Melanoma

Gerard J Bayley
M.B.B.S. (Uni of Qld), F.R.A.C.S. (Gen. Surg.), F.R.A.C.S.(Plast. Surg.)
Queensland Melanoma Project
Princess Alexandra Hospital

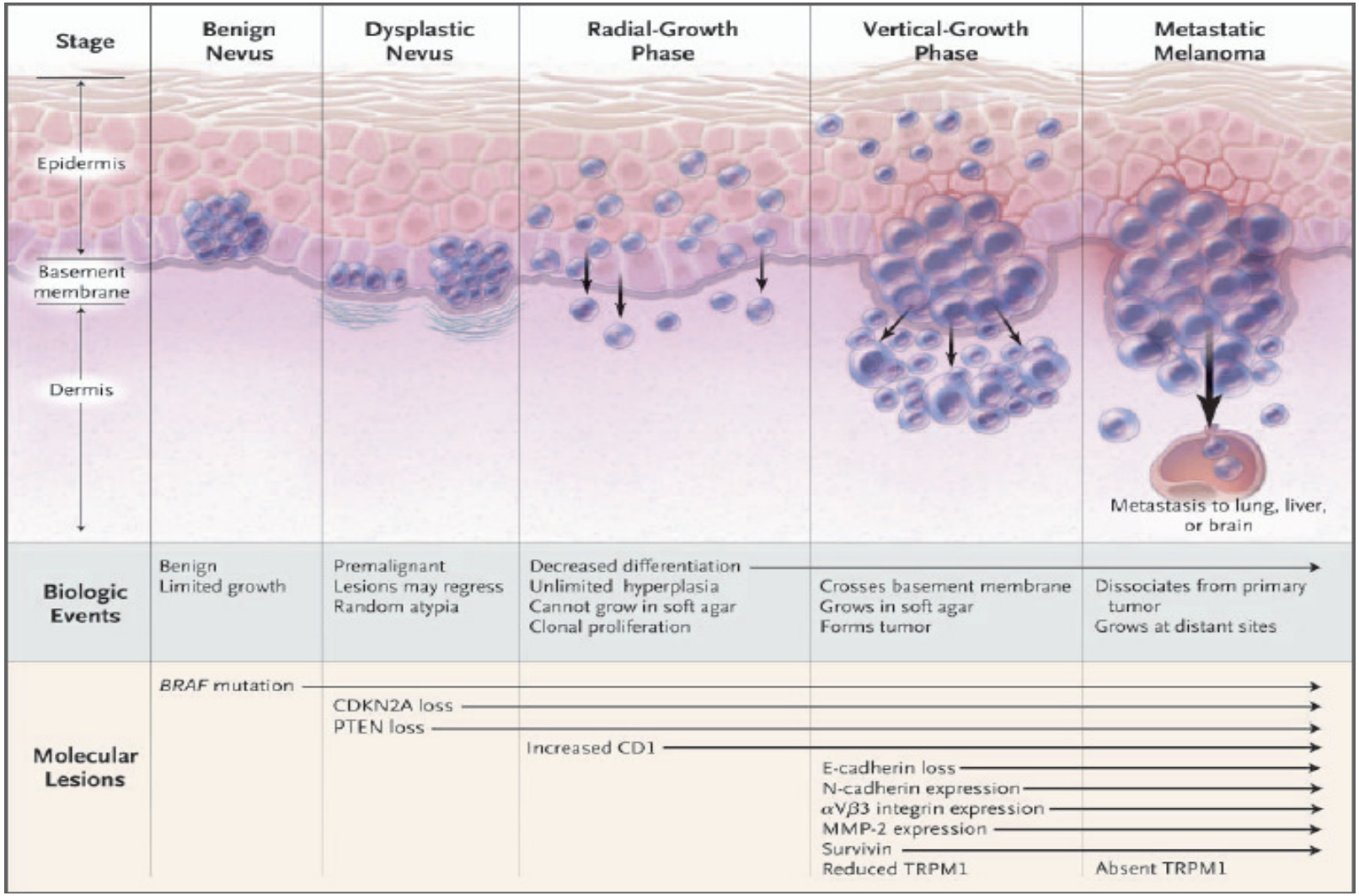
Disclaimer

- The copy in this file is protected by the copyright of the author or authors. Consent was provided for the express purpose of educating attendees of the 2012 Registrar's Conference in Brisbane.
- You **MAY NOT** copy or distribute the contents or images in any form.
- You **MAY PRINT** the document for your own personal use as an educational resource.

Melanoma

- is a malignant tumour of melanocytes.
- Melanocytes are cells that produce the dark pigment, melanin, which is responsible for the colour of skin.
- They predominantly occur in skin, but are also found in other parts of the body, including the bowel and the eye

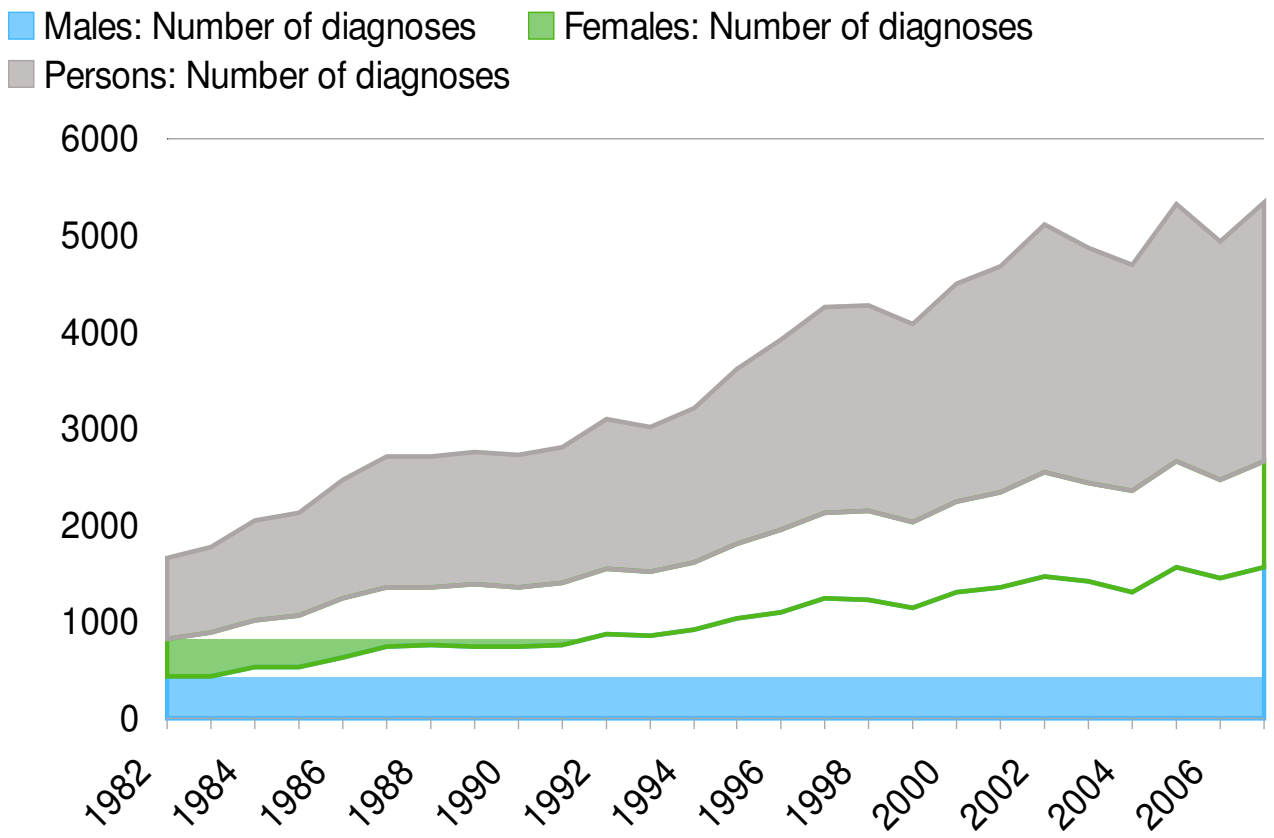
Genetics


Stage
Benign Nevus
Dysplastic Nevus
Radial-Growth Phase
Vertical-Growth Phase
Metastatic Melanoma
Epidermis
Basement membrane
Dermis
Metastasis to lung, liver, or brain
Biologic Events
Benign
Limited growth
Premalignant
Lesions may regress
Random atypia
Decreased differentiation
Unlimited hyperplasia
Cannot grow in soft agar
Clonal proliferation
Crosses basement membrane
Grows in soft agar
Forms tumor
Dissociates from primary tumor
Grows at distant sites
Molecular Lesions
BRAF mutation
CDKN2A loss
PTEN loss
Increased CD1
E-cadherin loss
N-cadherin expression
αVβ3 integrin expression
MMP-2 expression
Survivin
Reduced TRPM1
Absent TRPM1

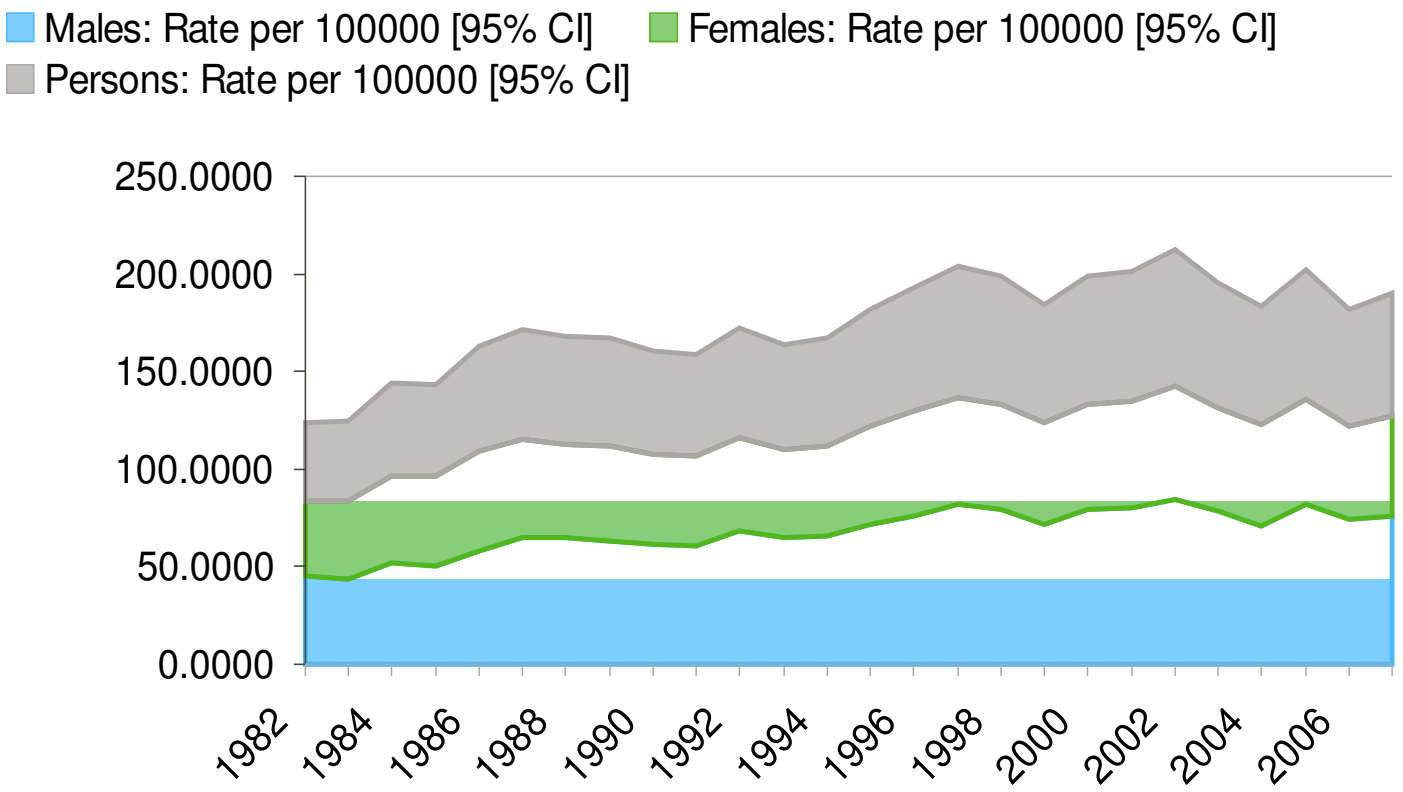
Queensland Statistics

- 2668 Queenslanders were diagnosed with a melanoma of the skin in 2007, with 285 dying from the disease
- Of the 2668 diagnosed, 1558 were male and 1110 were female
- The approximate lifetime risk of a Queensland male to be diagnosed with melanoma before the age of 85 is one in 11, and for females it is one in 19

Annual incidence of melanoma by sex in Queensland 1982-2007



Annual incidence of melanoma by sex in Queensland 1982-2007



Mortality Rate

- The melanoma mortality rates have been rising in fair-skinned populations throughout the world at a rate of increase lower than that for incidence rates
- In Australia, 5-10 per 100 000 per year in fair-skinned population
- Case fatality rates for melanoma, is now approximately 20% or less
- Age standardised mortality rates show
  - Over 60 years, continue to increase
  - Younger cohorts, stabilised or even begun to fall

Definitions

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed (for example, curettaged or severely regressed melanoma)
- **T0** No evidence of primary tumor
- **Tis** Melanoma in situ
- **T1** Melanomas 1.0 mm or less in thickness
- **T2** Melanomas 1.01–2.0 mm
- **T3** Melanomas 2.01–4.0 mm
- **T4** Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and number of mitoses per mm², as shown below:

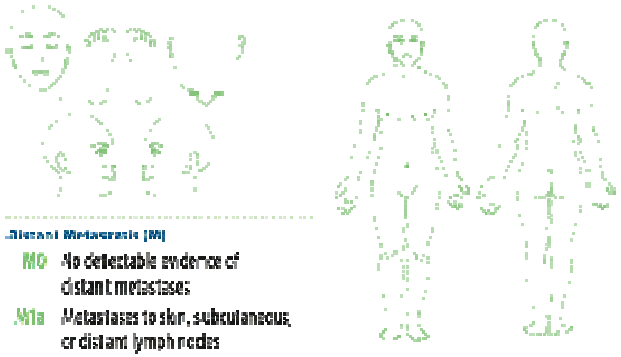
T Classification	Thickness (mm)	Ulceration Status/Mitoses
T1	≤1.0	a: w/o ulceration and mitosis < 1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

- **NX** Patients in whom the regional nodes cannot be assessed (for example, previously removed for another reason)
- **N0** No regional metastases detected
- **N1–3** Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

NOTE: N1–3 and a–c subcategories assigned as shown below:

N Classification	No. of Metastatic Nodes	Nodal Mets/Associated Mass
N1	1 node	a: micrometastasis b: macrometastasis*
N2	2–3 nodes	a: micrometastasis b: macrometastasis* c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	



Distant Metastasis (M)

- **M0** No detectable evidence of distant metastases
- **M1a** Metastases to skin, subcutaneous, or distant lymph nodes
- **M1b** Metastases to lung
- **M1c** Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

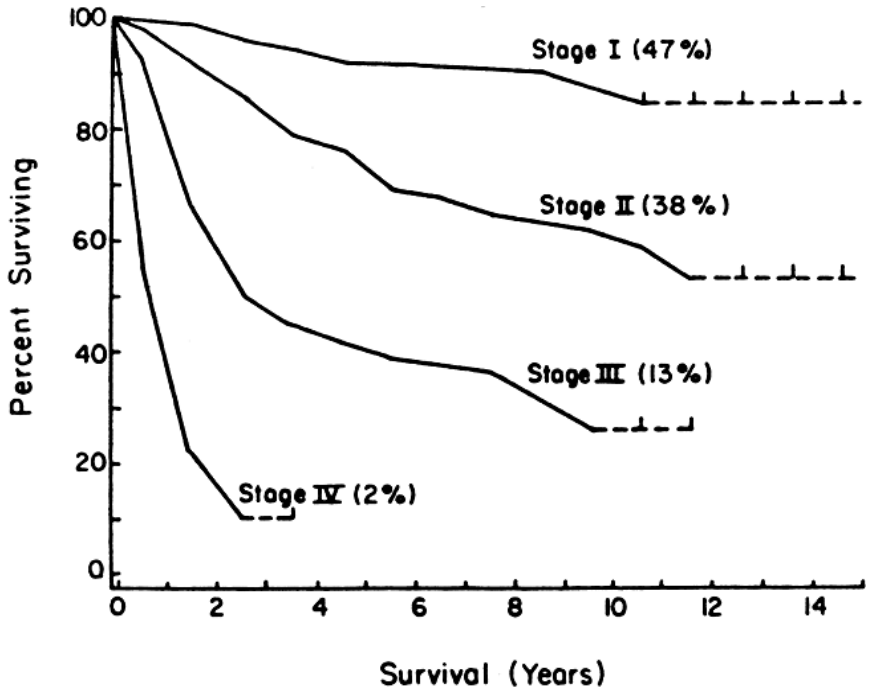
NOTE: Serum LDH is incorporated into the M category as shown below:

M Classification	Site	Serum LDH
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS

	Clinical Staging†				Pathologic Staging†		
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1–4a	N1a	M0
					T1–4a	N2a	M0
				IIIB	T1–4b	N1a	M0
					T1–4b	N2a	M0
					T1–4a	N1b	M0
					T1–4a	N2b	M0
					T1–4a	N2c	M0
				IIIC	T1–4b	N1b	M0
					T1–4b	N2b	M0
					T1–4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

Survival by stage



- Fifteen-year survival results for over 4000 melanoma patients treated at University of Alabama at Birmingham and the Sydney Melanoma Unit by AJCC stage. Distribution of patients is shown in parentheses. (Adapted with permission from Stadelmann, W. K., Rapaport, D. P., Soong, S. J., Reintgen, D. S., Buzaid, A. C., and Balch, C. M. Prognostic Clinical and Pathologic Features. In C. M. Balch, A. N. Houghton, A. J. Sober, and S. J. Soong (Eds.), Cutaneous Melanoma, 3rd Ed. St. Louis: Quality Medical Publishing, 1998. P. 12.)

Tumour site and Thickness

- There has been a different rate of increase in the incidence of melanoma in different body sites.
  - Head and neck, no rise or fall
  - Trunk, higher rate of increase (particularly in men)
- Thickness at primary removal
  - Increasing proportion of thin melanomas (<1.5mm)
  - Decrease in thick melanomas
  - In situ melanoma is increasing

Causation

- The major constitutional risk factor for melanoma is skin colour.
  - Caucasian, blond, or red hair colour
- The presence of a large number of both common acquired and dysplastic (atypical) melanocytic naevi is a major constitutional risk factor in fair-skinned people.

