Melanoma

What We Should Know About

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Skin Cancer in The U.S.

(Estimated No. New Patients Per Year)

- Melanoma: > 120,000 *(2013)*
  - Melanoma, invasive *76,700*
  - Melanoma, in situ *51,000*
- NMSC: > 1,300,000
  - Basal Cell Carcinoma *700,000*
  - Squam. Cell Carcinoma *200,000*
  - Bowen's disease/SCC in-situ *200,000*
  - Keratoacanthoma *200,000*
- Cut. T-Cell Lymphoma *2,500*
- Others *3,000*

MELANOMA

How Big Is The Problem

- The Cost: **5 Billion** dollars/year by 2010
- The Impact: **14%** *(Whites)* would die*(Life Time Risk)*

  [*in Comparison: 94% of lung CA pt would eventually die*]
- Incidence of MM: 1/3 of Breast CA; 1/3 of Prostate CA but
- Mortality of MM: equal to Breast CA or Prostate CA

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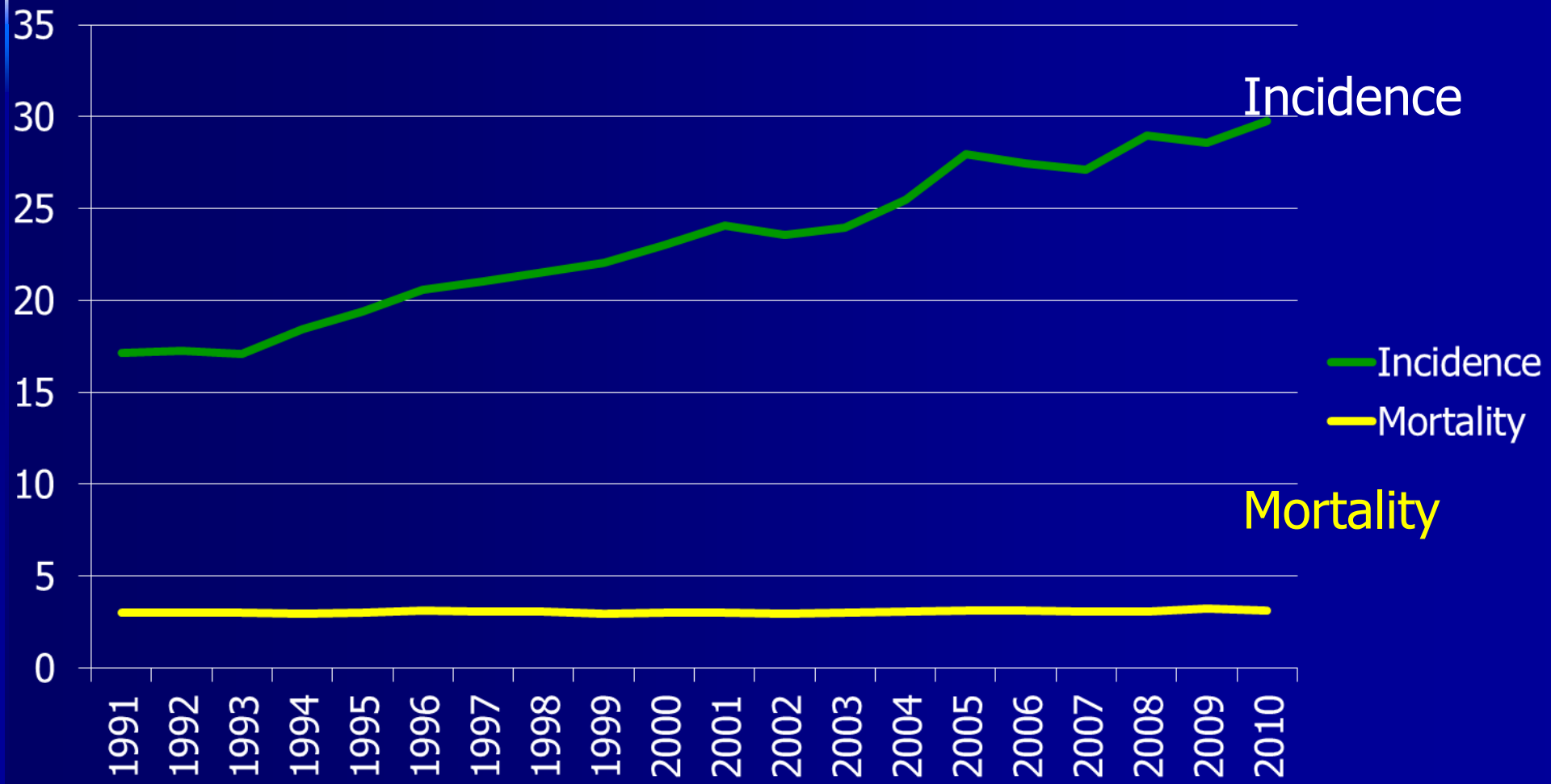
Incidence/Mortality Trend, US White, per 10^6



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Incidence and Mortality , US Minorities, per 10^6

SEER, 2006-10	***Incidence***	***Case-fatality***
Black	1.0/100,000	40%
Asians	**1.3/100,000**	**30%**
American Indians	3.7/100,000	24%
Hispanic/non-White	4.5/100,000	20%
Whites	29.2/100,000	12%

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Types & Distribution, Chinese Vs. Caucasians

(JAMA Derm 2013, 149:272; JAAD 2013, 68:568)

Types of Melanoma	***Chinese***	***Caucasians***
Acral Lentiginous MM	45%	2%
Nodular MM	23%	16%
Mucosal MM	20%	1%
Superficial Spreading MM	8%	65%
Lentigo Maligna MM	4%	15%
Others		1%

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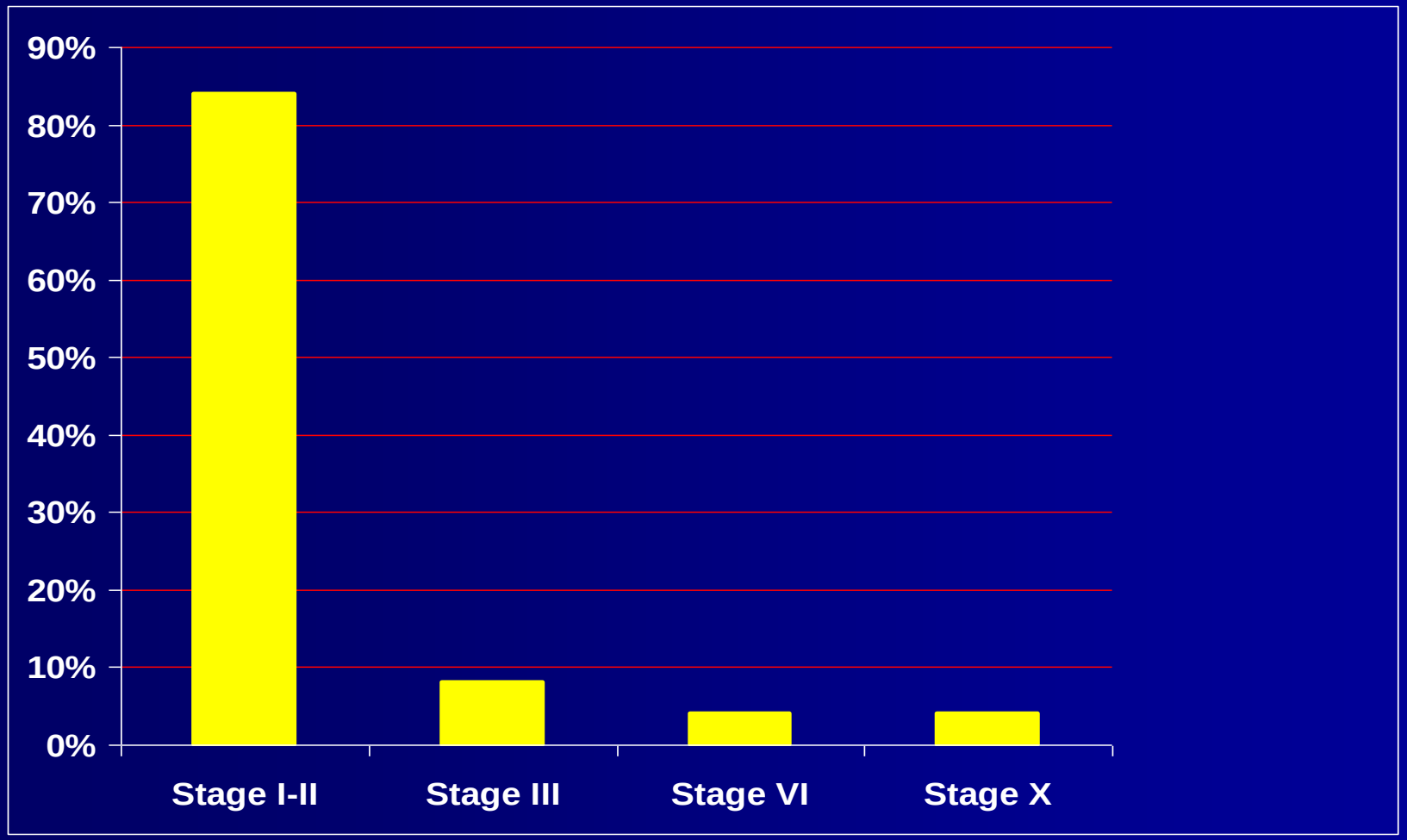
Stage Distribution, US White, 2003-2009



