that connects adjacent rete ridges.



Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 9 - Histopathological Assessment & Synoptic Reporting

Systemic therapy

The use of a treatment that works throughout the body, such as chemotherapy, targeted therapy or immunotherapy.

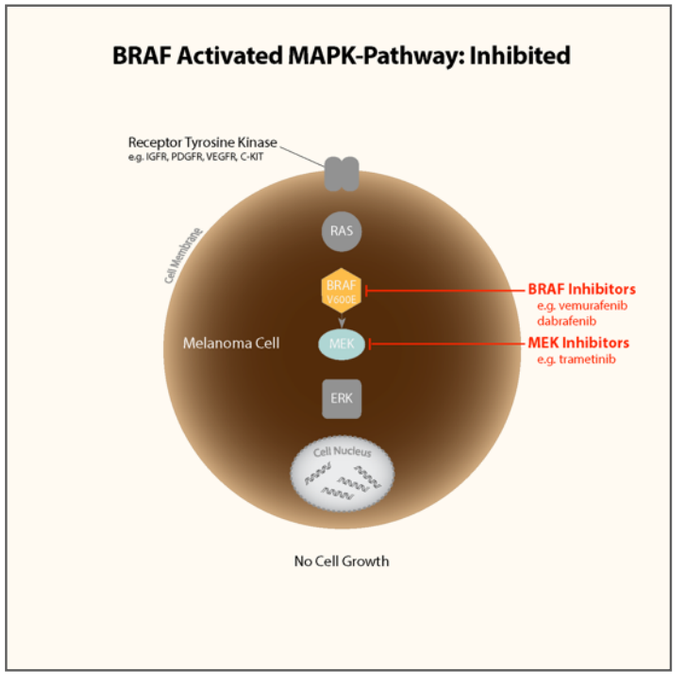
Related Glossary Terms

Immunotherapy, Targeted therapy

Index Find Term

Targeted therapy

The use of a therapy that selectively blocks a specific target, such as a mutated BRAF protein.



Related Glossary Terms

BRAF, Mitogen-activated protein kinase (MAPK) pathway, Systemic therapy

Index Find Term

Chapter 15 - Systemic Therapies

TGF-β

The full name for TGF-β is transforming growth factor-beta. This family of growth factors are involved in the regulation of cell proliferation, differentiation, adhesion and migration and play a significant role in wound healing. However, TGF-β expression is also frequently increased in tumours.

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 7 - Biopsy Techniques

Therapeutic lymph node dissection (TLND)

Therapeutic lymphadenectomy is the process of removing all lymph nodes within a nodal ‘basin’. This is performed for clinically detected metastatic melanoma within one or more nodes. Pre-operative confirmation of the diagnosis is usually performed using fine needle aspiration biopsy.

Related Glossary Terms

Completion lymphadenectomy (CLND), Lymph

Index Find Term

Chapter 13 - Sentinel Lymph Node Evaluation

Chapter 14 - Surgery for Stage III and IV Disease

Tumour Infiltrating Lymphocytes (TILs)

White blood cells (typically T-lymphocytes) that extend into the tumour, disrupting and surrounding individual tumour cells. Studies into the prognostic significance of TILs mostly report a favourable outcome for patients whose tumours display significant numbers ("brisk") of TILs.

Related Glossary Terms

Melanophages

Index Find Term

Chapter 15 - Systemic Therapies

Tumour Mitotic Rate

The maximum number of mitotic figures per 1mm square of invasive tumour (intradermal) observed. This is abbreviated to TMR and given as 'x/mm^2'. It should be noted that the TMR is a non-linear scale, such that the difference between 0 and 2 is of much greater prognostic significance than the difference between 2 and 4. Furthermore, the TMR significance diminishes with increasing Breslow thickness.

Related Glossary Terms

AJCC staging system, High-risk melanoma, Intermediate-risk melanoma, Low-risk melanoma

---

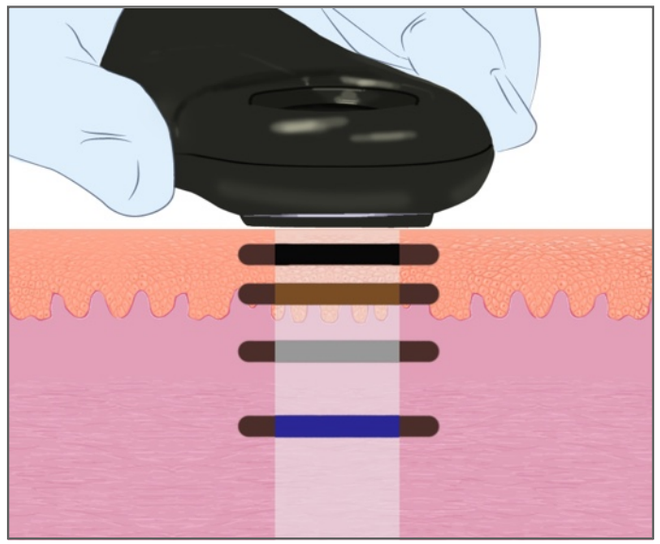
Index Find Term

Chapter 4 - Primary Melanoma Subtypes

Chapter 12 - General Concepts

Tyndall effect

Brown pigmentation appears as different colours under dermoscopy, depending on its depth in the skin. This is due to scattering of blue light more than red by the skin, known as the Tyndall Effect.



Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 2 - Benign Melanocytic Lesions

Chapter 6 - Clinical and Instrument-Aided Diagnosis

Ulceration

This is a full thickness loss of the epidermis. Ulceration has been shown to be an independent prognostic marker of poorer prognosis, roughly equivalent to an increase in the Breslow thickness to one category higher in the AJCC staging system.

Related Glossary Terms

AJCC staging system, High-risk melanoma, Intermediate-risk melanoma, Low-risk melanoma

---

Index Find Term

VEGF

The full name of VEGF is vascular endothelial growth factor-A. This family of growth factors potently increase vascular permeability (50,000 times more than histamine), stimulate the growth of new blood vessels from existing ones (angiogenesis) and also stimulate tumour growth. Anti-VEGF drugs have shown benefit in treating some cancers. The growth factors exists in both stimulatory and inhibitory versions (isoforms).

Related Glossary Terms

Drag related terms here

Index Find Term

Chapter 7 - Biopsy Techniques

Vital Blue Dye

Used to colour lymph vessels and nodes and assist with their identification intra-operatively.

Related Glossary Terms

Lymphoscintigraphy, Patent Blue V

Index Find Term

Chapter 13 - Sentinel Lymph Node Evaluation