Environmental risk factors

- **Sunlight Exposure**, particularly in childhood, is the major environmental risk factor for development of melanoma in those people who are constitutionally at risk
  - A history of exposure to large doses of sunlight **sufficient to cause sunburn** in childhood
  - continual vs. episodic exposures
- A history of solar keratoses and nonmelanoma skin cancer is also a risk factor for melanoma
- Sun Screens?

Cutaneous Melanoma

"Melanoma writes its message on the the skin with its own ink, and is there for all to see."

"Melanoma can be diagnosed at an early biological stage when relatively simple excisional surgery carries a remarkably good prognosis."

N. C. Davis

Cutaneous Melanoma

CLINICAL DIAGNOSIS

- History of lesion – understand implications
- Knowledge of appearance of types of melanoma
- Good light
- Magnification

Melanoma

QUEENSLAND MELANOMA REGISTRY

Clinico Pathological Types

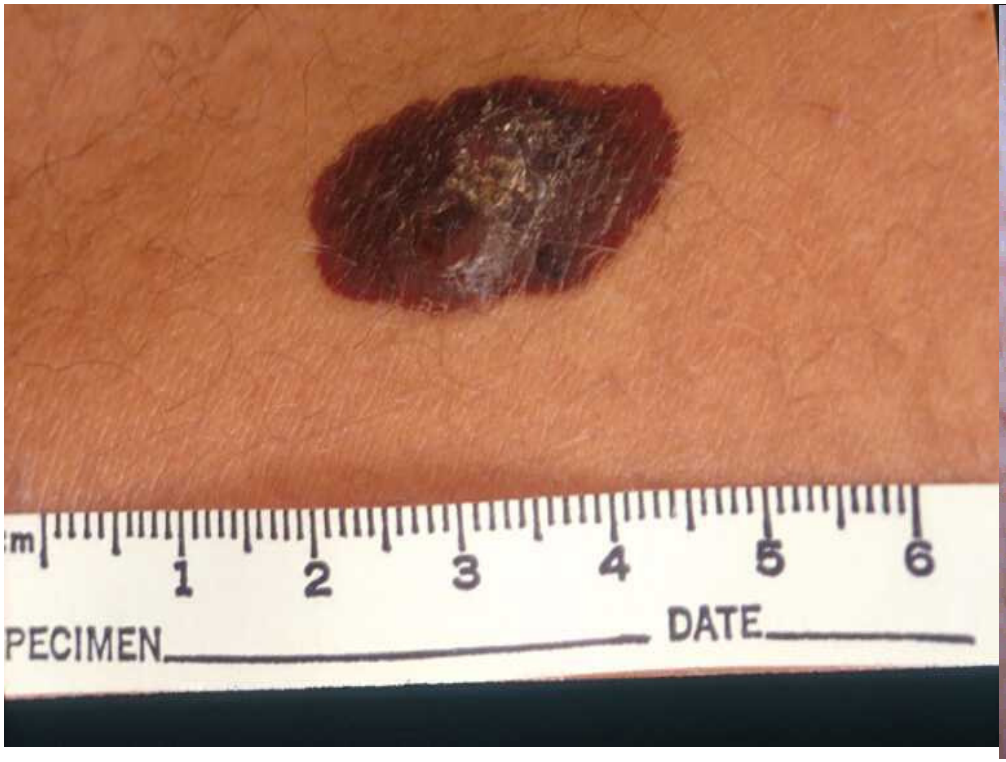
Superficial spreading melanoma	74%
Nodular melanoma	15%
Lentigo maligna melanoma	8%
Acral Lentiginous melanoma	1%
Other	2%

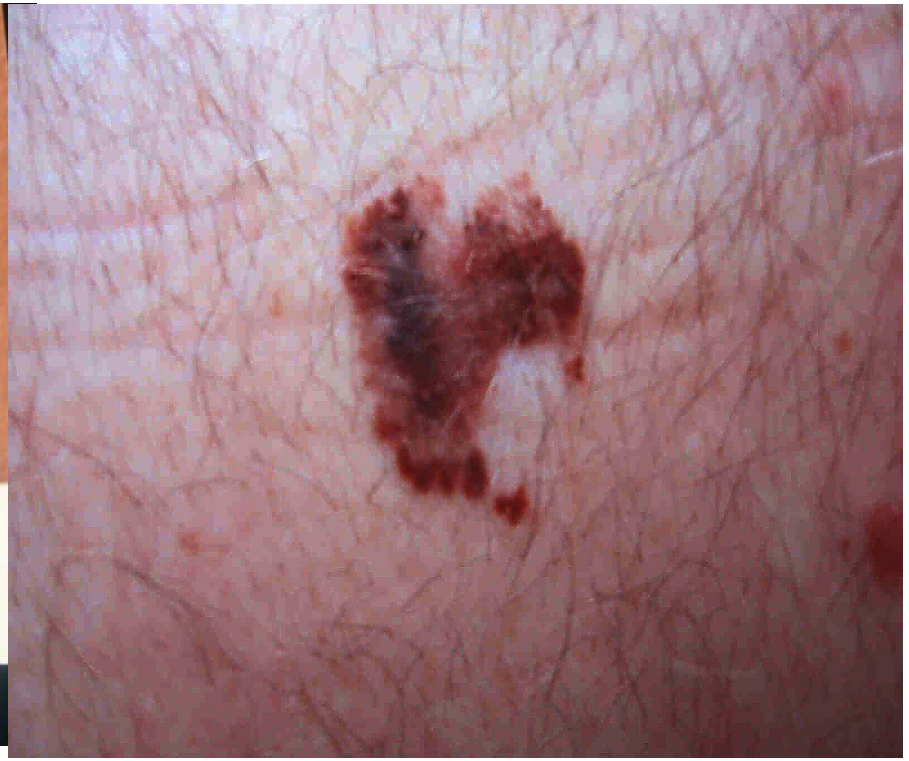
Melanoma

Superficial Spreading Melanoma

- Usually > 0.5 cm
- Variegated colour pattern – blue, black, brown, pink
- Irregular edge
- palpable +/- nodules

Superficial Spreading Melanoma



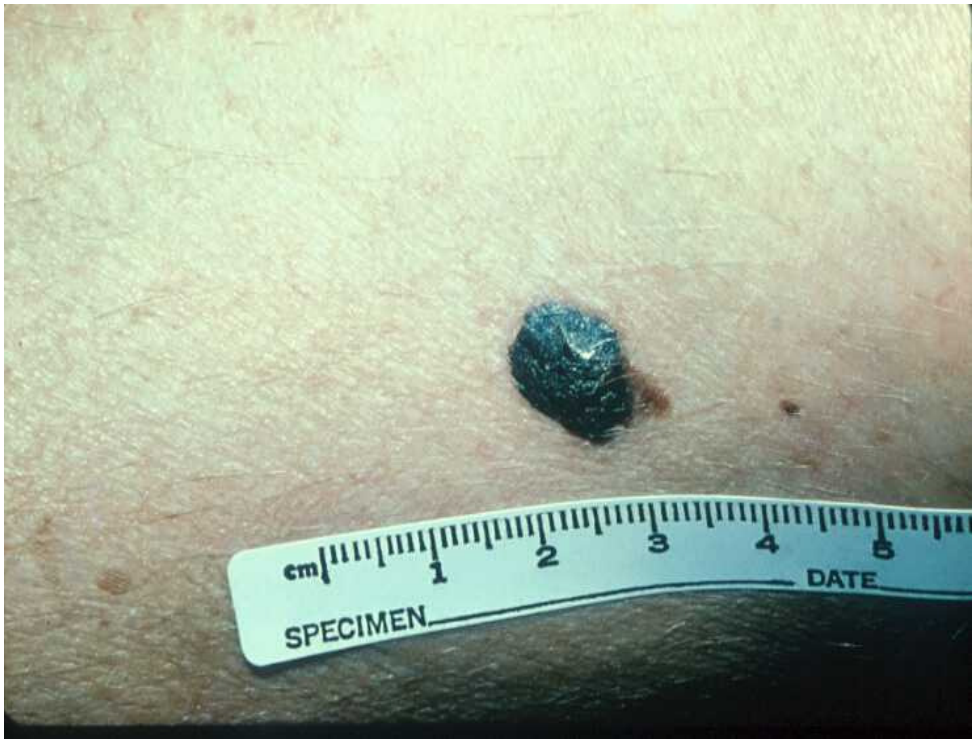


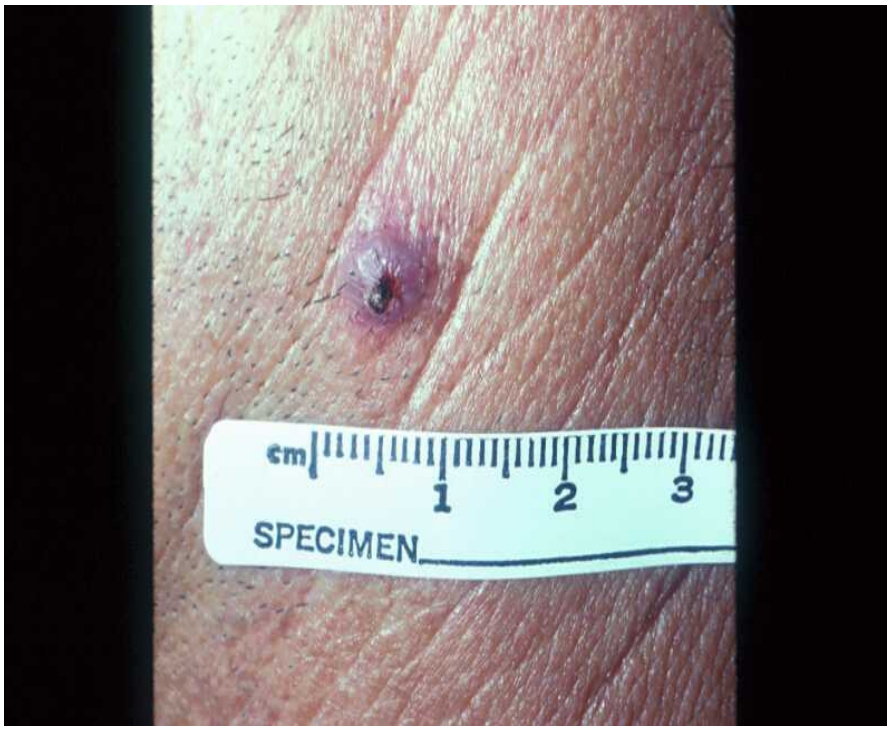
Melanoma

Nodular Melanoma

- Palpable nodule and convex
- Ulceration
- Uniform colour – blue, grey, black, pink, amelanotic
- Worse prognosis

Nodular Melanoma



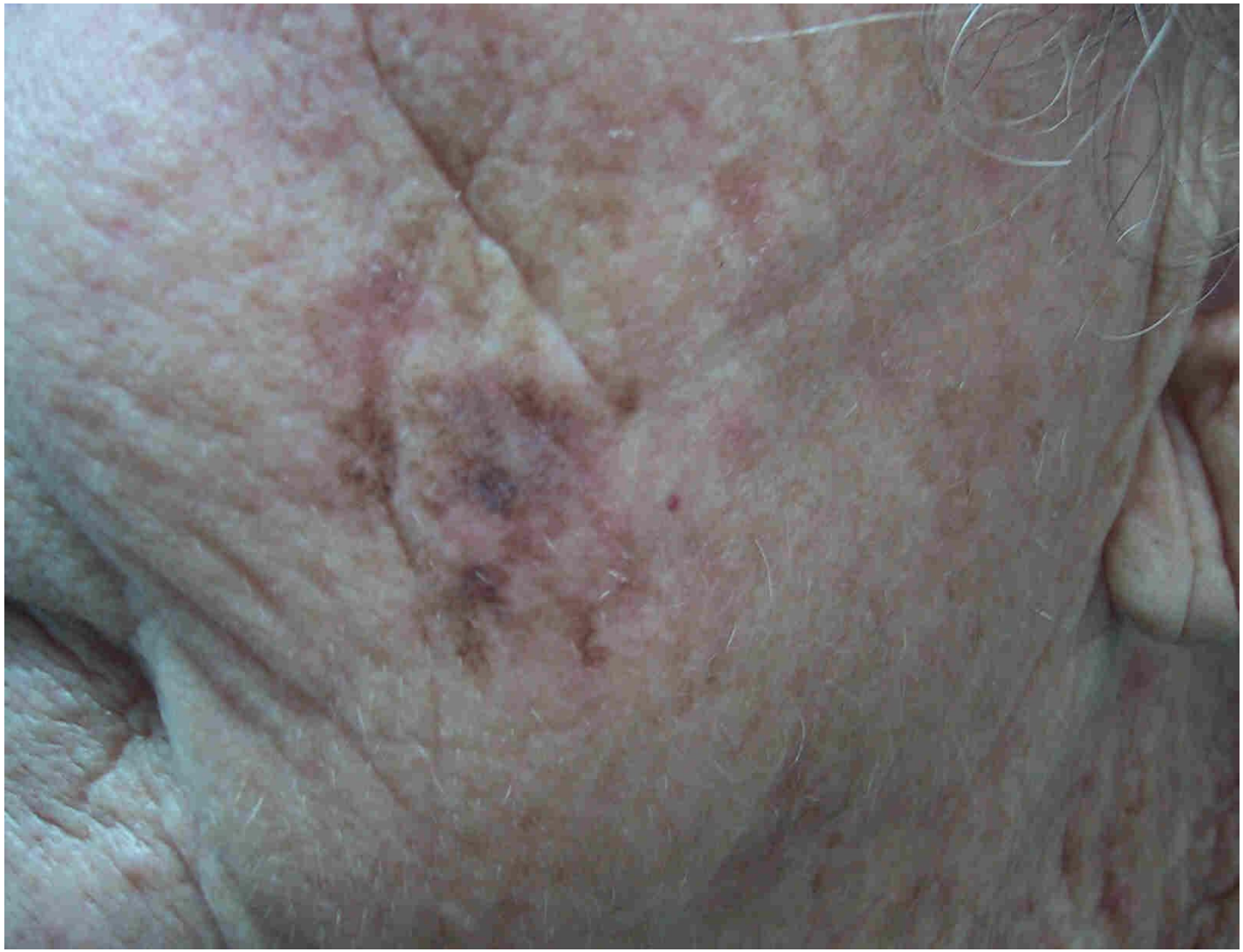


Melanoma

Lentigo Maligna Melanoma

- Arise in Hutchison's Melanotic Freckle
- Usually face or UV exposed skin
- > 60 years
- Flat macule, irregular outline
- Irregular pigment, brown, black, loss of pigment
- Can be very large

Lentigo Maligna Melanoma

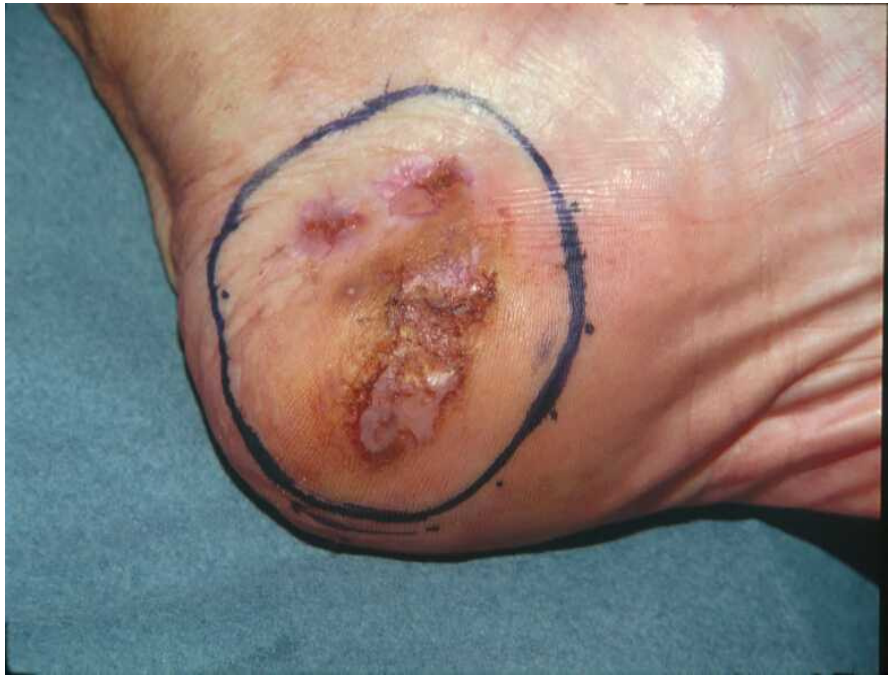


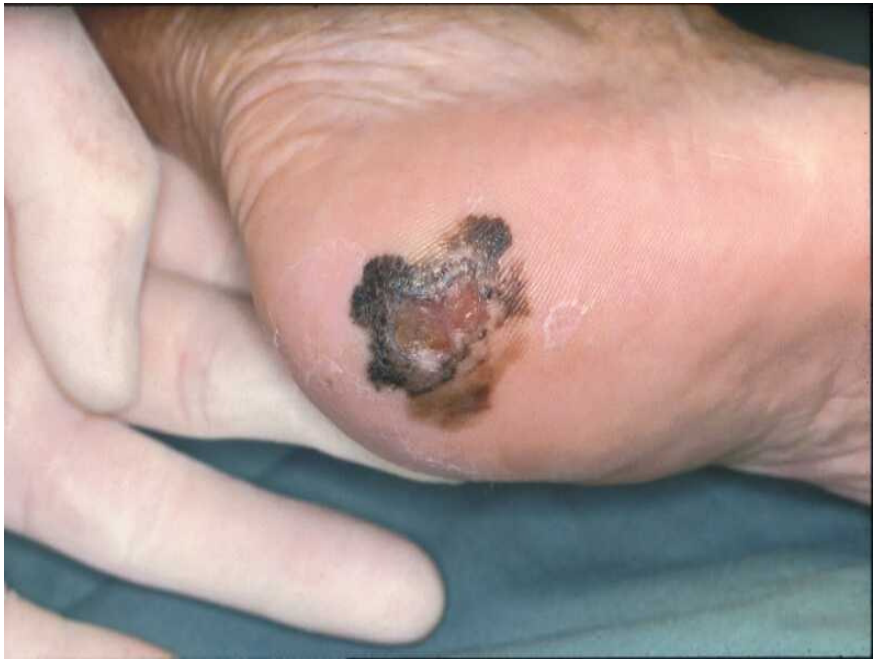
Melanoma

Acral Lentiginous Melanoma

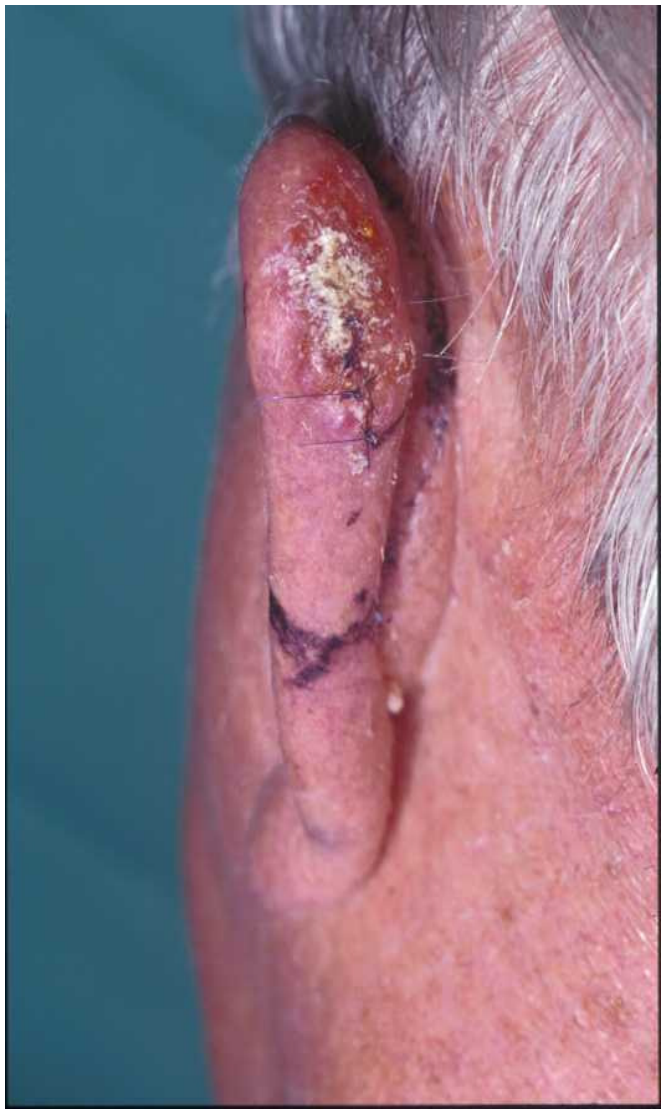
- Soles, palms, nail bed
- High incidence in orientals and black skinned people
- Brown – black stain, amelanotic, ulceration
- Late diagnosis – poor prognosis