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Risk Factors

- Atypical moles (as marker) + PH/FH of MM
- Atypical moles (as marker) + FH of MM
- Atypical moles without PH/FH of MM
- Giant Congenital nevi: 3%
- Personal history of prior MM: *10x risks*
- Family history of MM among 1º relatives: *>3x risks*
- Number of nevi >100
- The "Sun Factor" :

  Intense/intermittent sun exposure;
  skin color/skin type,
  hair/eye color,
  freckling [low capacity of DNA repair]

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Risk Factors - Melanoma Genetics

- Chromosome region: *$9p_{21}$*
- Defect in Tumor Suppressor Gene*:
  p16 ^{INK4a} /CDKN2A :*60~90% would have MM in their life time.*
- MC1R(melanocortin-1-receptor)gene:
  Variant form of MC1R + UV-induced mutation of BRAF → MM

**Other def. genes: BRAF(~80% of MM), CDK4(and P16), CCND1, P14ARE(and P53), PTEN/MMAC1 & N-ras, N-ras alone, H-ras, MEK, MAPK[NF1]*

†In a study, 57% melanoma families had CDKN2A mutation

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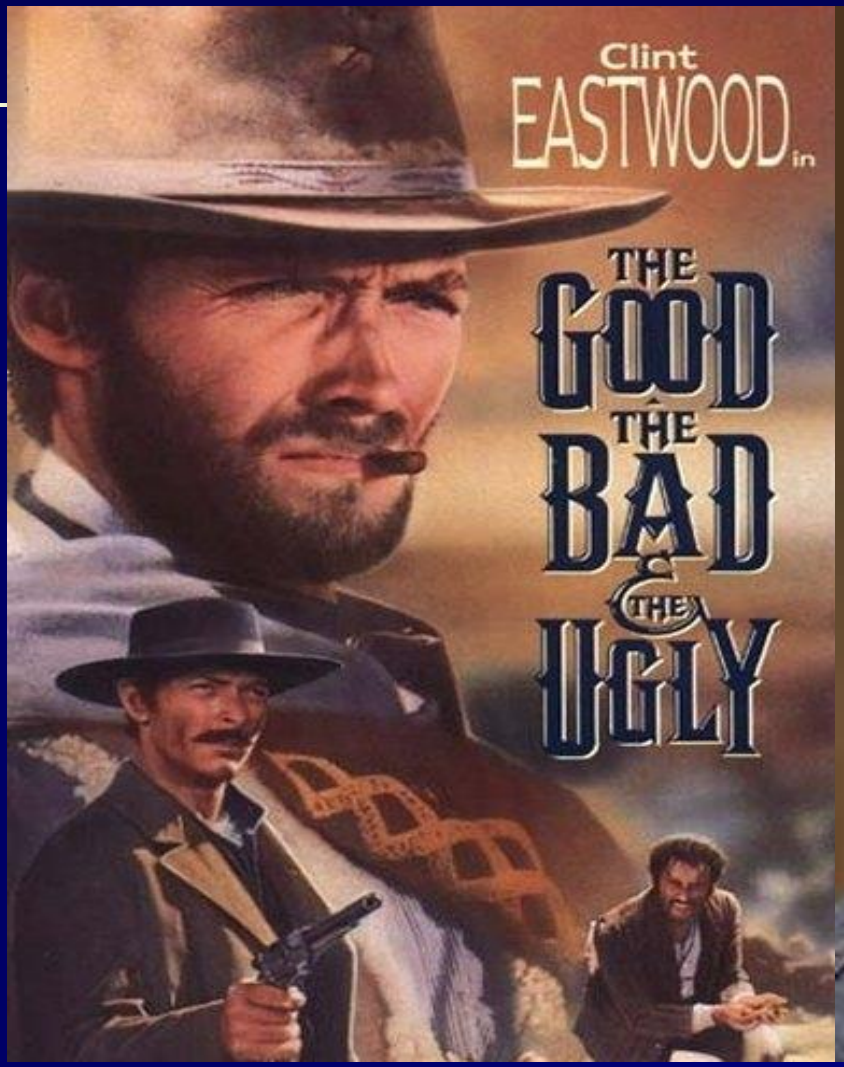
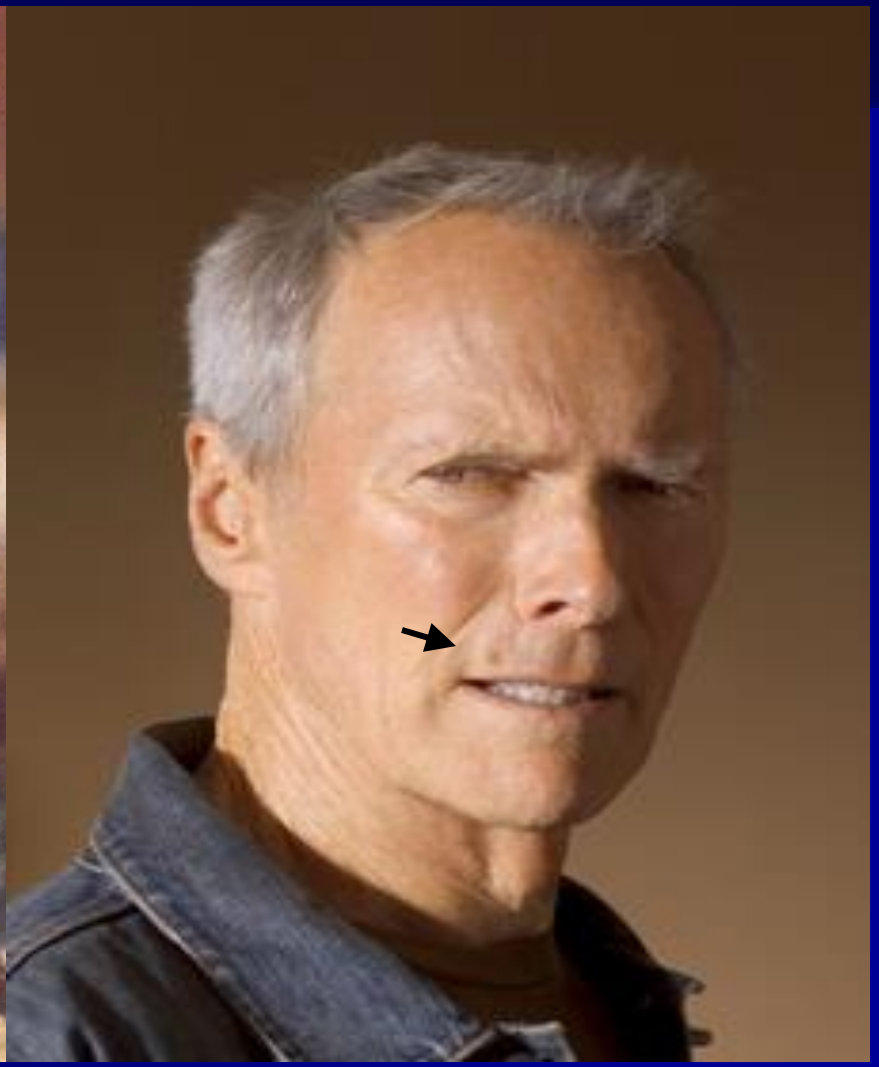
Diagnosis – Started from Moles