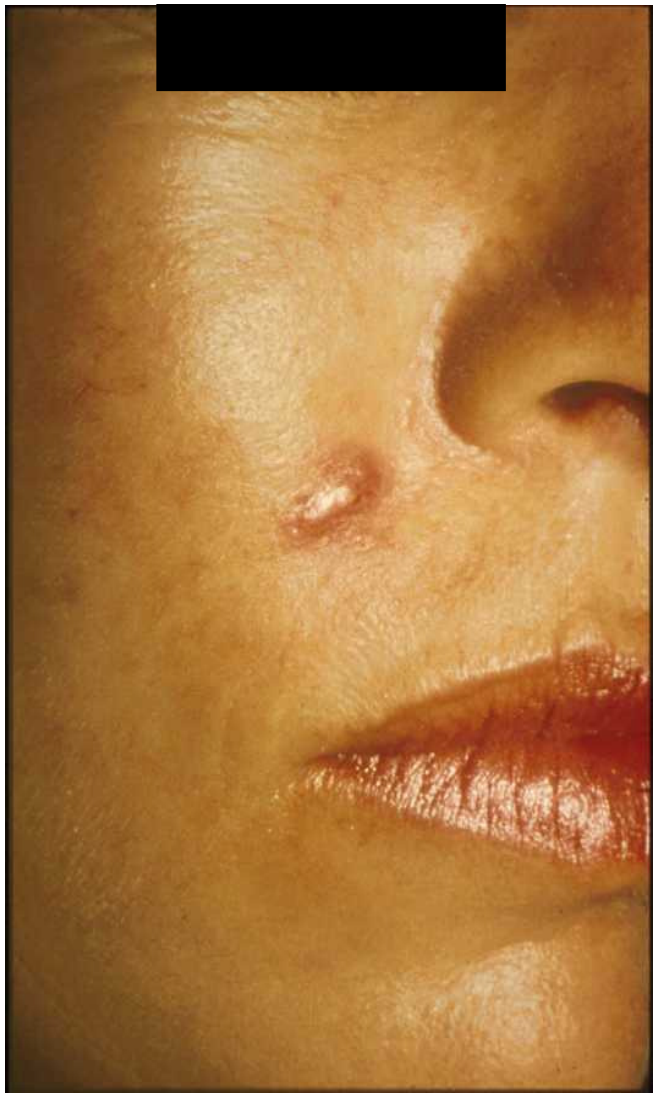
Acral Lentiginous Melanoma



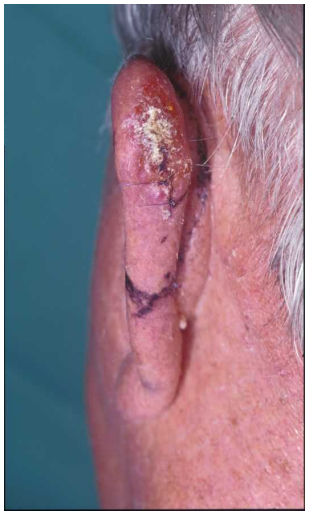


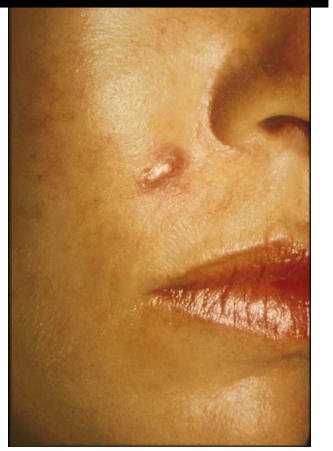
Desmoplastic / Neurotropic Melanoma

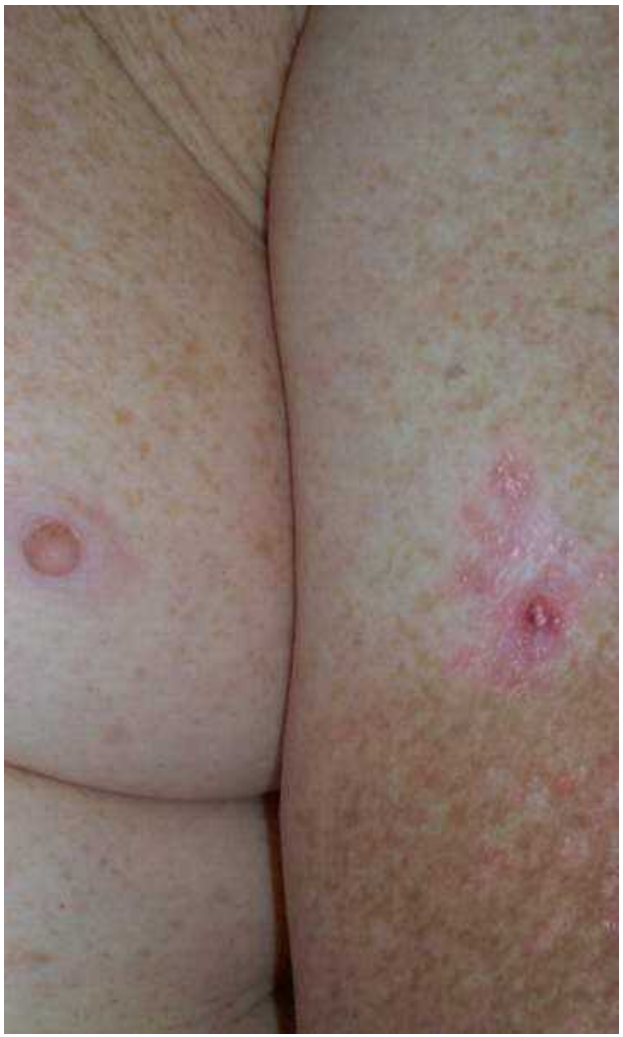


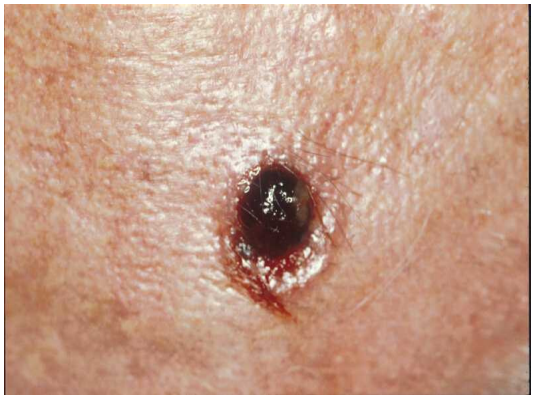


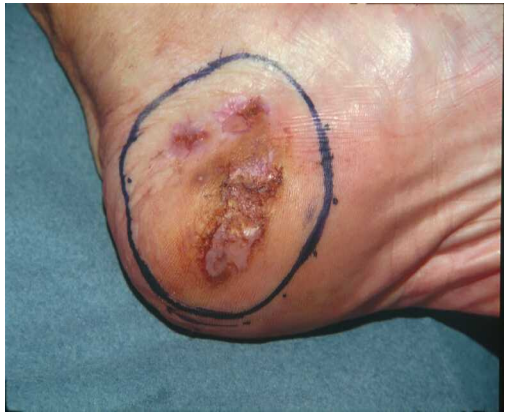
Amelanotic Melanoma

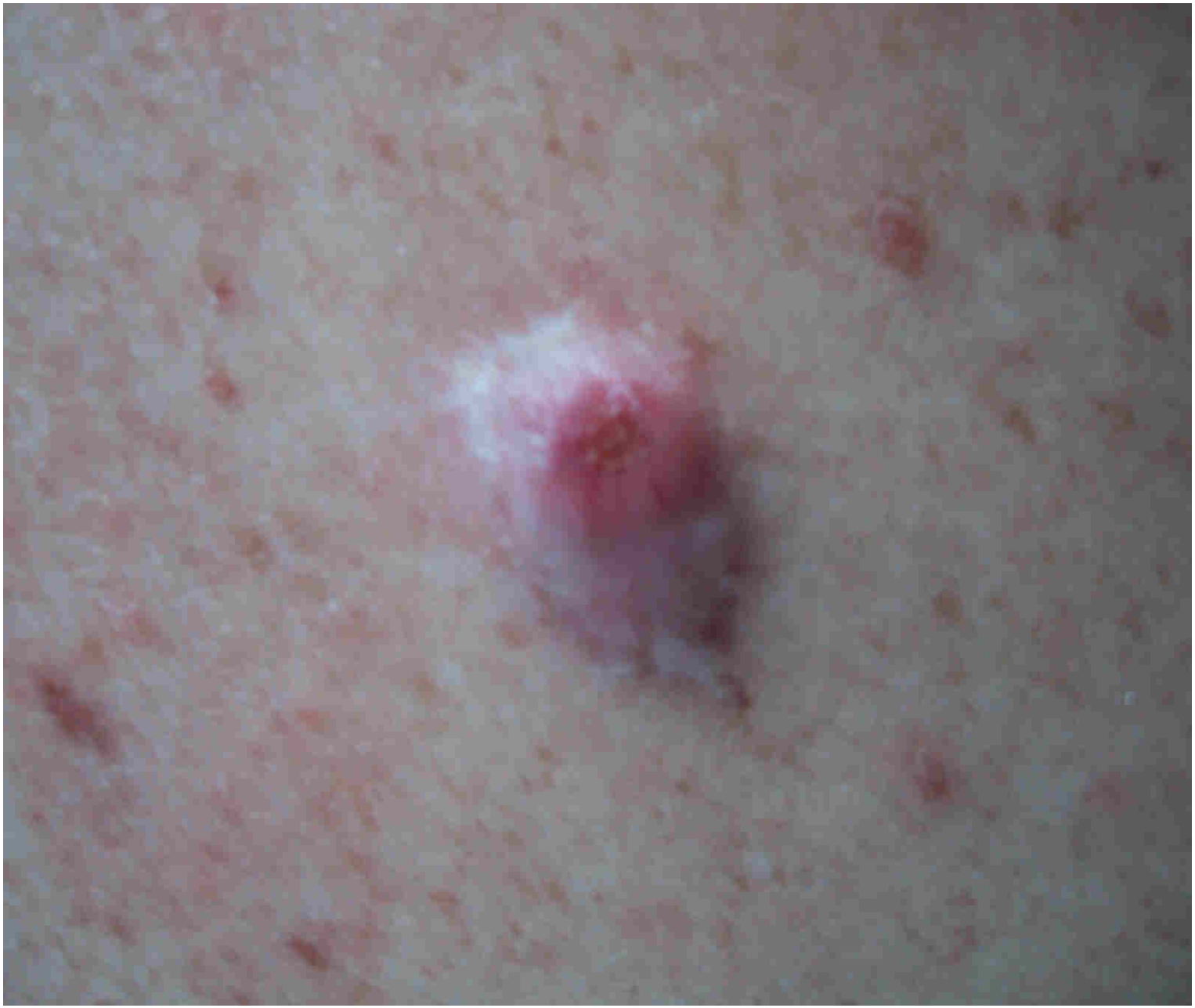












Cutaneous Melanoma

CLINICAL DIAGNOSIS

A = ASYMETRY

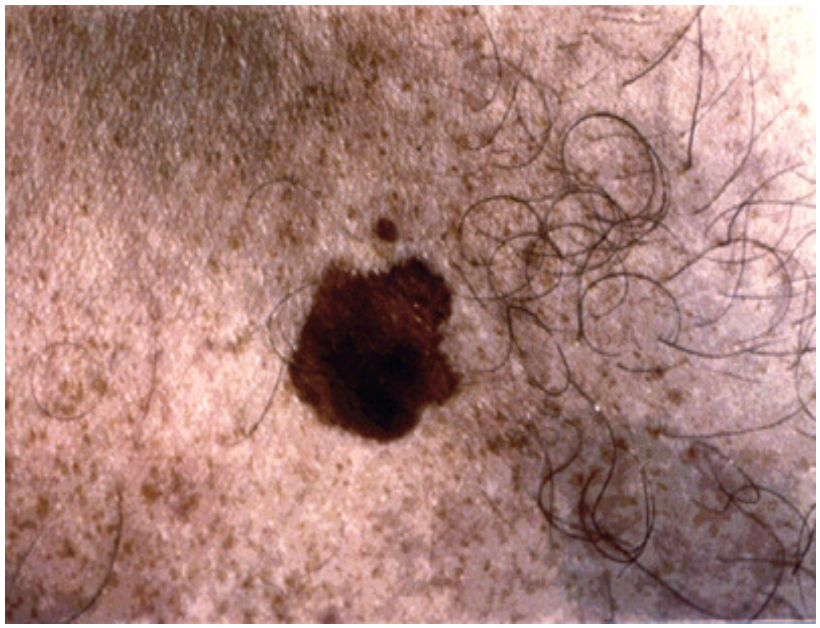
B = BORDER

C = COLOUR

D = DIAMETER

E = ELEVATION

Clinical Signs: A.B.C.D



Asymmetry: The shape of one half does not match the other

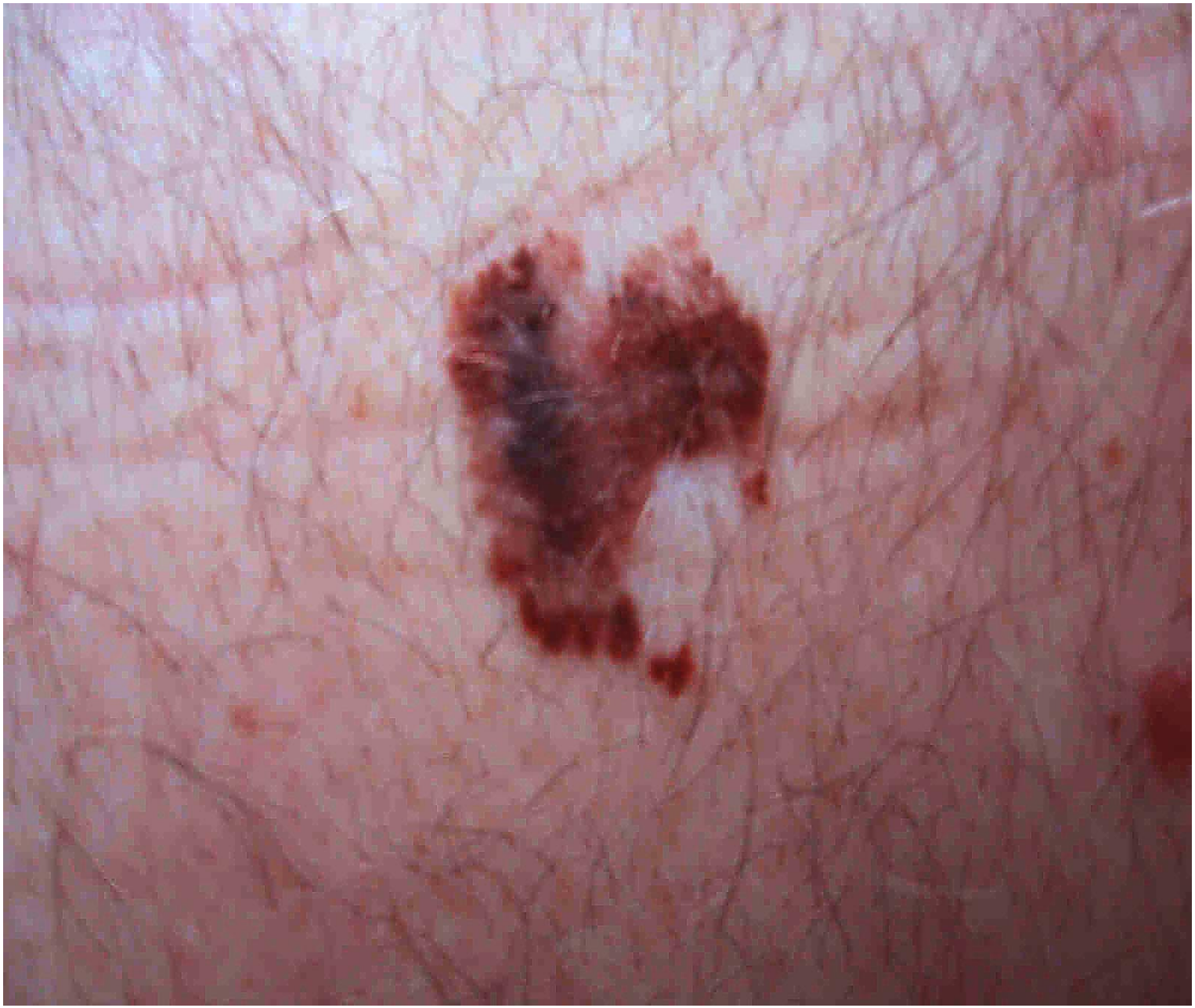
Border: uneven edges

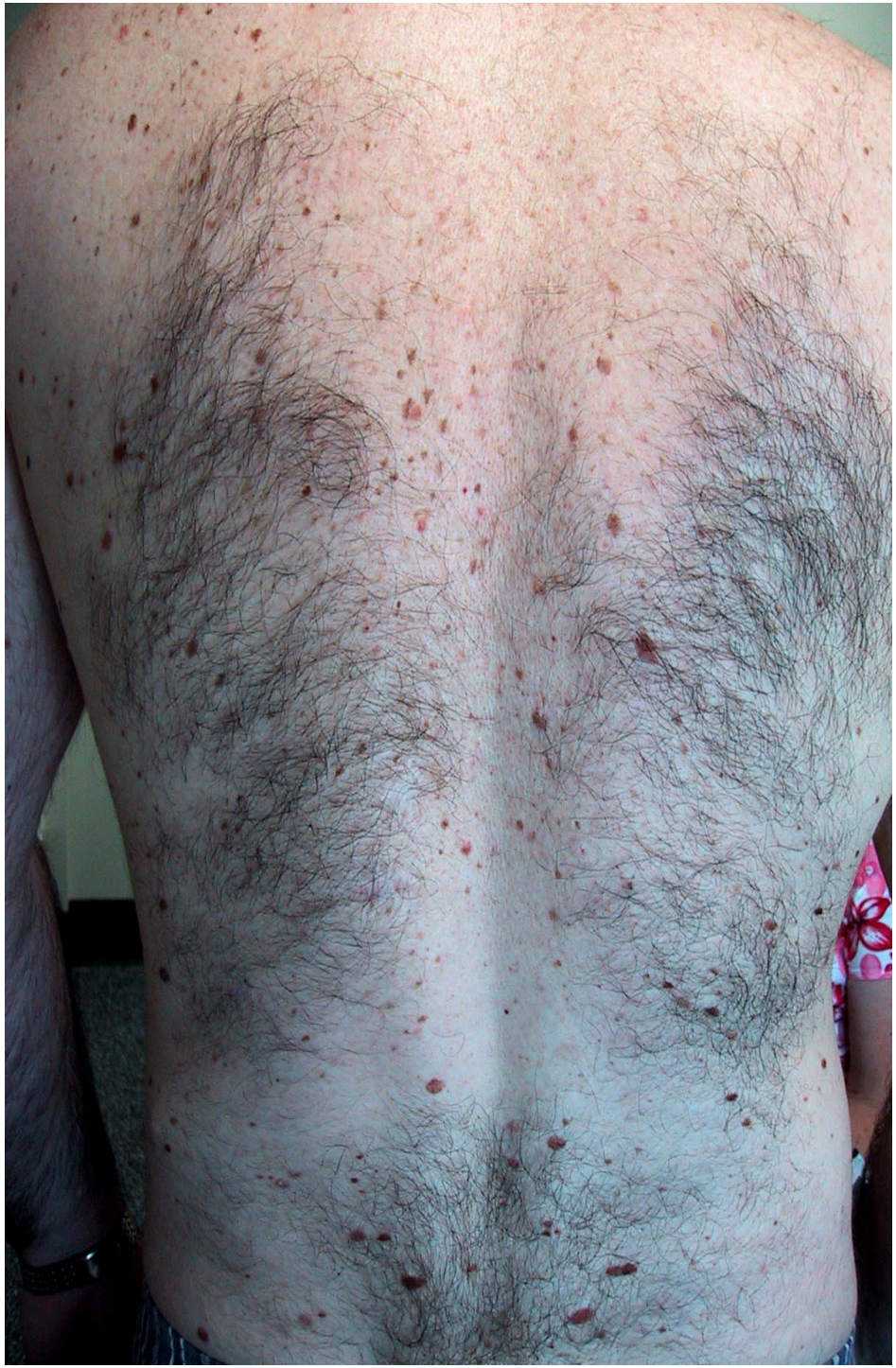
Colour: different shades of brown, blue, pink, or black

Diameter: >6 mm

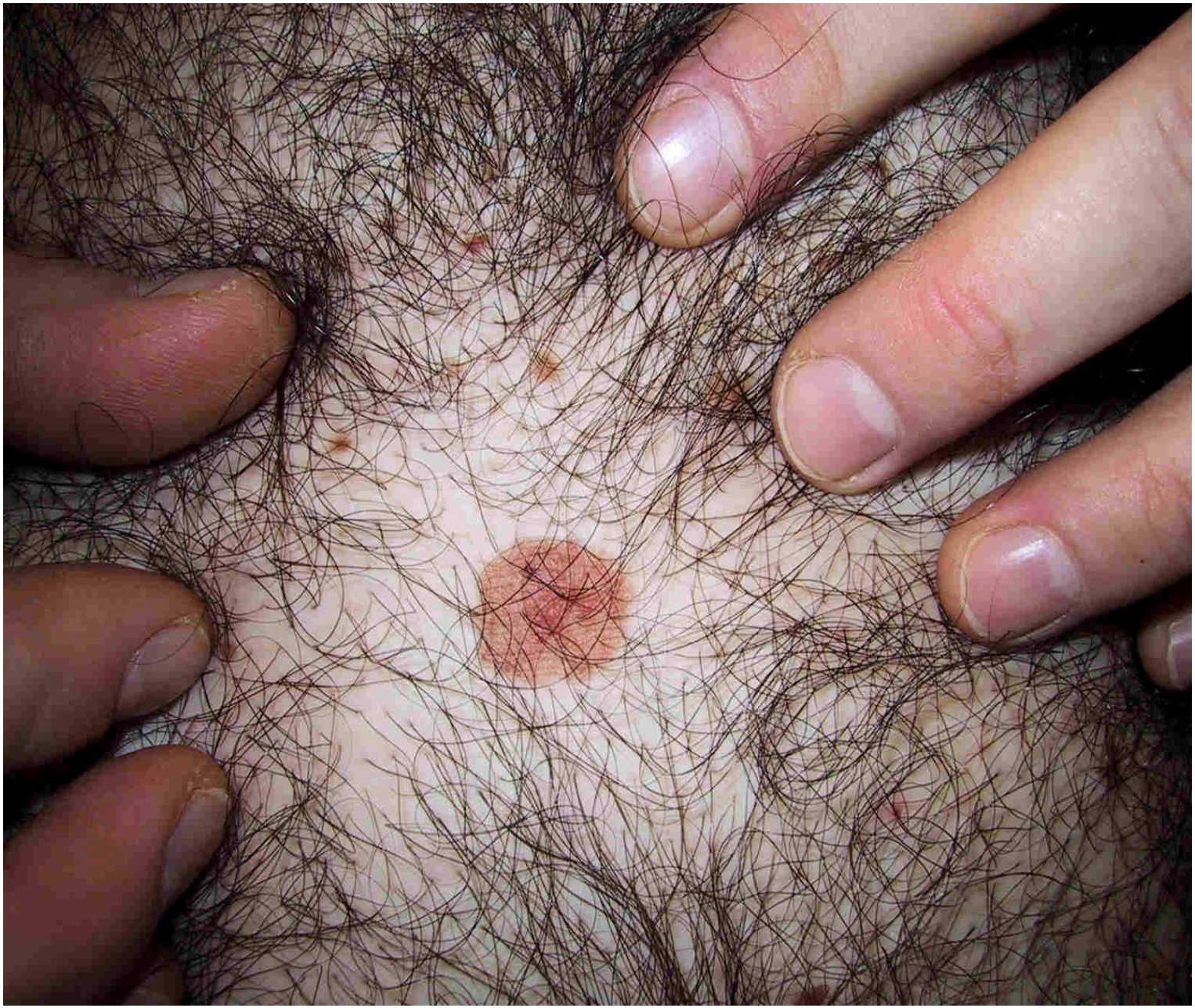
change in size

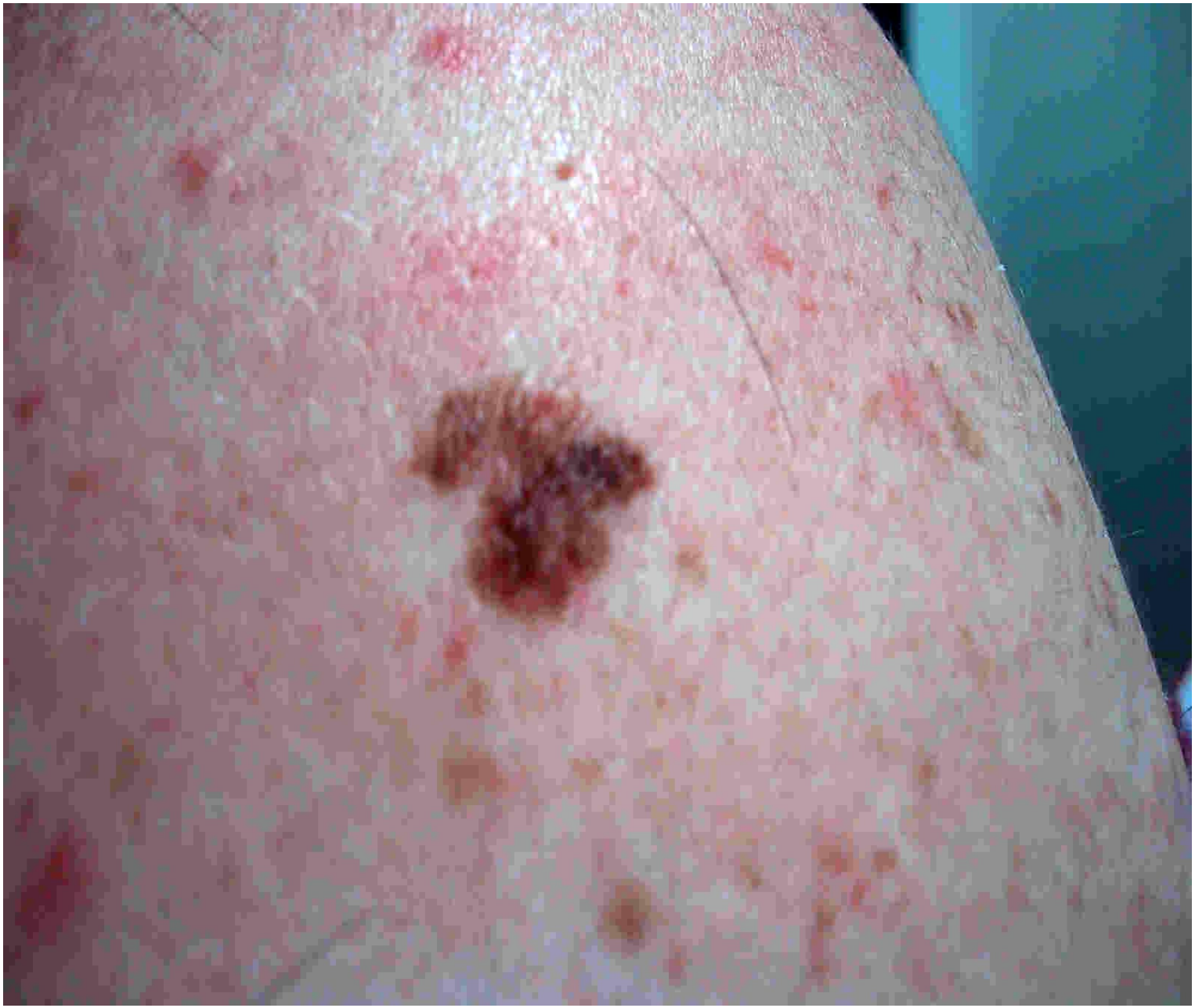
and ANY RECENT CHANGE





Multiple Dysplastic Naevi





Cutaneous Melanoma

Differential Diagnosis

Pigmented Lesions:

- Naevi
- Pigmented BCC
- Seborrhoetic Keratosis
- Solar Keratosis
- Dermatofibroma
- Lentigo / Freckle

Cutaneous Melanoma

Differential Diagnosis

Non-Pigmented Lesions:	SCC
	BCC (ulcerated)
	Pyogenic Granuloma
Haemorrhagic/Vascular:	Haemangioma
	Haemorrhage into nail bed or epidermis

Cutaneous Melanoma

Prognostic Indicators

Primary lesion thickness (Breslow)

Presence of ulceration in the primary

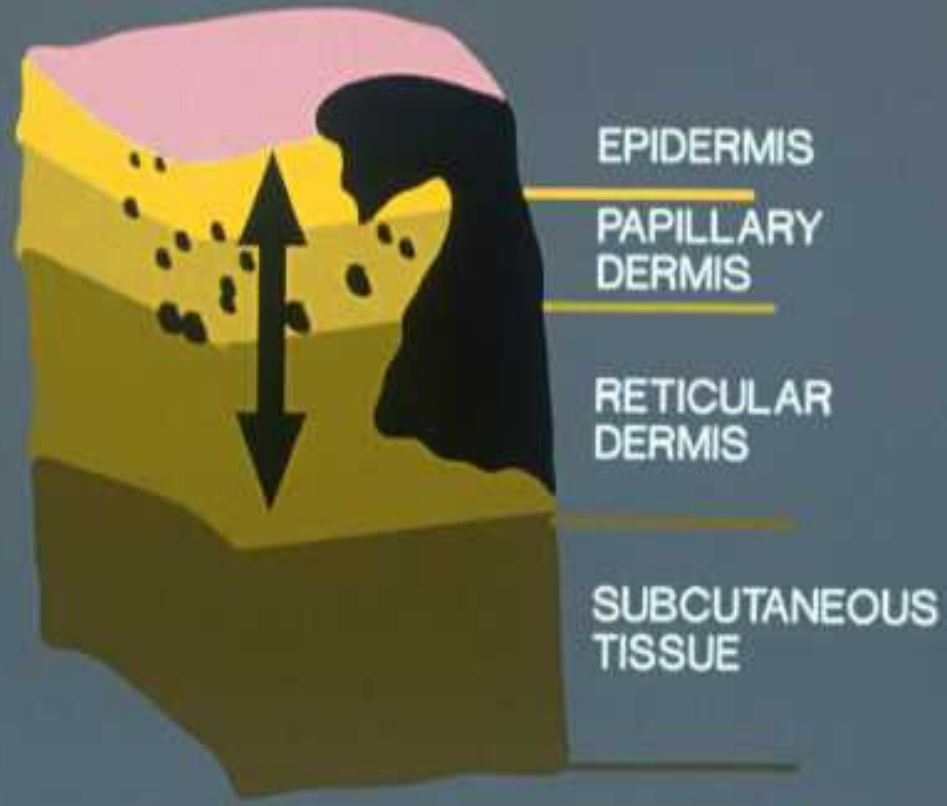
Lymph node status

(Stage of disease)

MELANOMA

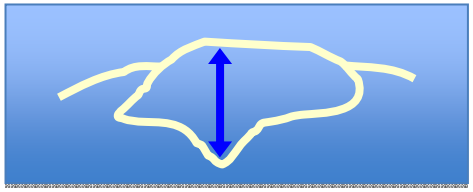
PROGNOSTIC FACTORS

THICKNESS (BRESLOW)



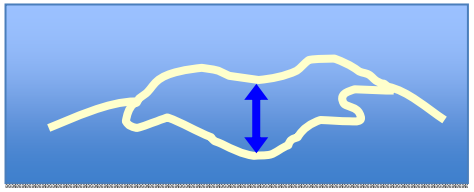
Malignant Melanoma
Measuring Thickness (Breslow)

by ocular micrometer – from granular layer



Total Height Is Measured
Vertically At Maximum Thickness

Nonulcerated Melanoma



Measured From Ulcer Base

Ulcerated Melanoma

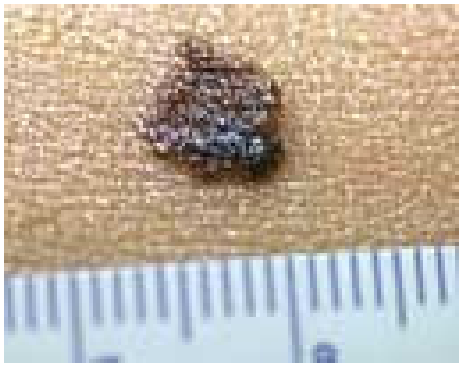
T1 1MM
T2 1 TO 2 MM
T3 2 TO 4 MM
T4 > 4 MM