- What does a mole look like?
- ABCDE of a mole

The Beauty Marks





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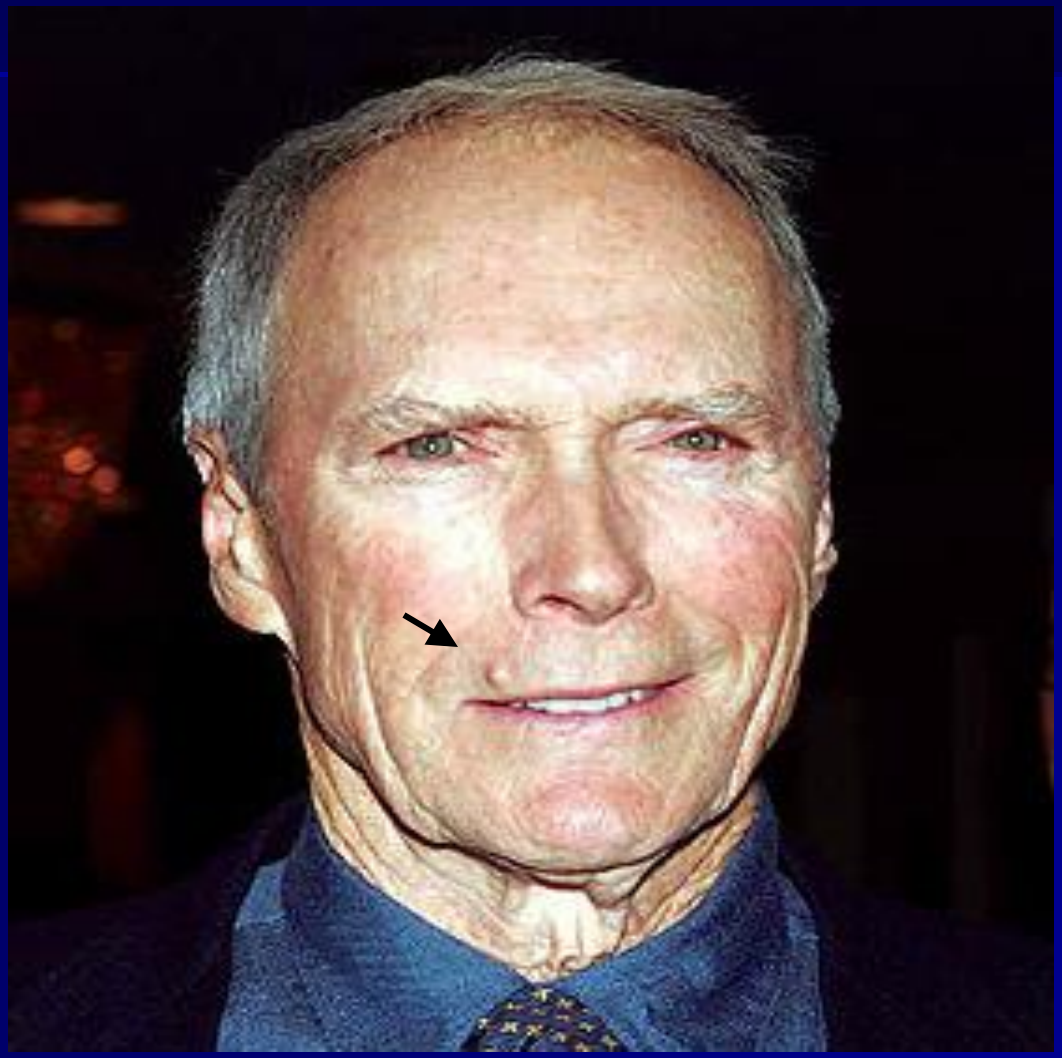
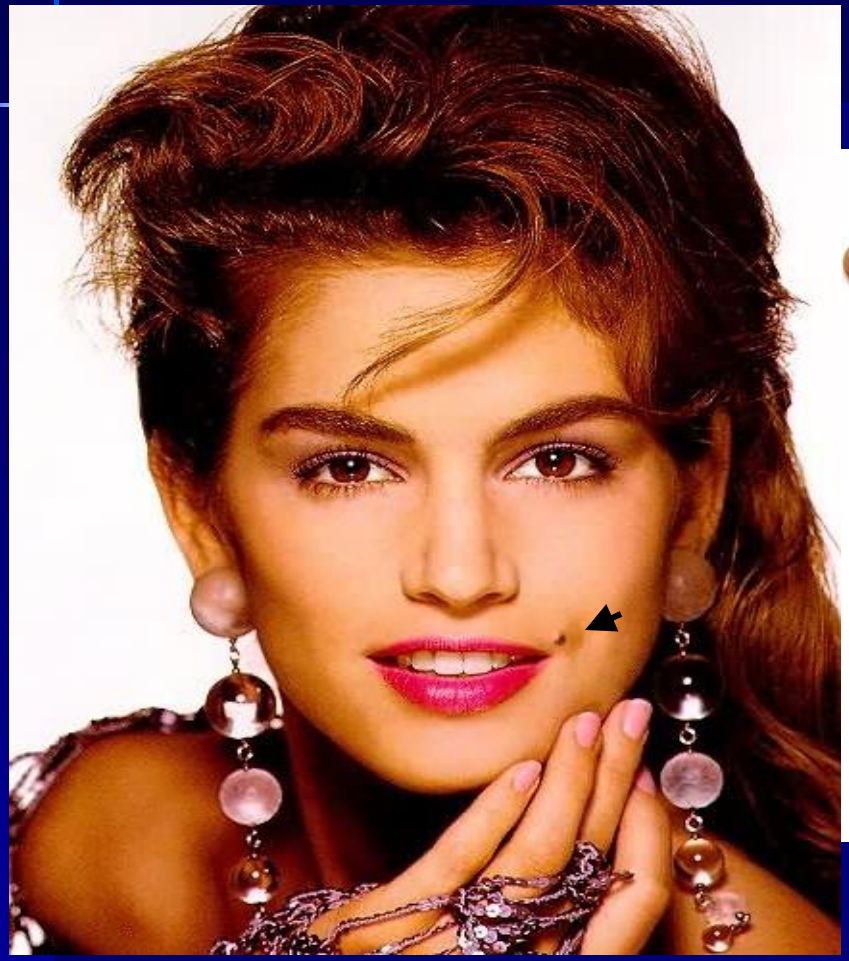
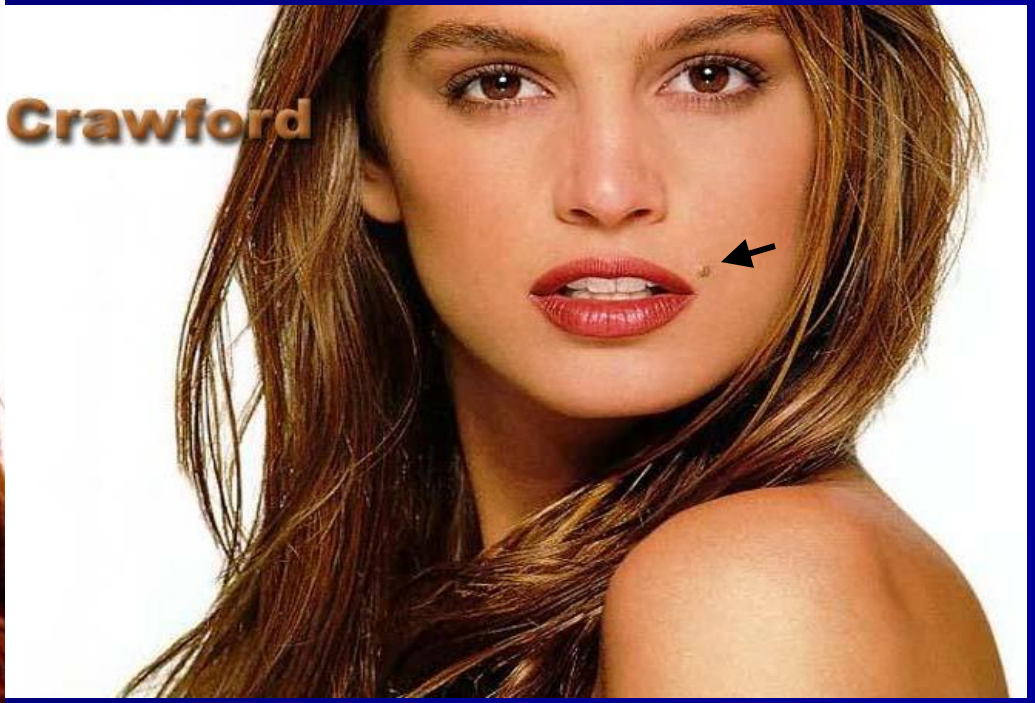
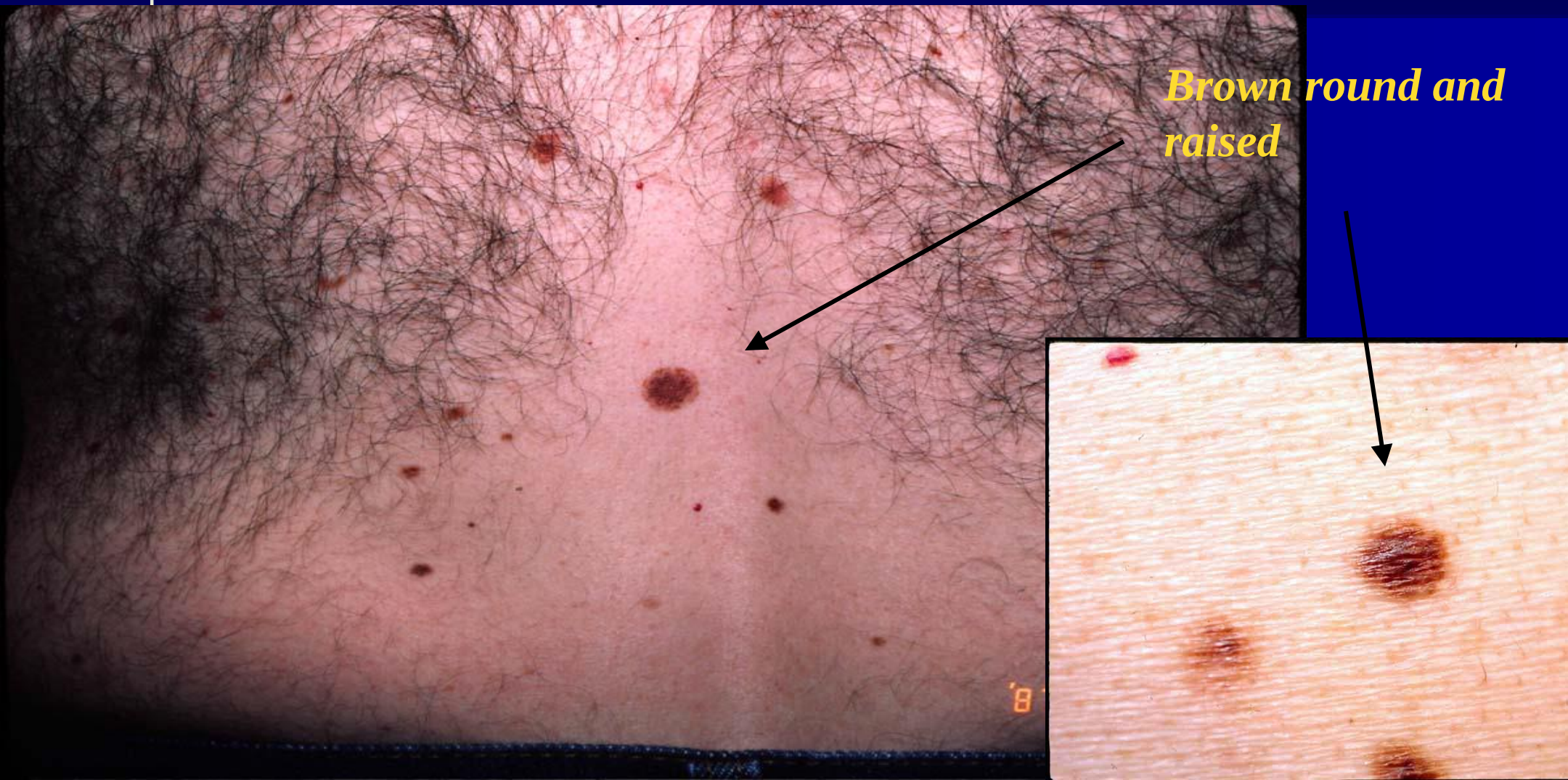