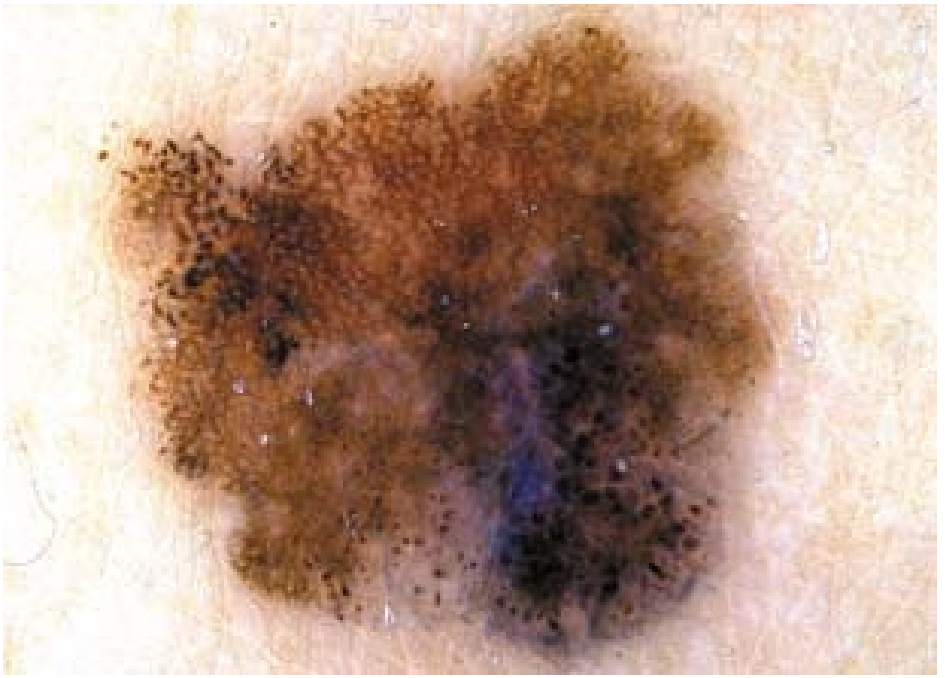
Problems – Regression

Ulceration

Diagnosis- Dermatoscopy

- Visual / Clinical
- Dermatoscopic
- Histological





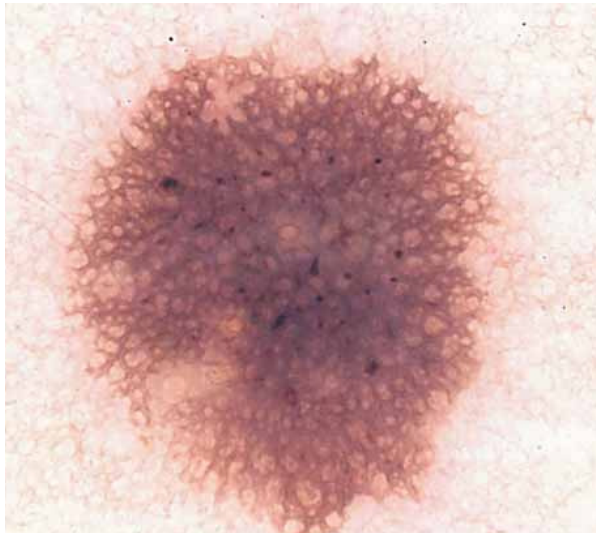
Dermatoscopic Features

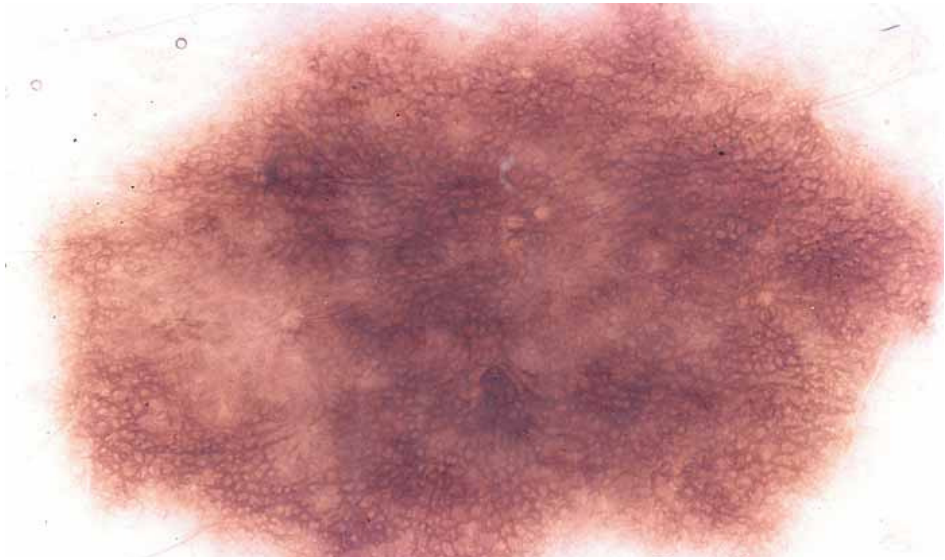
- Global
  - Reticular Pattern
  - Globular Pattern
  - Cobblestone Pattern
  - Homogeneous Pattern
  - Starburst Pattern
  - Parallel Pattern
  - Multicomponent Pattern
  - Lacunar Pattern
  - Unspecific Pattern
- Local
  - Pigment Network
  - Dots & Globules
  - Streaks
  - Blue whitish veil
  - Pigmentation
  - Hypopigmentation
  - Regression Structures
  - Vascular Structures

Dermatoscopic Features of Melanoma

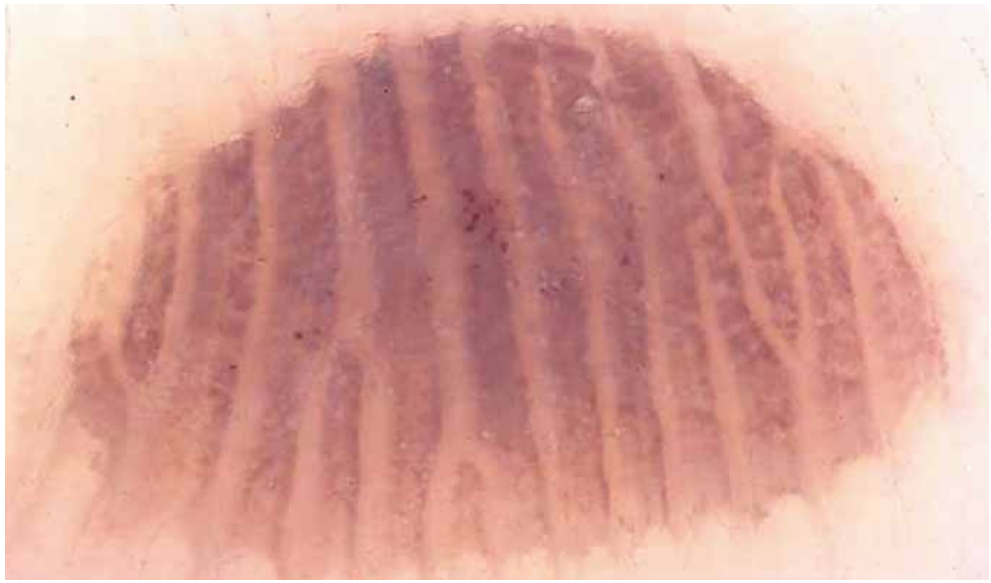
Diagnosis	Global Patterns	Specific Local Features	Additional Local Features	Confounding Features
Melanoma	Multicomponent Reticular globular parallel-ridge unspecific	Atypical pigment network irregular dots/globules irregular streaks blue-whitish veil irregular pigmentation regression structures dotted or linear irregular vessels	Hypopigmented areas hairpin vessels red globules	Homogeneous or starburst pattern typical pigment network regular dots/globules regular streaks milia-like cysts

Reticular Pigment Pattern

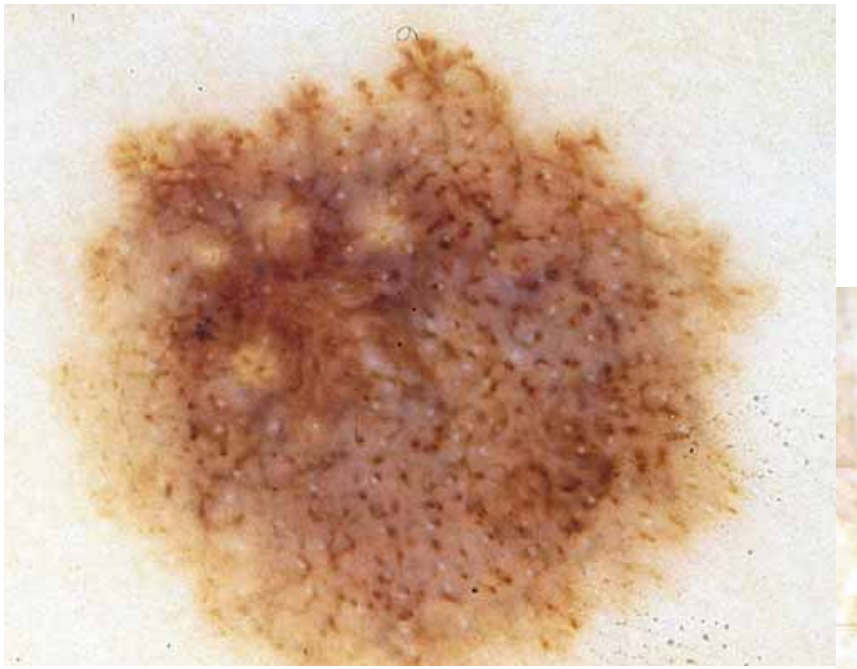


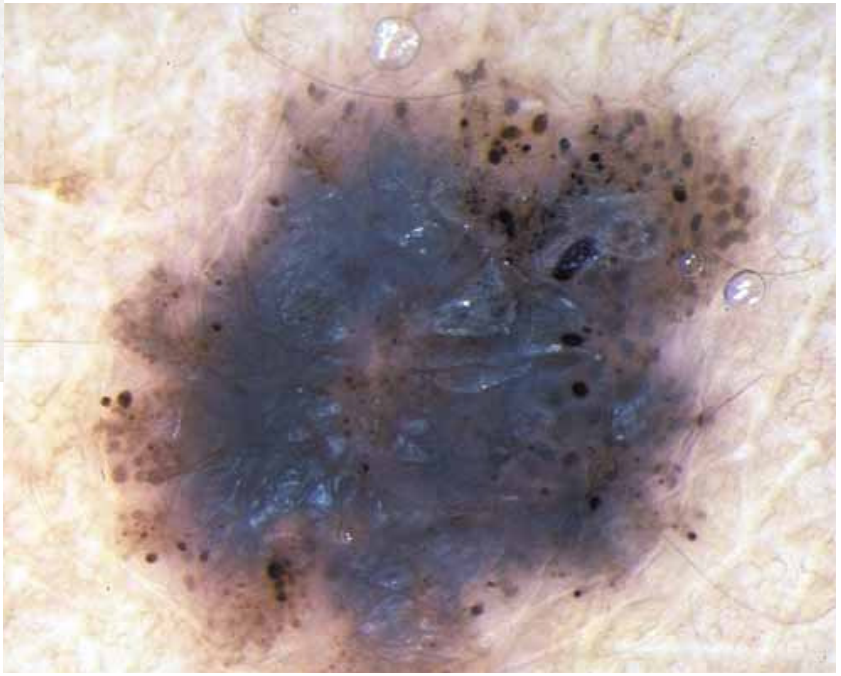


Parallel Pattern

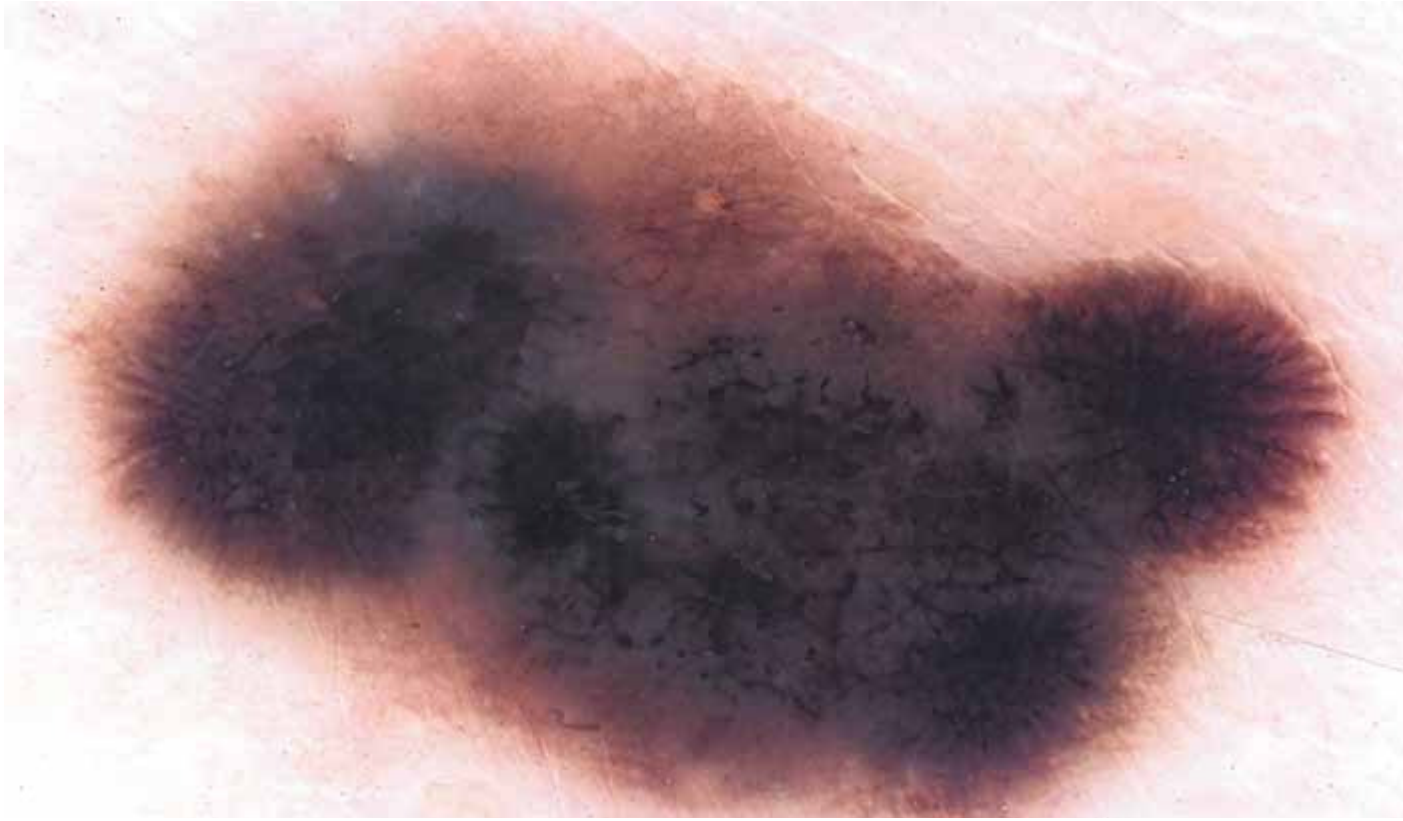


Dots & Globules

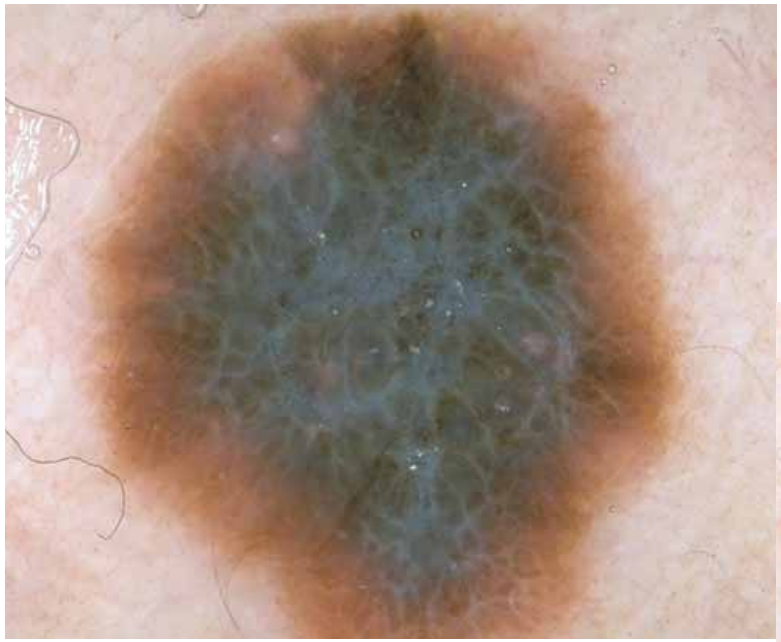


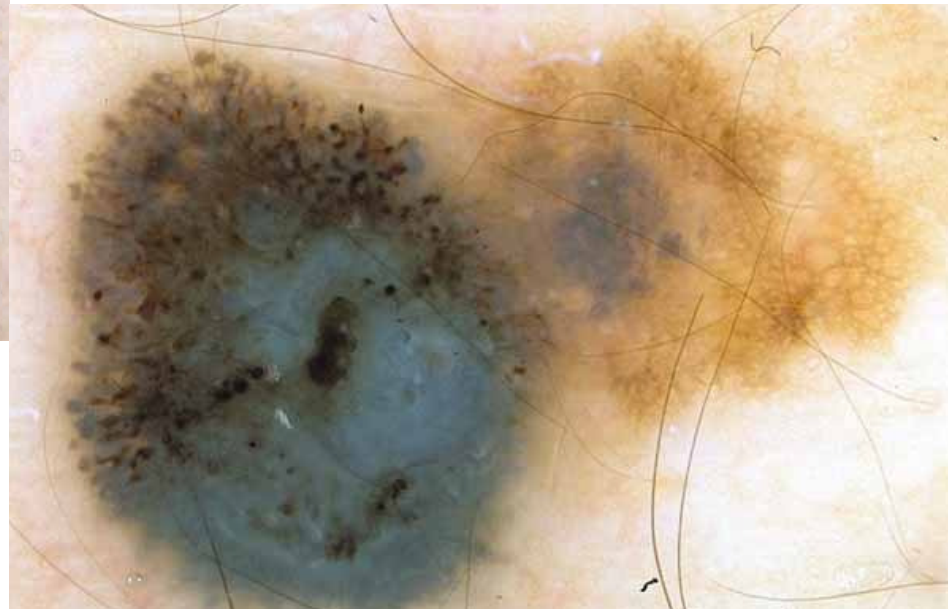


Streaks

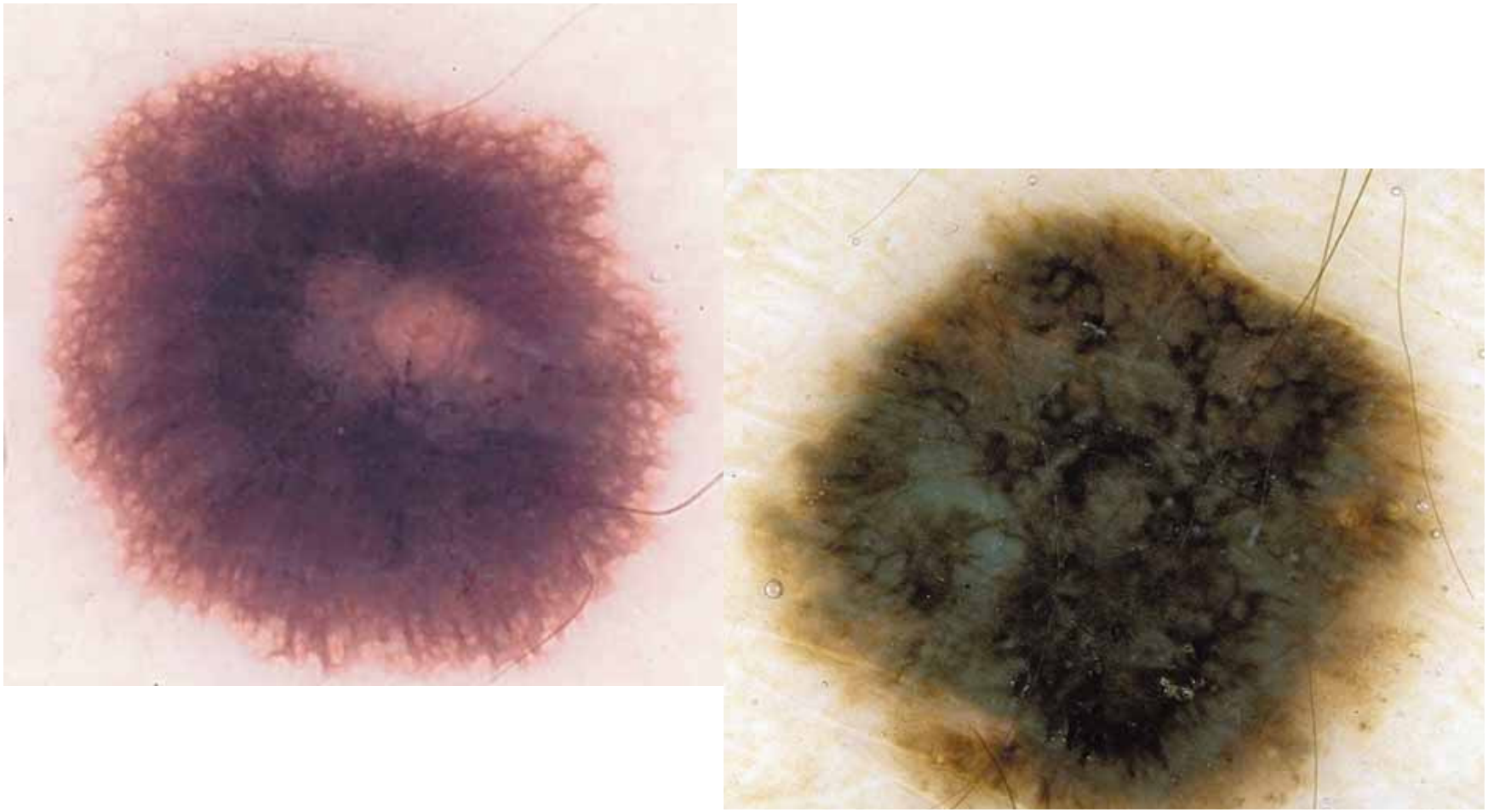


Blue-whitish veil





Pigmentation



Pattern Analysis

- The classic approach for diagnosis in dermoscopy is the so-called pattern analysis set forth by Pehamberger and colleagues in 1987
- because of problems inherent to the reliability and reproducibility of the diagnostic criteria used in pattern analysis, two additional diagnostic methods based on diagnostic algorithms have been introduced in the last few years with the aim to increase sensitivity in detecting cutaneous melanoma
- For both methods, ABCD rule of dermatoscopy and 7-point checklist, first a given pigmented lesion must be classified as melanocytic or non-melanocytic
- www.dermoscopy.org

ABCD rule of Dermoscopy
(Modified according to Stolz 1994)

Criterion	Description	Score	Weight factor
Asymmetry	In 0, 1, or 2 axes; assess not only contour, but also colors and structures	0-2	X 1.3
Border	Abrupt ending of pigment pattern at the periphery in 0-8 segments	0-8	X 0.1
Color	Presence of up to six colors 1-6 (white, red, light-brown, dark-brown, blue-gray, black)	1-6	X 0.5
Differential structures	Presence of network, structureless or homogeneous areas, streaks, dots, and globules	1-5	X 0.5

Formula for calculating TDS:

[(A score x 1.3) + (B score x 0.1) + (C score x 0.5) + (D score x 0.5)]

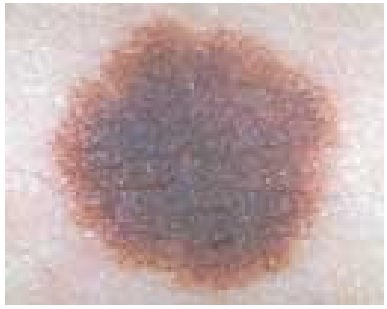
Total Dermatoscopy Score

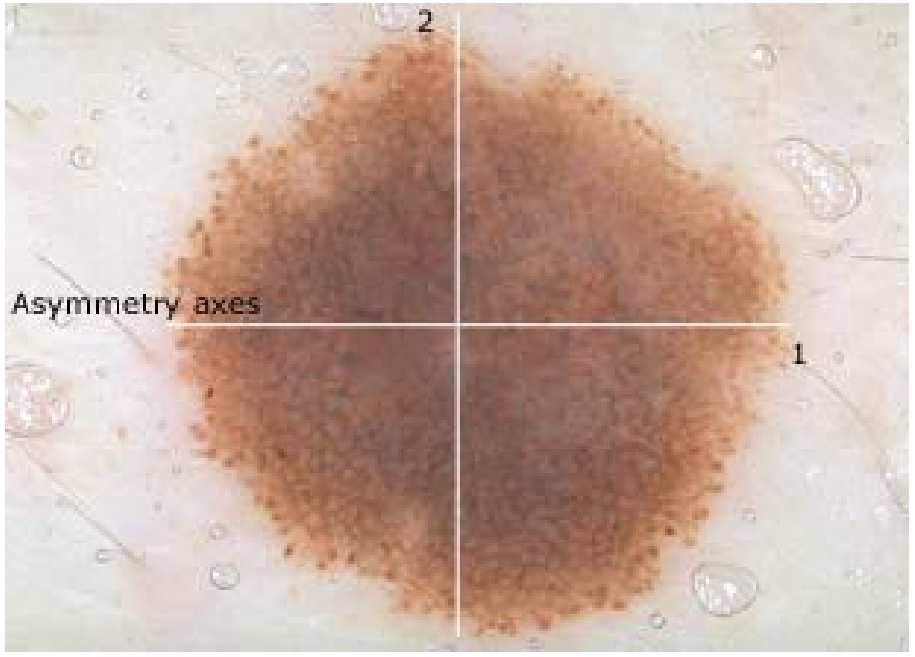
Total Dermoscopy Score (TDS)	Interpretation
<4.75	Benign melanocytic lesion
4.8-5.45	Suspicious lesion; close follow-up or excision recommended
>5.45	Lesion highly suspicious for melanoma
False-positive score (>5.45) sometimes observed in:	•Reed and Spitz nevi •Clark nevus with globular pattern •Congenital melanocytic nevus •Melanocytic nevus with exophytic papillary structure

The ABCD Rule

- **A** = 0 (x 1.3) = 0;
  B = 8 (x 0.1) = 0.8;
  C = 2 [light-brown, dark-brown] (x 0.5) = 1;
  D = 2 [network, globules] (x 0.5) = 1;
  TDS = 2.8 (benign)

  Histopathologic diagnosis: Clark nevus

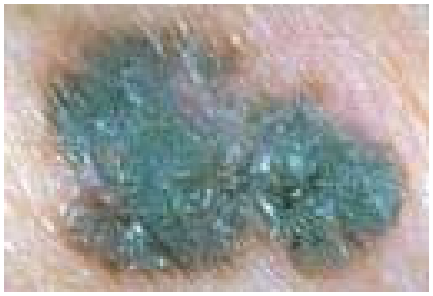


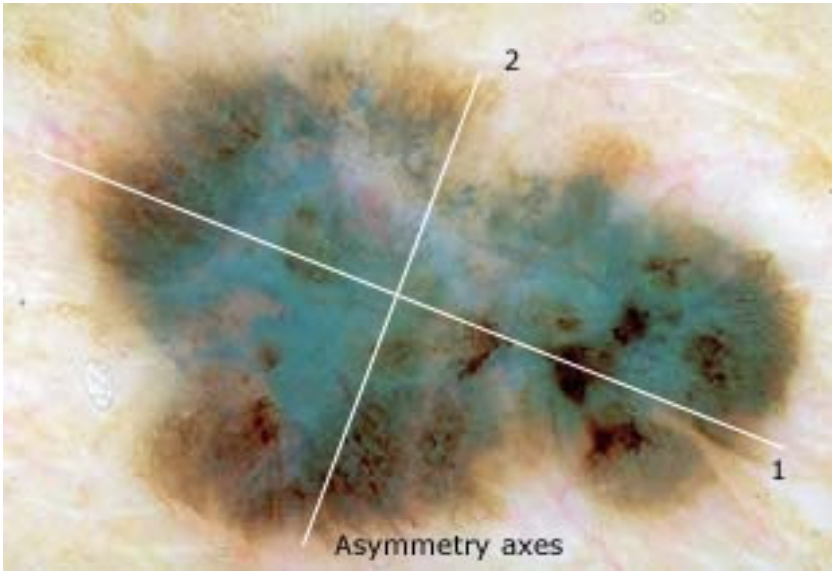


ABCD Rule

- **A** = 2 (x 1.3) = 2.6;
  B = 5 (x 0.1) = 0.5;
  C = 4 [light/dark-brown, blue-gray, black, white] (x 0.5) = 2;
  D = 4 [homogeneous areas, streaks, dots, globules] (x 0.5) = 2;
  TDS = 7.1 (malignant)

  Histopathologic diagnosis: melanoma





The 7-point checklist: Definition and histopathologic correlates of the 7 melanoma-specific dermoscopic criteria

Criterion	Definition	Histopathologic correlates
1. Atypical pigment network	Black, brown, or gray network with irregular meshes and thick lines	Irregular and broadened rete ridgesd
2. Blue-whitish veil	Confluent, gray-blue to whitish-blue diffuse pigmentation associated with pigment networkalterations, dots/globules and/or streaks	Acanthotic epidermis with focal hypergranulosis above sheets of heavily pigmented melanocytes in the dermis
3. Atypical vascular pattern	Linear-irregular or dotted vessels not clearly combined with regression structures and associated with pigment network alterations, dots/globules and/or streaks	Neovascularization
4. Irregular streaks	Irregular, more or less confluent, linear structures not clearly combined with pigment network lines	Confluent junctional nests of melanocytes
5. Irregular pigmentation	Black, brown, and/or gray pigmented areas with irregular shape and/or distribution	Hyperpigmentation throughout the epidermis and/or upper dermis
6. Irregular dots/globules	Black, brown, and/or gray round to oval, variously sized structures irregularly distributed within the lesion	Pigment aggregates within stratum corneum, epidermis, dermo-epidermal junction, or papillary dermis
7. Regression structures	White areas (white scarlike areas) and blue areas (gray-blue areas, peppering, multiple blue-gray dots) may be associated, thus featuring so-called blue-whitish areas virtually indistinguishable from blue-whitish veil	Thickned papillary dermis with fibrosis and/or variable amounts of melanophages

The 7-point checklist: a minimum total score of 3 is required for the diagnosis of melanoma

ELM criterion	Odds ratio[a]	Seven-point score[b]
Major criteria:		
1. Atypical pigment network	5.19	2
2. Blue-whitish veil	11.1	2
3. Atypical vascular pattern	7.42	2
Minor criteria:		
4. Irregular streaks	3.01	1
5. Irregular pigmentation	4.9	1
6. Irregular dots/globules	2.93	1
7. Regression structures	3.89	1

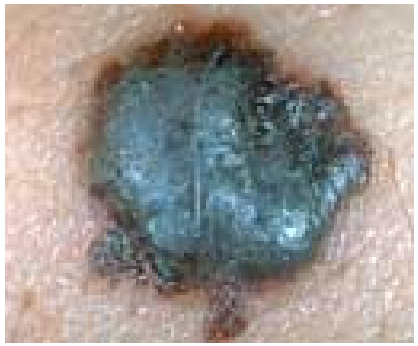
[a] Odds ratios measuring the capacity of each criterion to increase the probability of melanoma diagnosis.

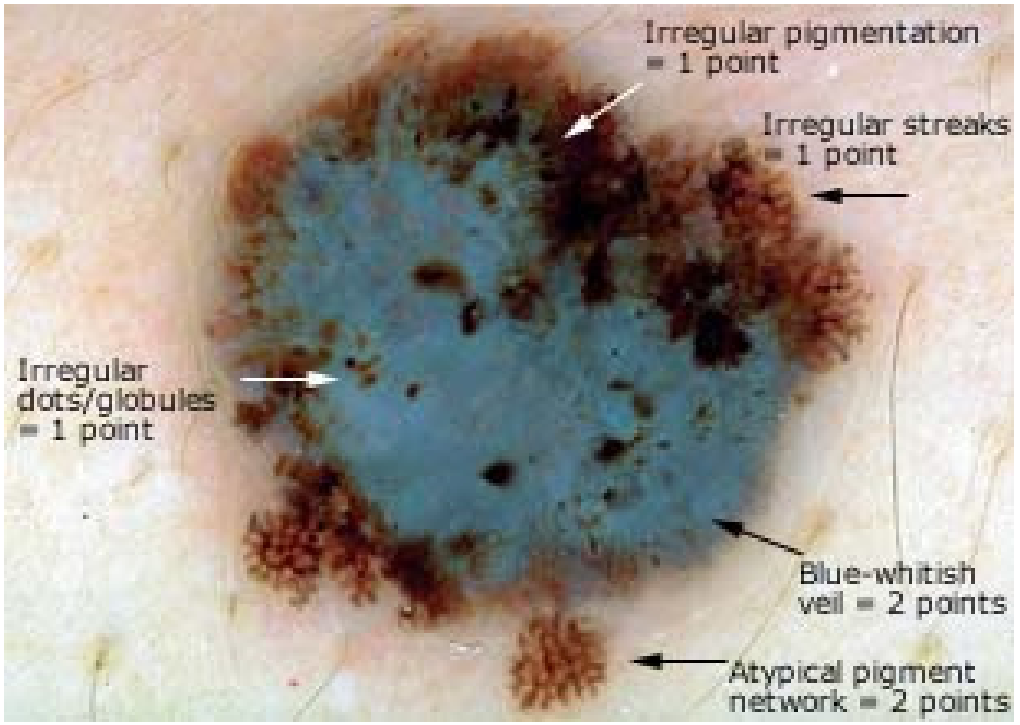
[b] The score for a criterion is determined on the basis of the odds ratio: >5 (score 2), and <5 (score 1).

Simply add the scores of each criterion that is present within a pigmented lesion

7-point Checklist

- Melanoma: 7-point score = 3





Cutaneous Melanoma

Pigmented Lesion - Suspicious

excision biopsy – 2mm margin

Punch and shave biopsies – only when excision is difficult or not appropriate

Management

- NHMRC Guidelines
- Excision margins are dependent on Stage
- The only new treatment that needs clarification would be Sentinel Lymph Node biopsy

Cutaneous Melanoma

- Excision Margins
  - Level I / *In situ:* 5 mm margin recommended
  - Invasive Melanoma: what evidence for margins?

Cutaneous Melanoma

EXCISION MARGINS - R.C.T.

- W.H.O. melanoma group 1979 - 1987

  300 patients
  melanoma less than 2 mm
  margin 1cm vs 3cm

CONCLUSIONS

- Margins did not influence survival
- 1cm margin higher local recurrence
  (all melanomas > 1mm)

Veronesi U. N.Eng J Med 1988

Cutaneous Melanoma

INTER GROUP MELANOMA STUDY
Median follow-up 10 years

Patients	Thickness	Local Recurrence	Regional Recurrence	10 Year Survival
445	1-2mm	2%	9%	83
215	2-3mm	4%	16%	67
77	3-4mm	12%	30%	50%

Ulceration poor prognostic indicator

Overall Local recurrence 4%

Regional recurrence 13%

Cutaneous Melanoma

EXCISION MARGINS - R.C.T.

US Inter group melanoma study

486 patients

melanoma 1- 4mm (trunk & proximal extremities)

margin 2cm vs 4cm

CONCLUSIONS

- No difference in survival
- 2cm margin. Less time in hospital (less grafts)
- Local recurrence affected by thickness **not** margin
- Ulceration higher local recurrence

Balch C et al. Ann Surg 1993

Cutaneous Melanoma

EXCISION MARGINS - R.C.T

French multicentred study:337 patients

melanoma < 2mm
margin 2cm vs 5cm

CONCLUSIONS

- No difference in survival
- No difference in locoregional recurrence.

Khayat et al. Cancer 2003;97:1941-6

Cutaneous Melanoma

EXCISION MARGINS - R.C.T

UK multicentre study: 900 patients
melanoma > 2mm
margin 1cm vs 3cm

CONCLUSIONS

- No difference in survival
- 3cm margin. Higher inpatient treatment and GA
- 1cm higher locoregional recurrence

Thomas MJ et al. NEJM 2004:350:757-66

Cutaneous Melanoma

EXCISION MARGINS

- 4 randomised / controlled trials. 1cm vs 3cm
  2cm vs 4cm
  2cm vs 5cm
- Local recurrence influenced by thickness
- Local recurrence only if > 1mm thick
- Ulceration increased local recurrence
- Locoregional recurrence higher if > 2mm
- Margin influence on survival if > 2mm after combined statistical analysis.