The Beauty Marks





Mole - *Nevus*



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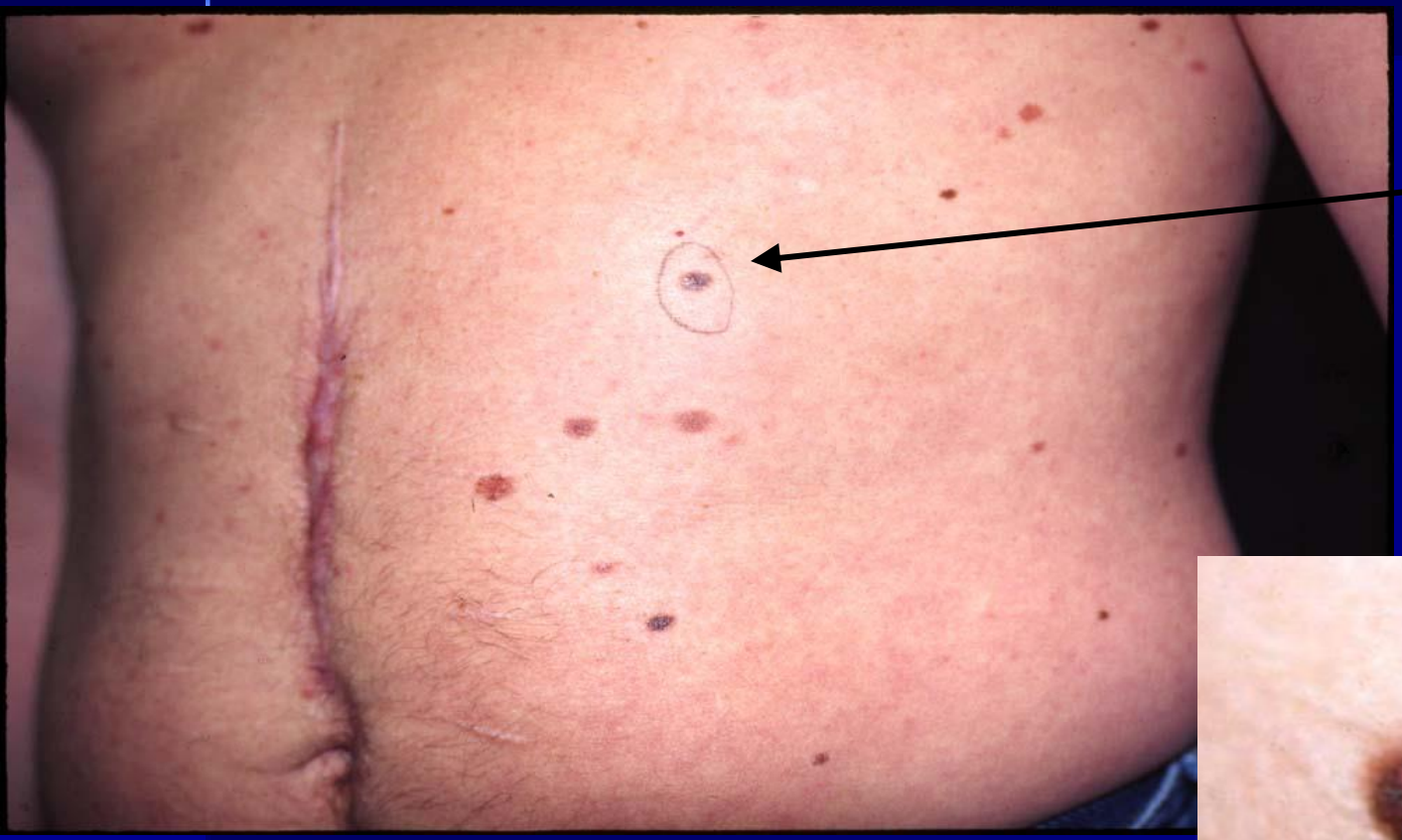
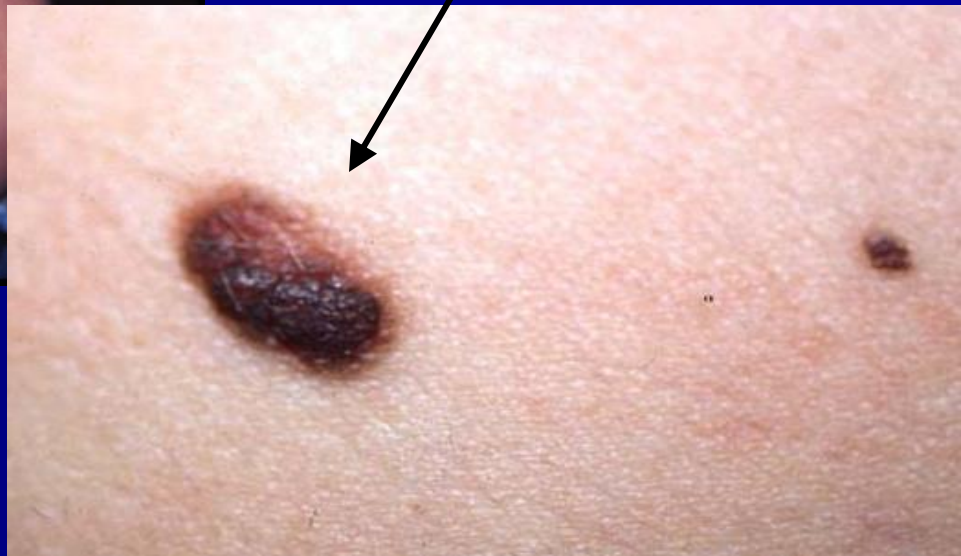


Brown round and raised



SIGN *(ABCDE)* of a BAD Mole:

- ABCDE:

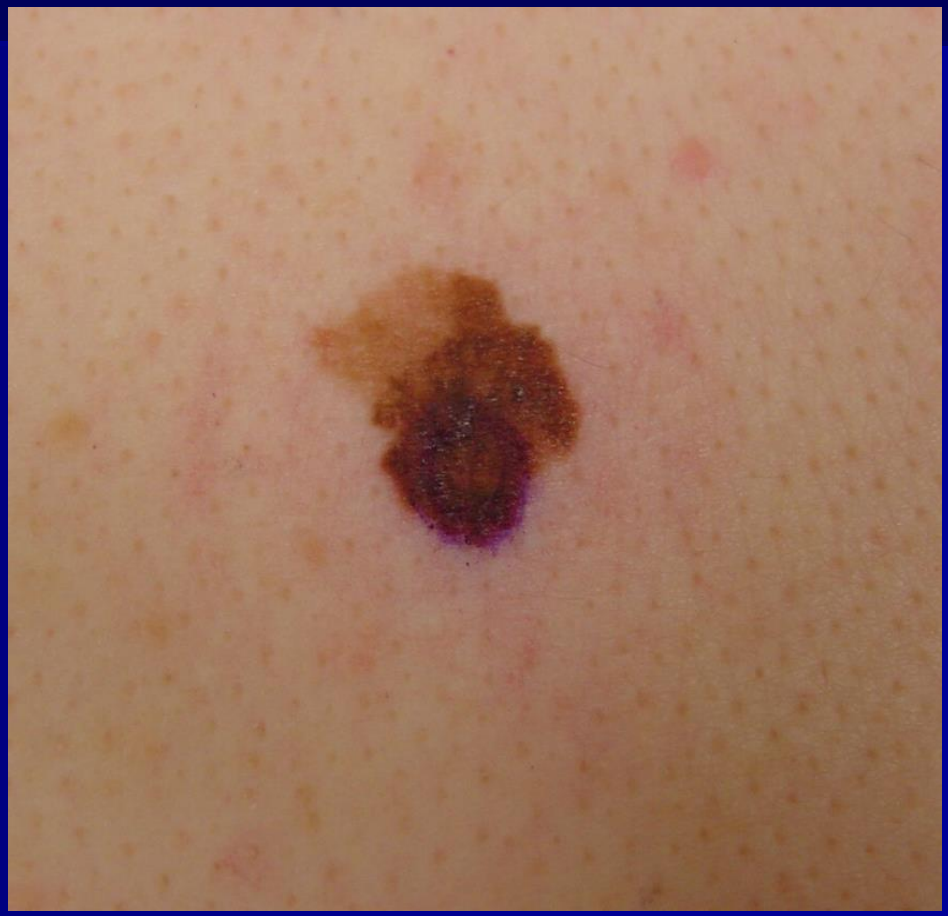
  Asymmetry

  Border irregularity

  Color variability

  Diameter > 6mm

  Elevated



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Diagnosis of Melanoma

- Clinical Features
- Dermatoscopy/Episcopy
- Histopathology:

  H&E, S-100 (high sens, low spec); HMB45 (75% sens, high spec); Melan-A/Mart-1 (80% sens, high spec); Tyrosinase (T311); MIB-1 (for Ki-67)

- Confocal Scanning Laser Microscopy:

  low sensitivity, limited specificity, high cost

- Ultrasound, high-resolution
- Computerized Image Analysis System
- Spectrophotometric intracutaneous analysis

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Dermatoscope

Pattern analysis:

global features, local features and site related features- *More sensitive and specific than others but need "experience"*

ABCD algorithm

Menzies method: two neg. and one pos.