Cutaneous Melanoma

EXCISION MARGINS

Recommendation

MM < 2mm: Minimum margin 1cm

Consider wider margin – 2cm:

thick melanoma > 2mm

desmoplastic / neurotropic variant

Regional Node Management

OPTIONS – Observe

Elective node dissection

Lymph node mapping/ sentinel node biopsy

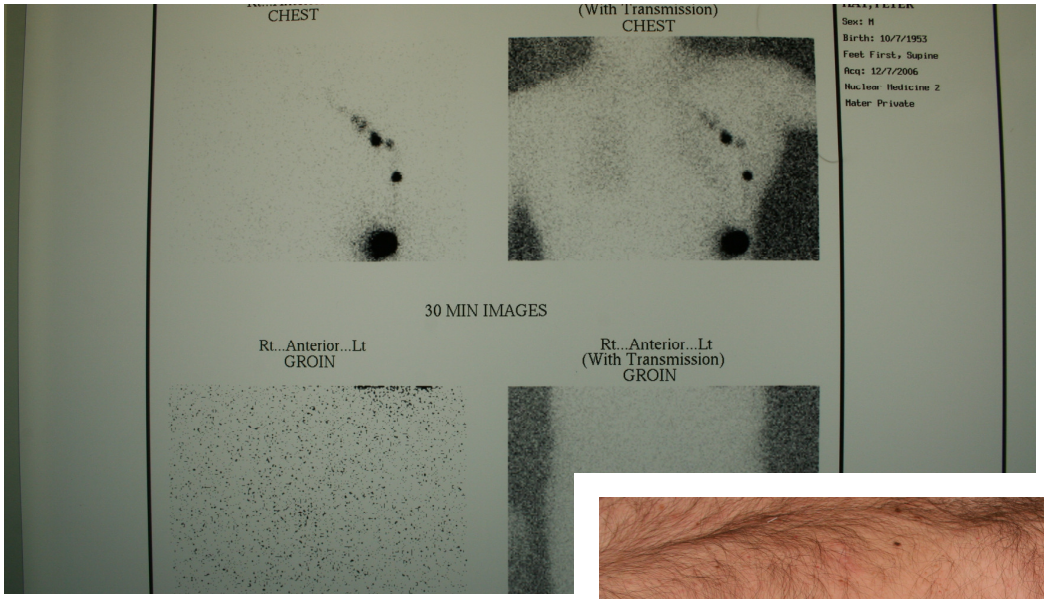
Therapeutic node dissection

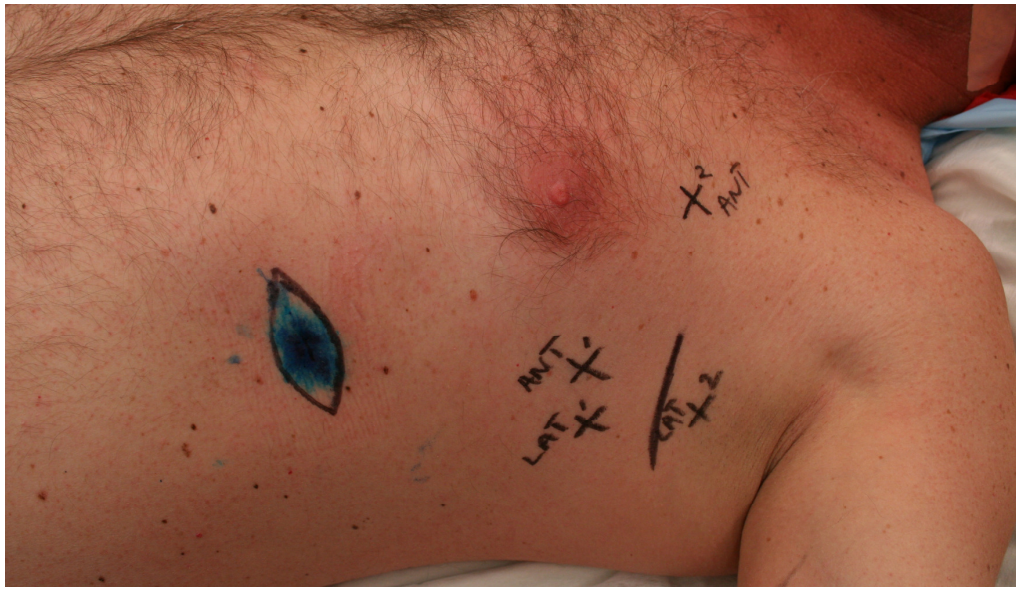
Place of Sentinel Lymph Node Biopsy

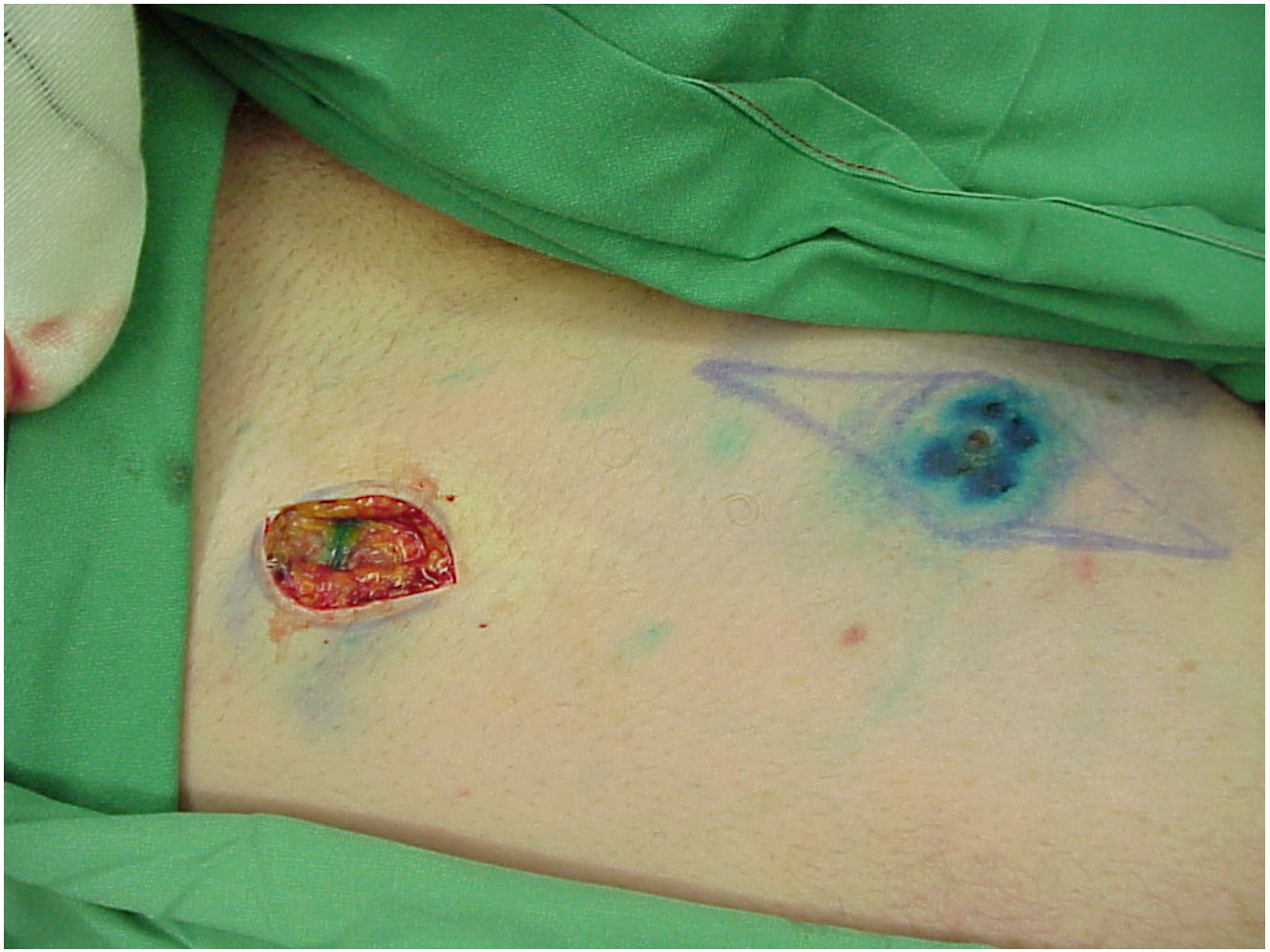
- Good Prognostic Test
- Jury still out on if it provides any survival advantage
  - MSLT 1 interim analysis (@8years) is possibly being misinterpreted in the US at this time

Sentinel Lymph node Biopsy

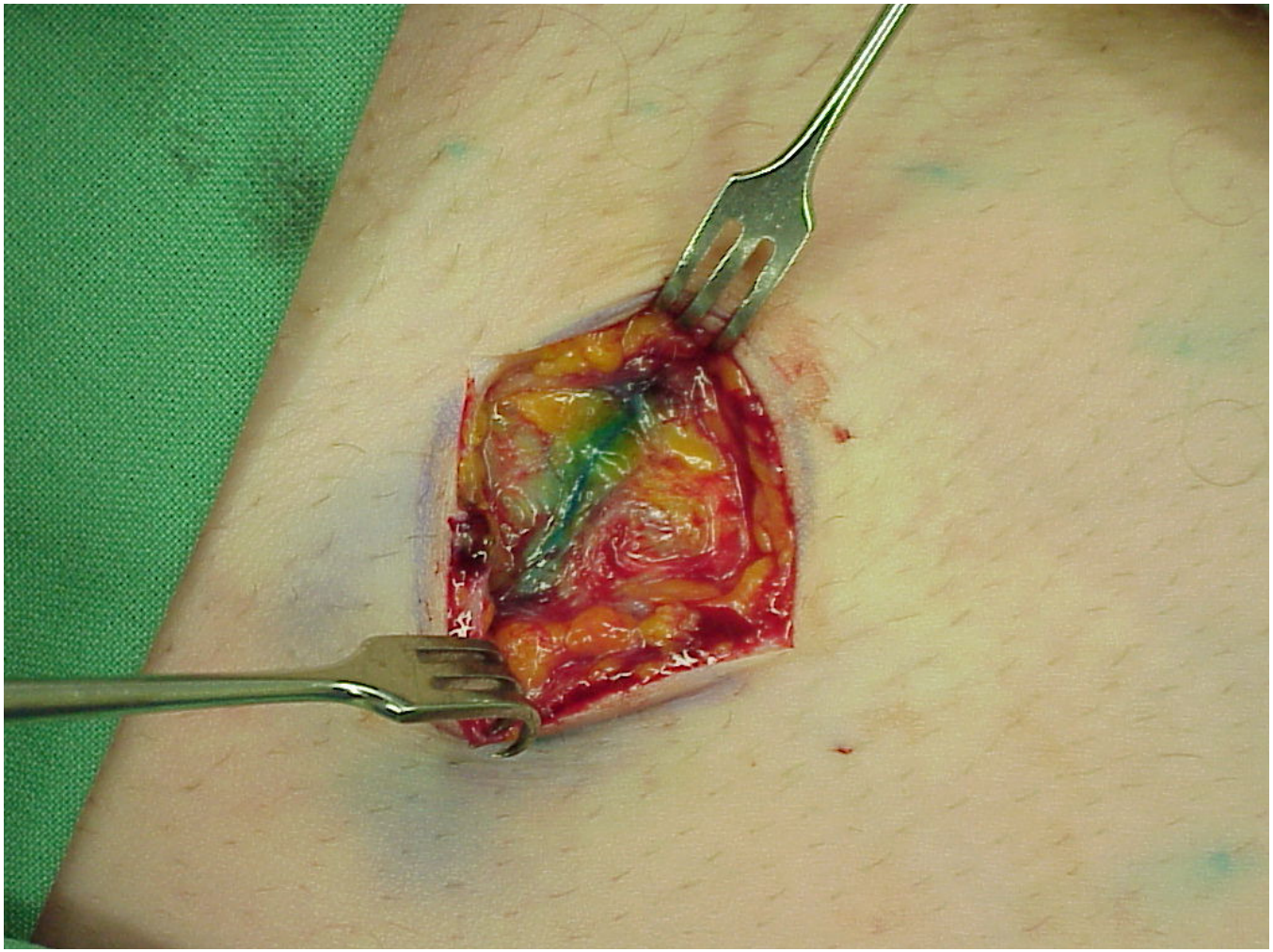
- Preoperative Lymphoscintigraphy
  - Injection with Radioactive dye
- General anaesthetic
- Injection with Patent Blue
- Dissection of the Sentinel Node


CHEST
(With Transmission)
CHEST
Sex: M
Birth: 10/7/1953
Feet First, Supine
Acq: 12/7/2006
Nuclear Medicine 2
Mater Private
30 MIN IMAGES
Rt...Anterior...Lt
GROIN
Rt...Anterior...Lt
(With Transmission)
GROIN