7-point checklist: ≥ 3 is required for Dx.

Saida patterns: for Acral Volar Skin

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Histopathology

H&E
S-100 (high sens, low spec)
HMB45 (75% sens, high spec)
Melan-A/Mart-1 (80% sens, high spec)
Tyrosinase(T311)
MITF (microphthalmia transcription factor)
MIB-1(for Ki-67)

For children's melanoma: reliability of Dx is poor
(French Cut. Cancer Group, Arch Derm 2002, 138:625)

For adults: world-leading experts cannot agree upon the Dx of "classic" nevus/melanoma in *65%* of cases!
(Farmer et al, Hum Pathol. 1996, 27:528)

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Appraisal
of Evidence

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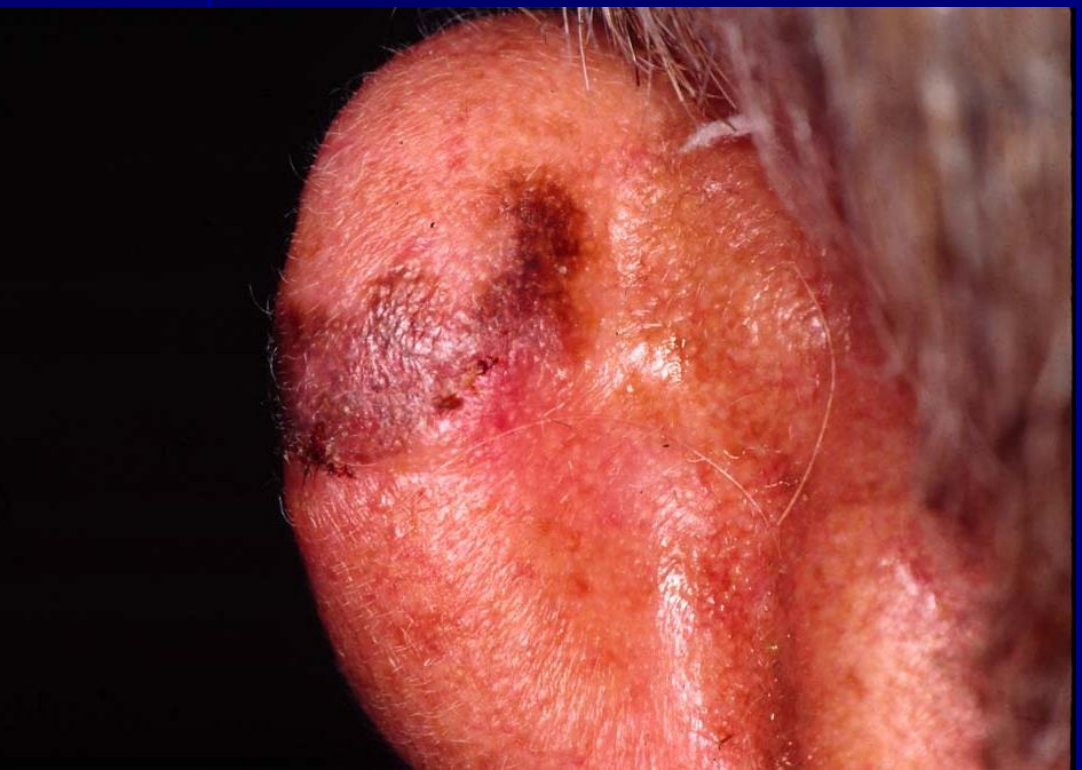
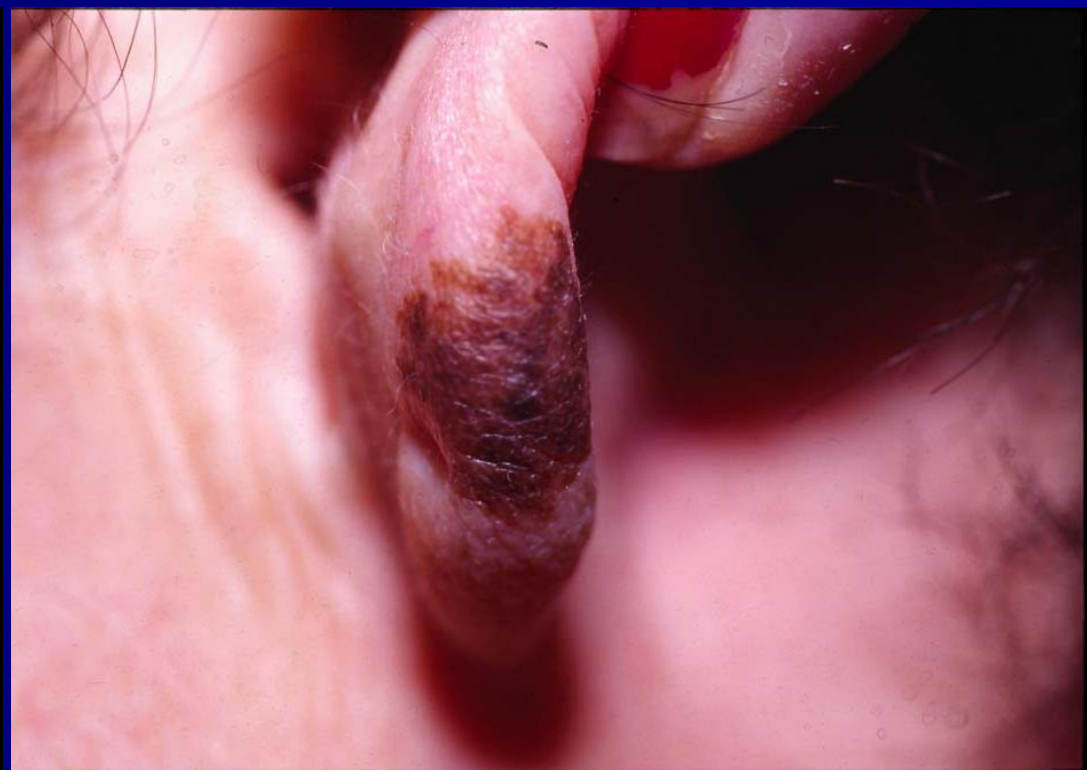
What You Should Do - SURGICAL

MM Thickness	*Recommend Margin*
■ in-situ	.5 cm





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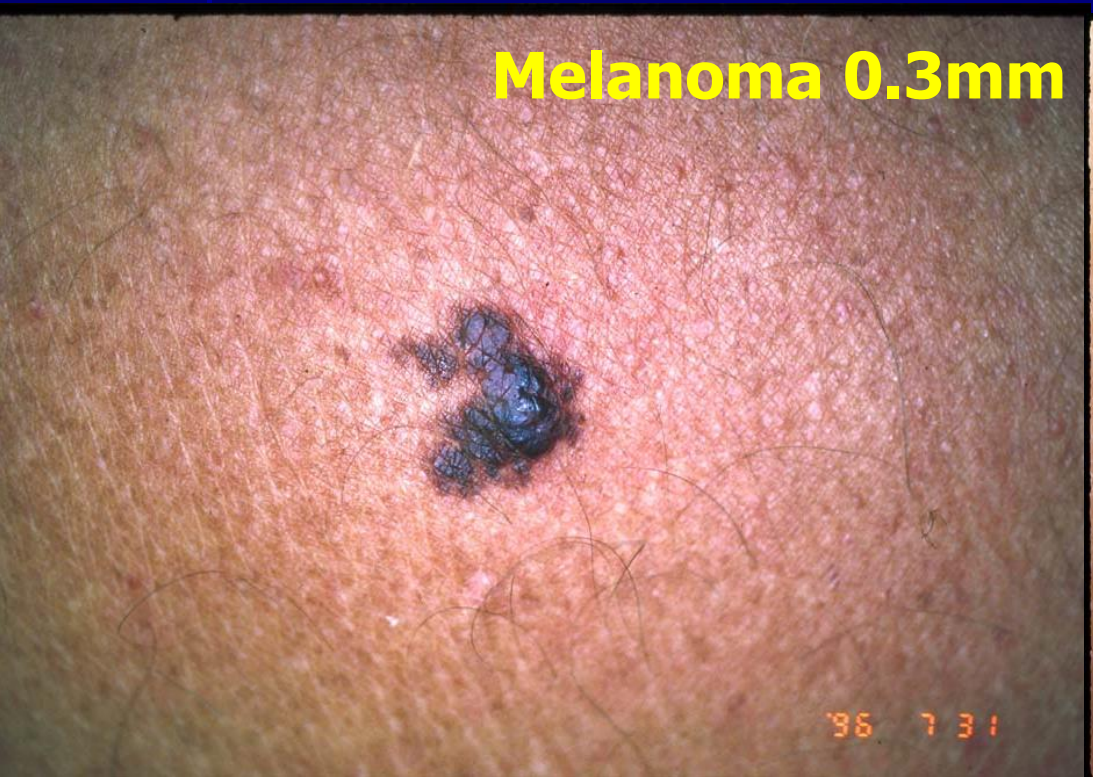
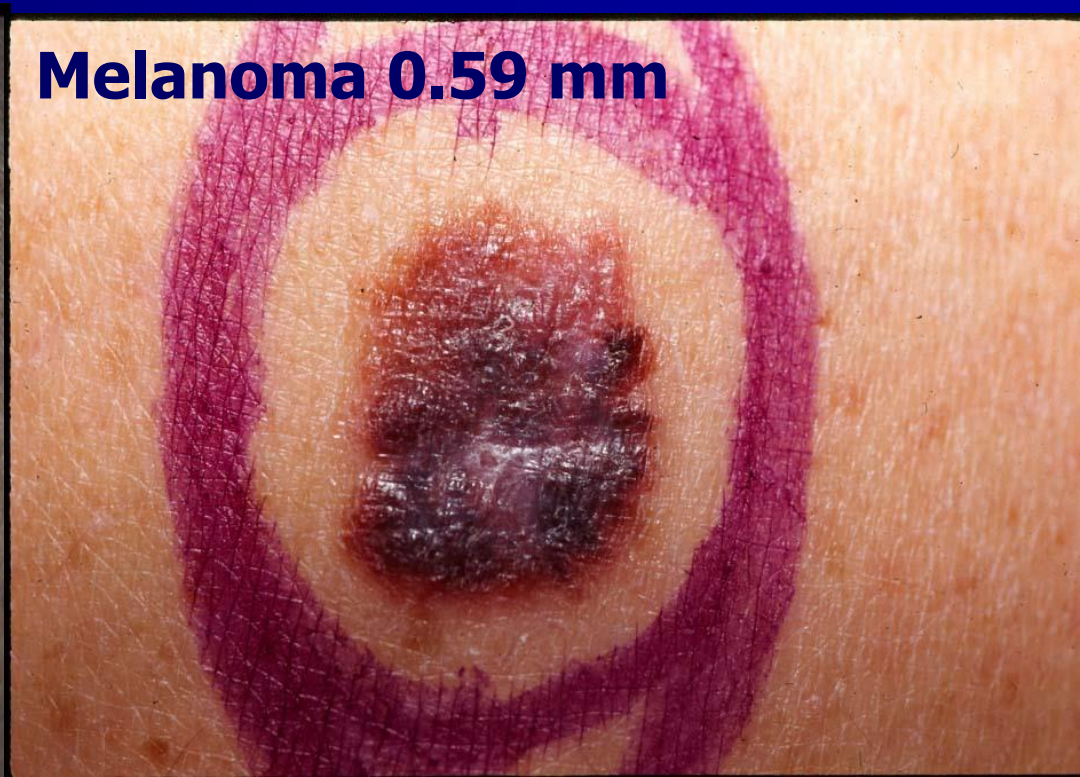
What You Should Do - SURGICAL

MM Thickness	*Recommend Margin*
.01- 2.00 mm	1 cm





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What You Should Do - SURGICAL

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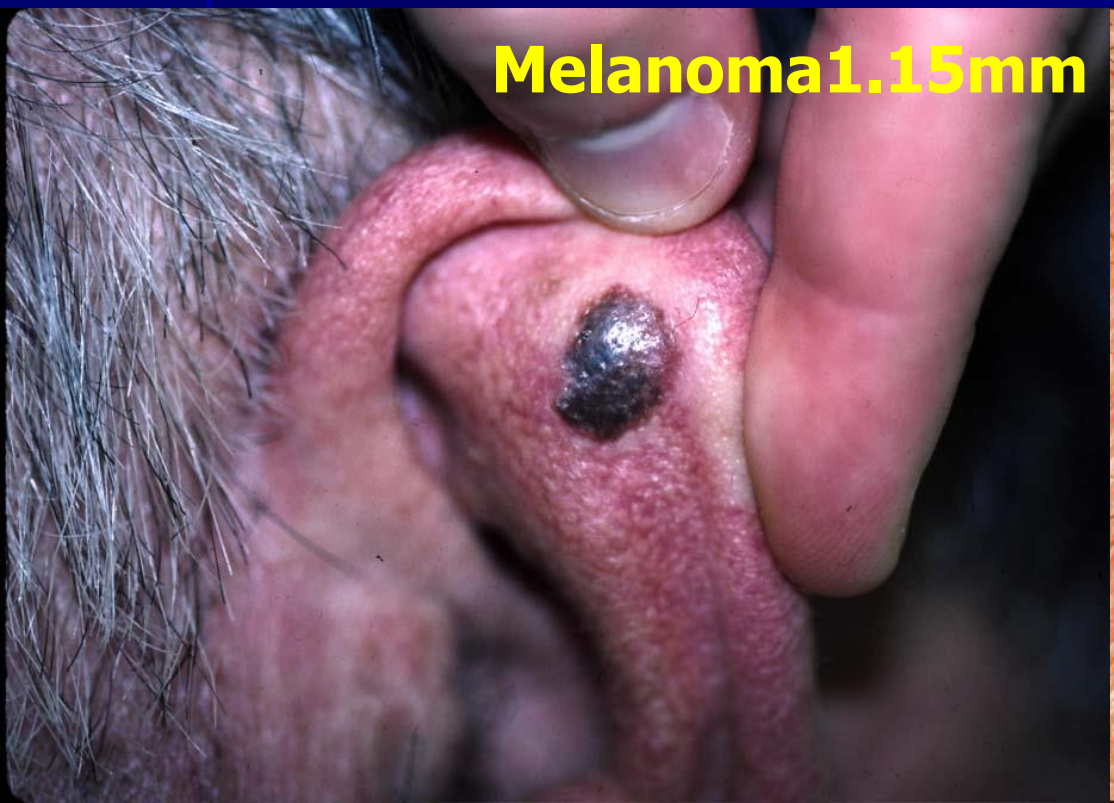