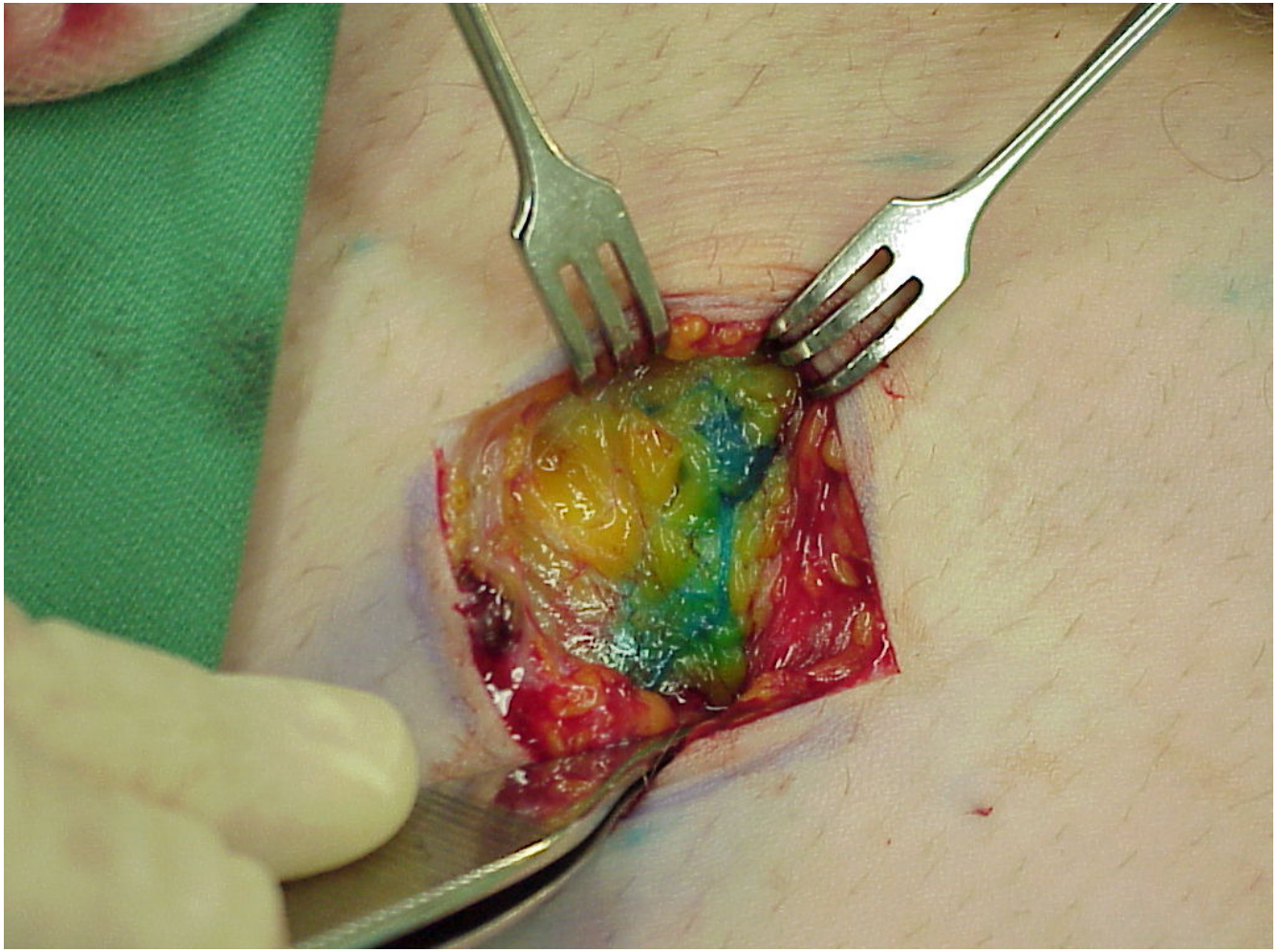

ANT
LAT



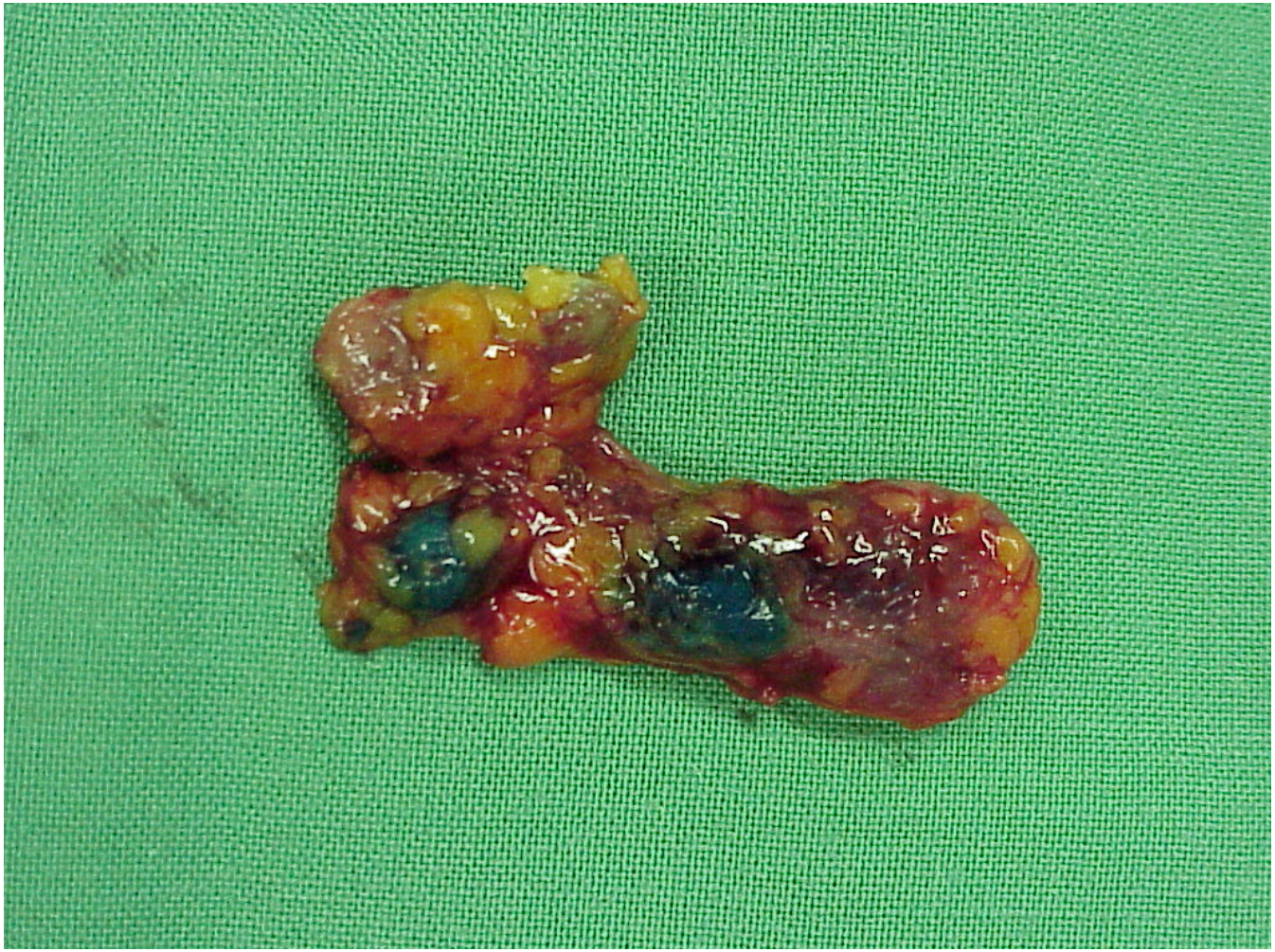
Sentinel Lymph Node Biopsy



Sentinel Lymph Node Biopsy



Sentinel Lymph Node Biopsy

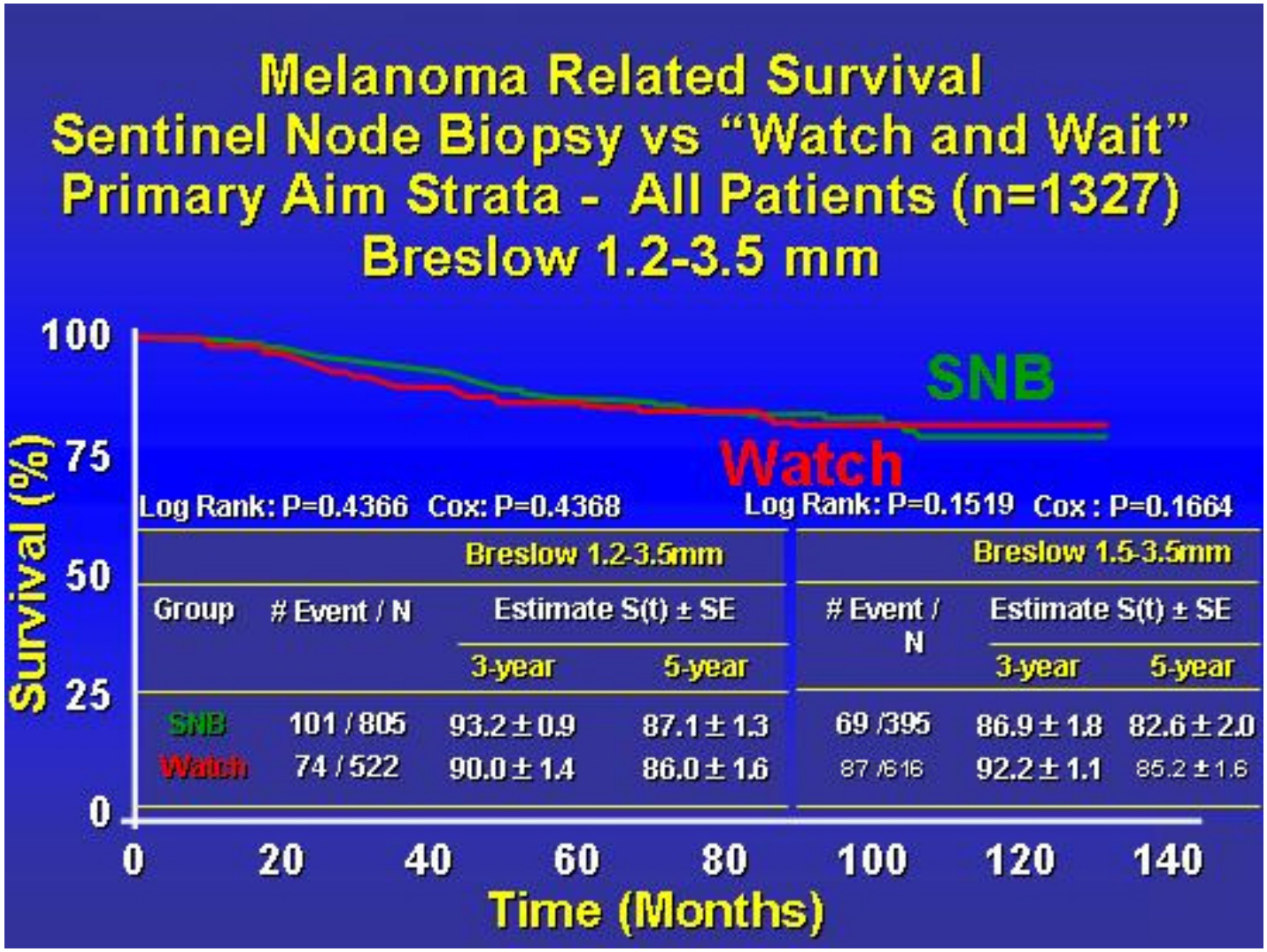


Sentinel Lymph Node Biopsy

Regional Treatment

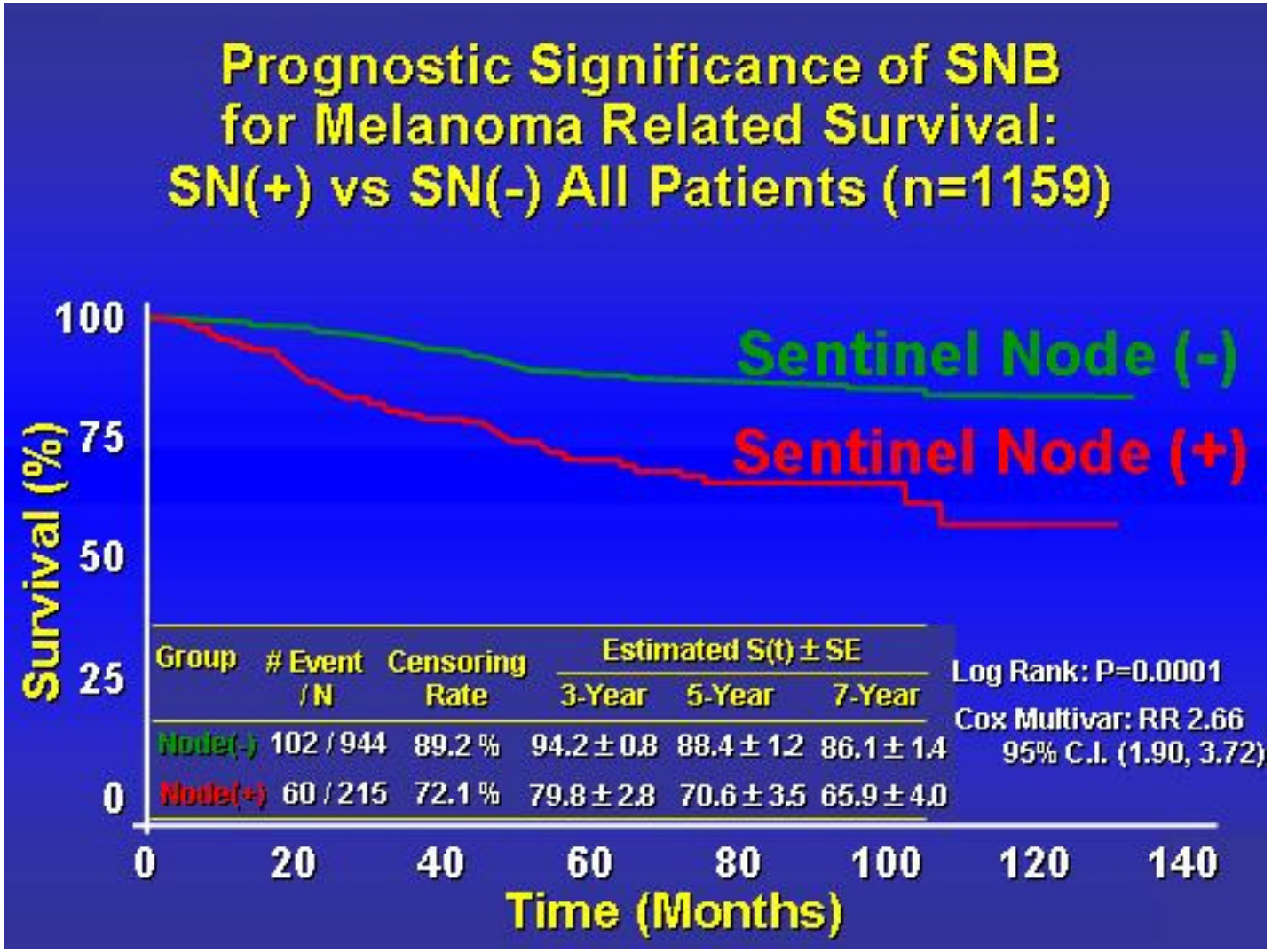
- Multicentre Selective Lymphadenectomy Trial 1 (MSLT 1)
  - 2001 patients
  - WLE alone vs WLE and SLNB
  - If SLNB positive – regional dissection.
  - End points = survival, overall and disease free

MSLT 1

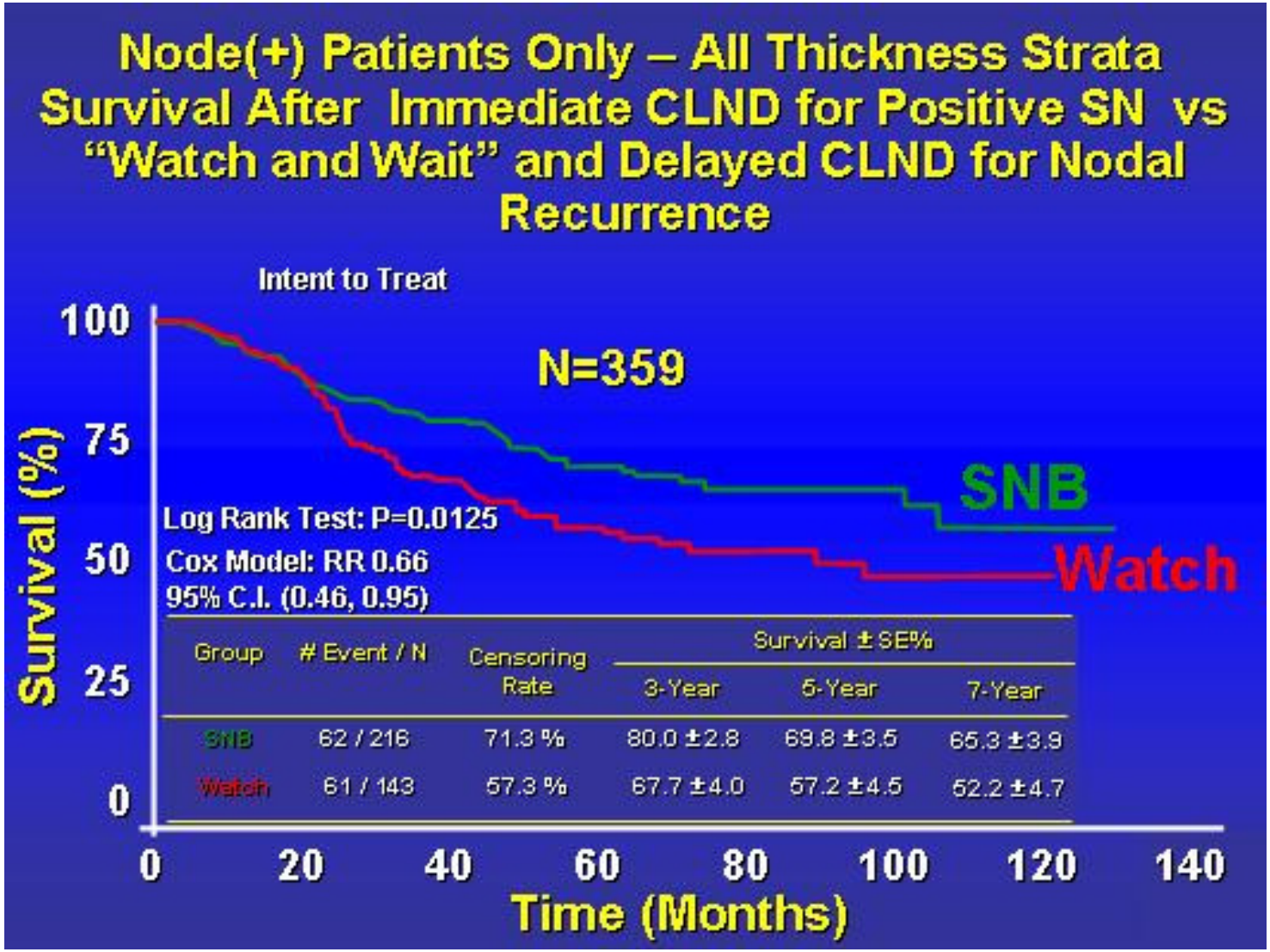


	Breslow 1.2-3.5mm			Breslow 1.5-3.5mm		
Group	# Event / N	Estimate S(t) ± SE		# Event / N	Estimate S(t) ± SE	
		3-year	5-year		3-year	5-year
SNB	101 / 805	93.2 ± 0.9	87.1 ± 1.3	69 /395	86.9 ± 1.8	82.6 ± 2.0
Watch	74 / 522	90.0 ± 1.4	86.0 ± 1.6	87 /616	92.2 ± 1.1	85.2 ± 1.6

Does SLNB have prognostic significance?



MSLT1



Group	# Event / N	Censoring Rate	Survival ± SE%		
			3-Year	5-Year	7-Year
SNB	62 / 216	71.3 %	80.0 ± 2.8	69.8 ± 3.5	65.3 ± 3.9
Watch	61 / 143	57.3 %	67.7 ± 4.0	57.2 ± 4.5	52.2 ± 4.7

Adjuvant Therapy in Melanoma

High Risk - Local recurrence

Consider Radiotherapy

Adjuvant Therapy in Melanoma

Adjuvant Radiotherapy

Improve local control of disease:

Primary site

Following nodal surgery

Adjuvant Therapy in Melanoma

Adjuvant Radiotherapy

Primary Site:

High Risk Group – Desmoplastic / Neurotropic Melanoma

Risk of Local Recurrence: Level V, Neurotropic variant, Head and Neck primary, Excision <1cm

Smithers et al World J Surg 1992

Adjuvant Therapy in Melanoma

High risk - Local Recurrence

Nodal metastasis - Extracapsular invasion

- Multiple nodes or >4cm
- Matted nodes
- post dissection recurrence

Adjuvant Therapy in Melanoma

Adjuvant Radiotherapy

Nodal metastasis – Extracapsular invasion

- Multiple nodes or >4cm
- Matted nodes

} NH&MRC sponsored randomised trial

- No evidence of survival benefit
- Weigh up risks and benefits

Adjuvant Therapy in Melanoma

Systemic Therapy

Risk Groups:

Intermediate – 2 – 4mm

High Risk – >4mm

Node positive (Stage III)

Adjuvant Therapy in Melanoma

Systemic Therapy- Chemotherapy

Stage I – II: 21 randomised trials, 2850 patients

Stage III: 15 randomised trials, 1972 patients.

No therapies tested proved effective

(including cytotoxic chemotherapy, immunotherapy, combined chemoimmunotherapy)

Lejeune FJ. Phase III adjuvant studies in operable malignant melanoma (review)

Anticancer Res 1987:7;701-05.

Adjuvant Therapy in Melanoma

INTERFERON Alfa 2b (ECOG 1684)

- Patients: Node positive, T4 (>4mm)
- High Dose IFN and surgery vs Surgery alone
- 20 mill units/m^2/day iv 5 days /week – 4 weeks

  10 mill units/m^2 x3 per week – 48 weeks

Kirkwood et al J Clin Oncol 1996

Adjuvant Therapy in Melanoma

INTERFERON Alfa 2b **(ECOG 1684)**

- Relapse Free Survival 11% Improvement
- Overall Survival 9% Improvement

Problems: Poor Compliance – *side effects in young patients*

Toxicity – *Severe 67%, Life threatening 9%*

Cost - *$US 50,000 per year*

Kirkwood et al J Clin Oncol 1996

Adjuvant Therapy in Melanoma

INTERFERON Alfa 2b **(ECOG 1690)**

- Patients: Node positive, T4 (>4mm)
- High Dose IFN vs Low dose IFN vs Surgery alone
- No overall survival advantage
- HDI – relapse free survival advantage

  (notably 2-3 nodes positive)
- Observation group did 10% better than 1684

Kirkwood J et al J Clin Oncol 2000

Adjuvant Therapy in Melanoma

INTERFERON Alfa 2b **(ECOG 1694)** 880 pts

- Patients: Node positive, T4 (>4mm)
- High Dose IFN vs GM2-KLH/QS-21 Vaccine
- More node negative patients in this trial
- Improved RFS and OS over the vaccine
- Vaccine survival curve similar to control in 1690
- Benefit mainly in Node negative patients

Kirkwood J et al J Clin Oncol 2001

Adjuvant Therapy in Melanoma

INTERFERON ALPHA – Summary (Control = no treatment)

High Risk Patients:	*Pts*	*R.F.S.*	O.S.
•High Dose Interferon (1684)	287	+ 11%	+9%
•High Dose Interferon (1690) and low dose INF	642	+ -	- -
•High Dose Interferon NCCTG 83-7052	262	+	-
•Low Dose InterferonWHO16	444	-	-
•Low Dose Interferon EORTC 18871	800	-	-

Adjuvant Therapy in Melanoma

INTERFERON ALPHA

- Conflicting results as to which subgroup receives the most benefit.
- Given OS negative trial (1690) can we extrapolate that HDI is beneficial when compared with a vaccine that has not been compared to observation.
- At least grade III toxicity common in all trials.

Adjuvant Therapy in Melanoma

INTERFERON ALPHA

- IFN alpha 2b does have some effect on the natural progression of melanoma metastasis
- Low dose IFN delays events rather than curing disease
- High Dose IFN delays events and may have a major impact on some subgroups of patients with high risk disease.
- Need to consider and discuss with high risk patients.

Trends in Melanoma Management

- MARGINS
  - 1 - 2cm
- NODES
  - routine dissection not proven (maybe subgroups)
  - role of sentinel node biopsy to be defined
    - Prognostic test
  - role of radiation after nodal dissection to be defined
- ADJUVANT THERAPY
  - none proven to definitively improve survival over surgery

Trends in Melanoma Management

- ADVANCED DISEASE
  - **Isolated limb infusion** has replaced limb perfusion
  - Immunotherapy likely to be a major influence in patients with stage IV disease
  - Immunotherapy may become adjuvant to surgery for high risk patients
  - Chemotherapy the major advance has been **BRAF**
    - BRAF mutations is found in 50% of patients
    - Median survival advantage is 6 months

Chemotherapy

- **Dacarbazine** is the mainstay of treatment with
  - a response rate of 7 to 12%
  - a median overall survival of 5.6 to 7.8 months after the initiation of treatment
- the use of **ipilimumab**, a monoclonal antibody that blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) on lymphocytes, has been associated with improved overall survival