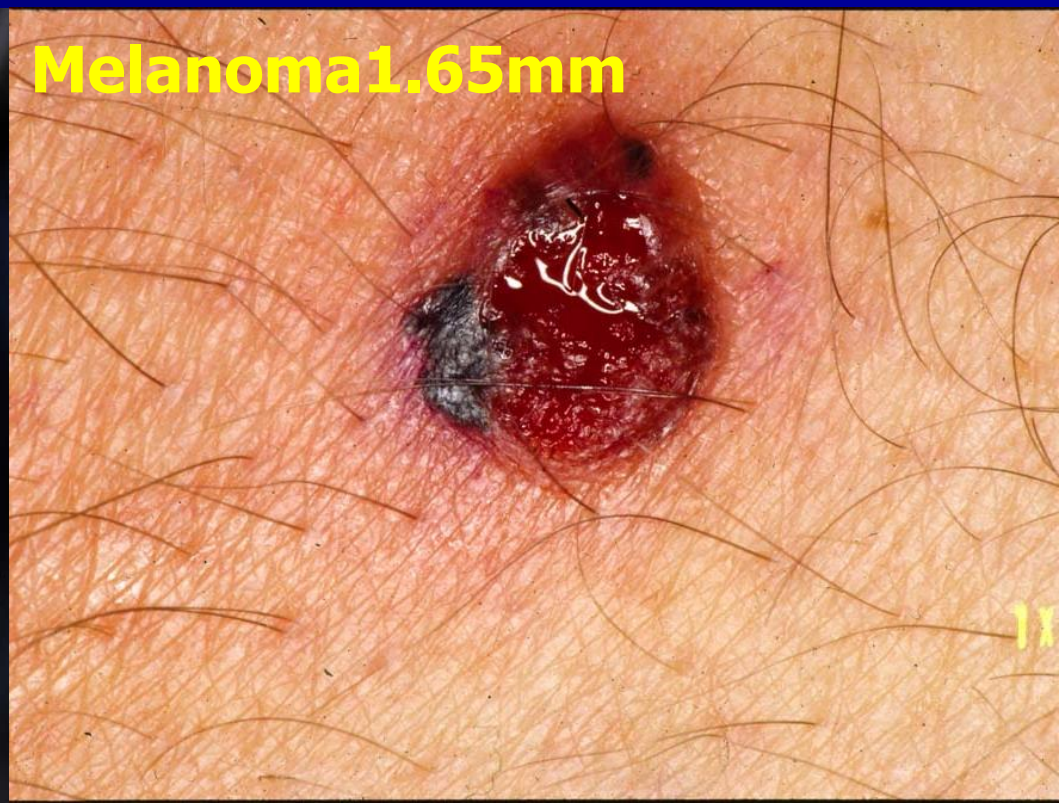

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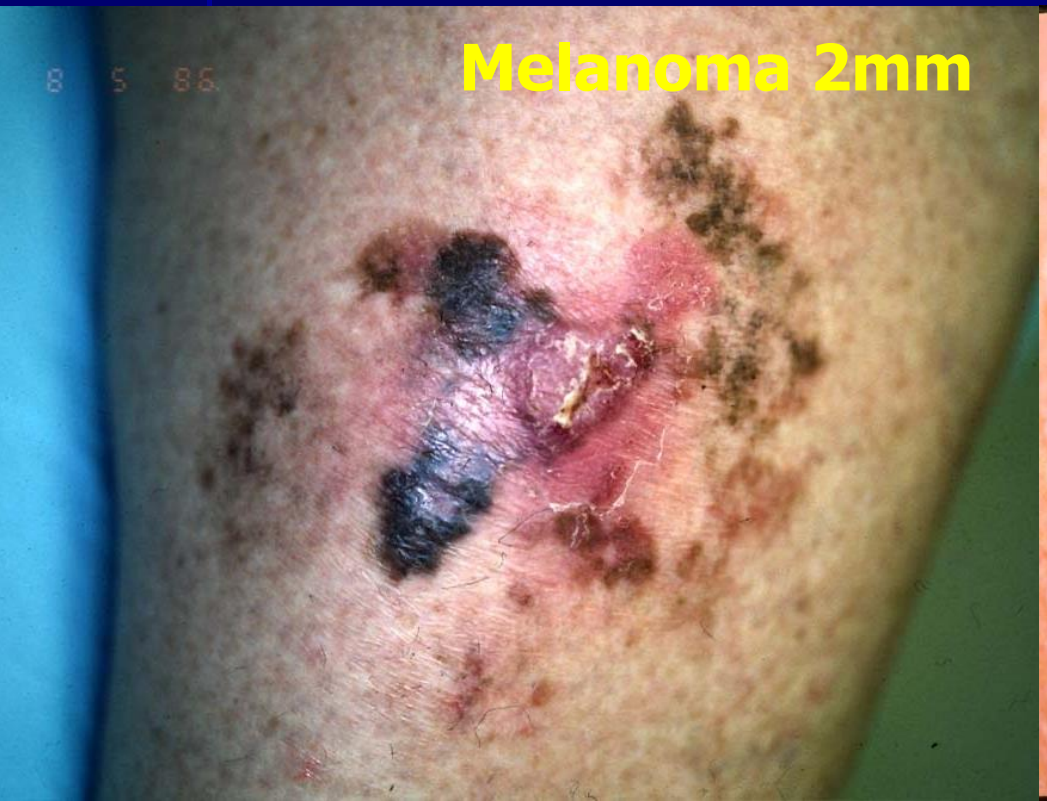
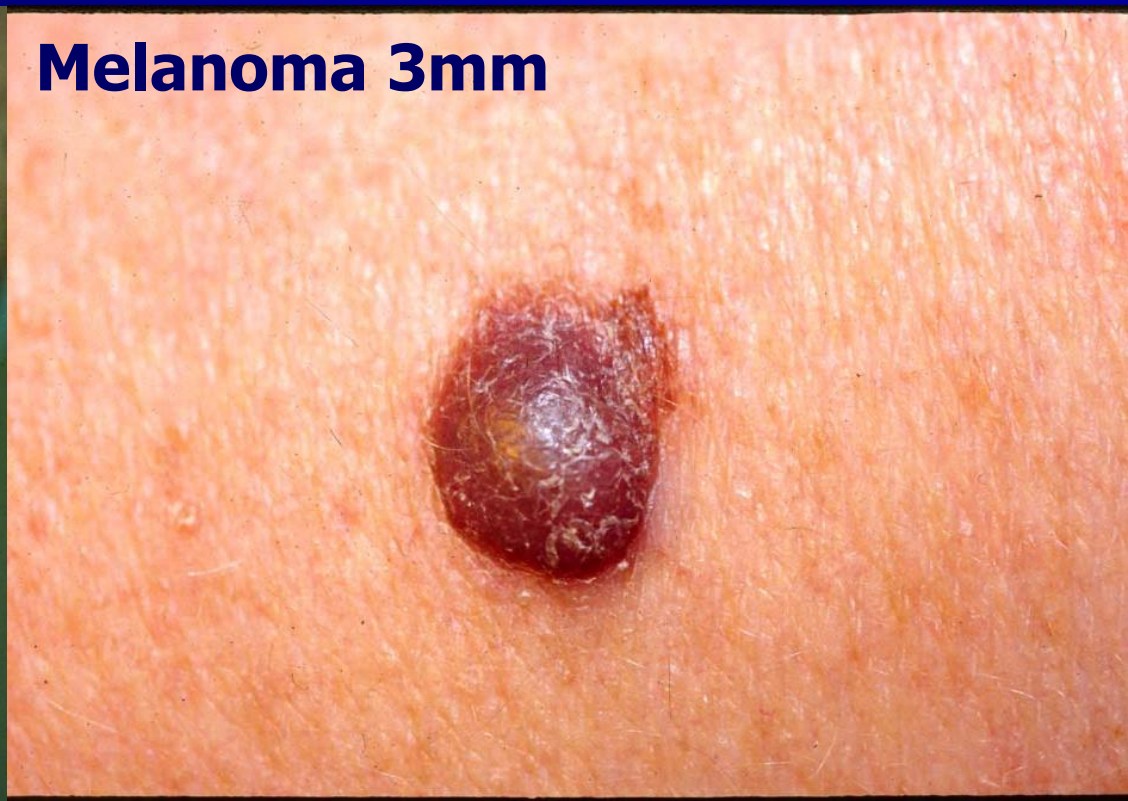
What You Should Do - SURGICAL

MM Thickness	*Recommend Margin*
> 2.00 mm	2 cm





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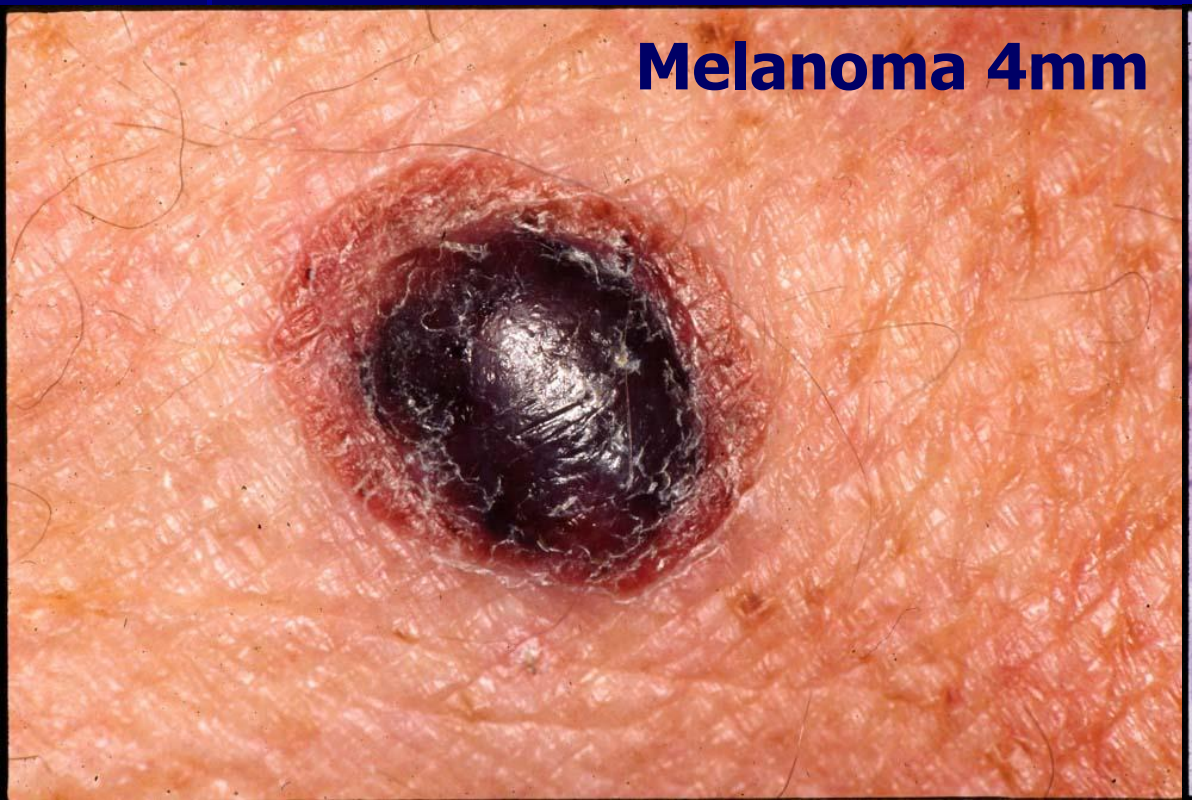

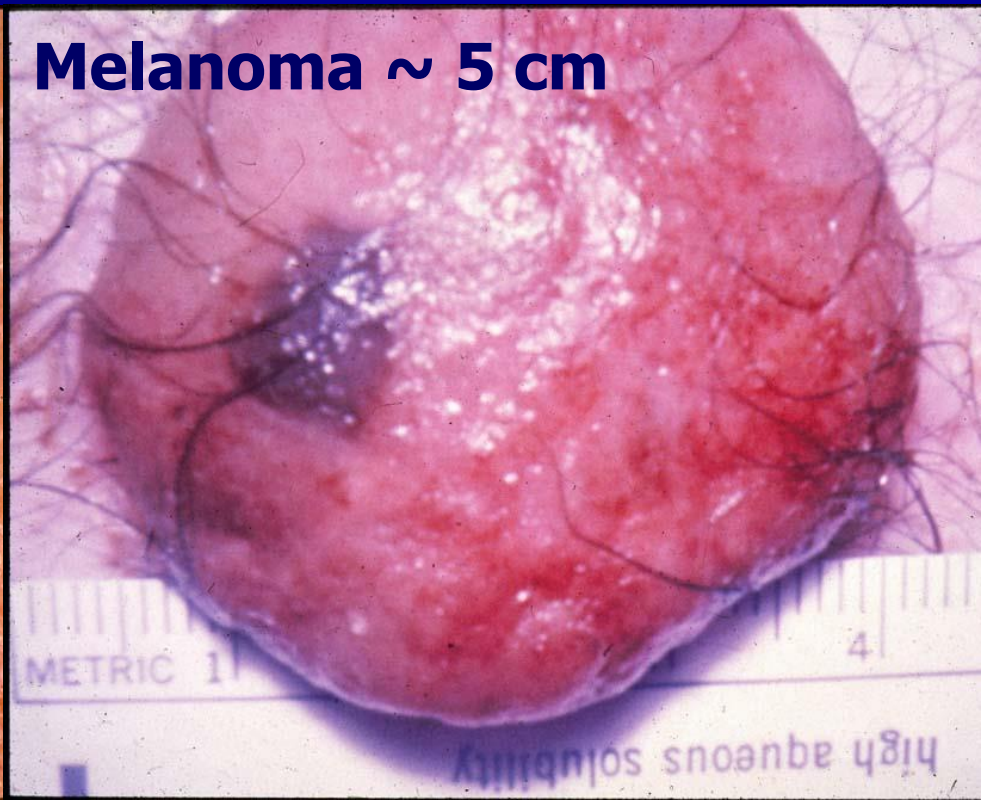

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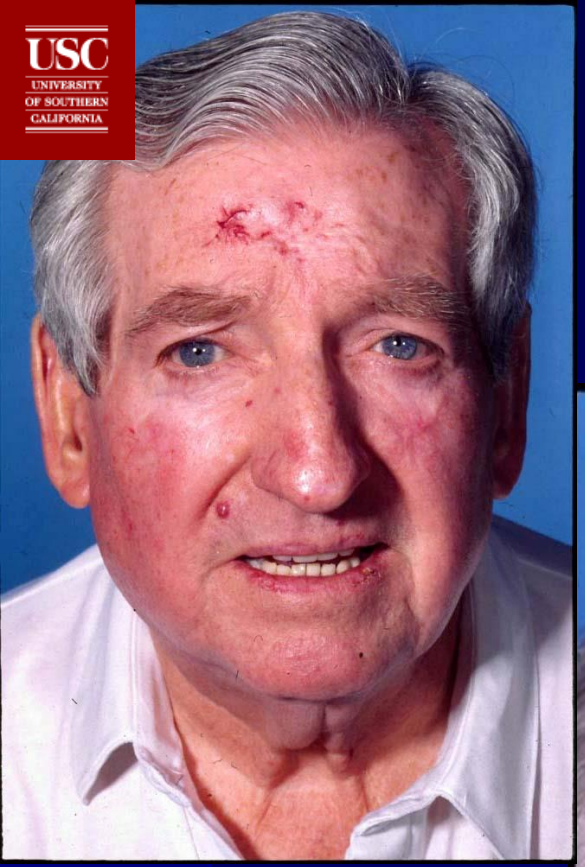
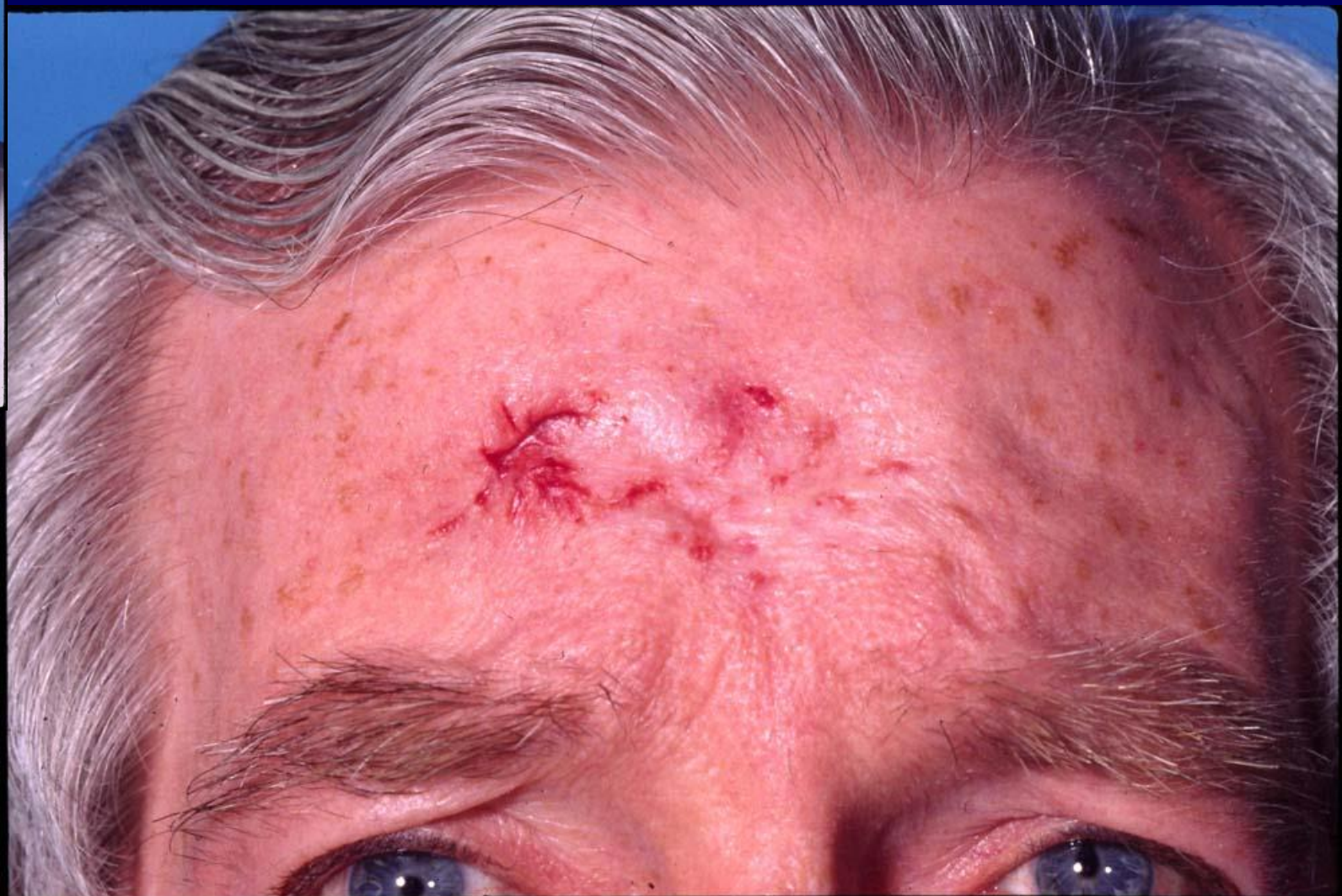
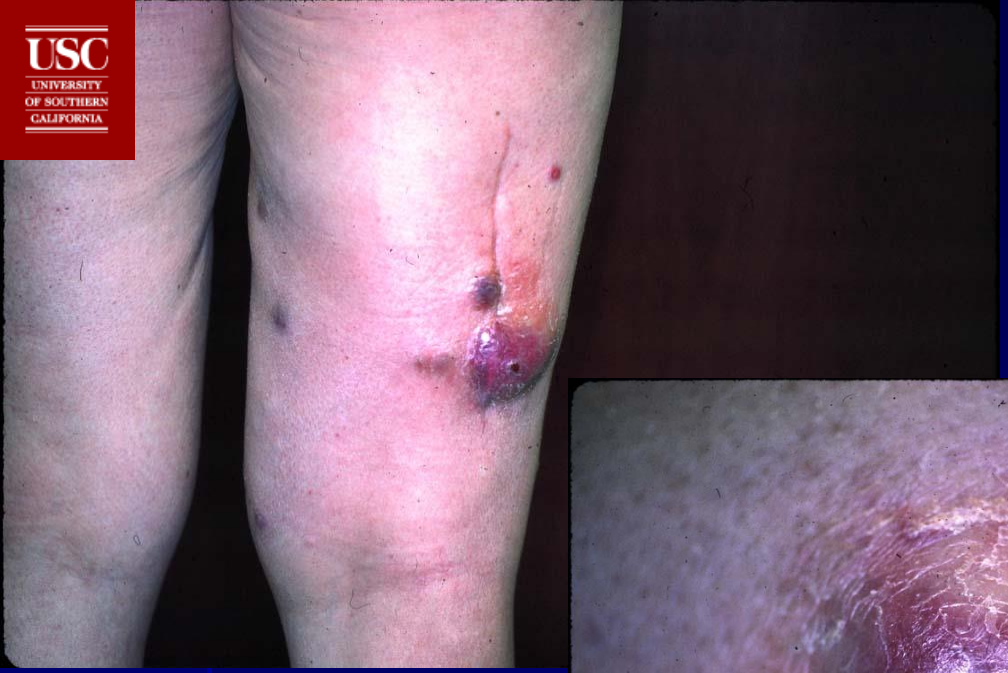
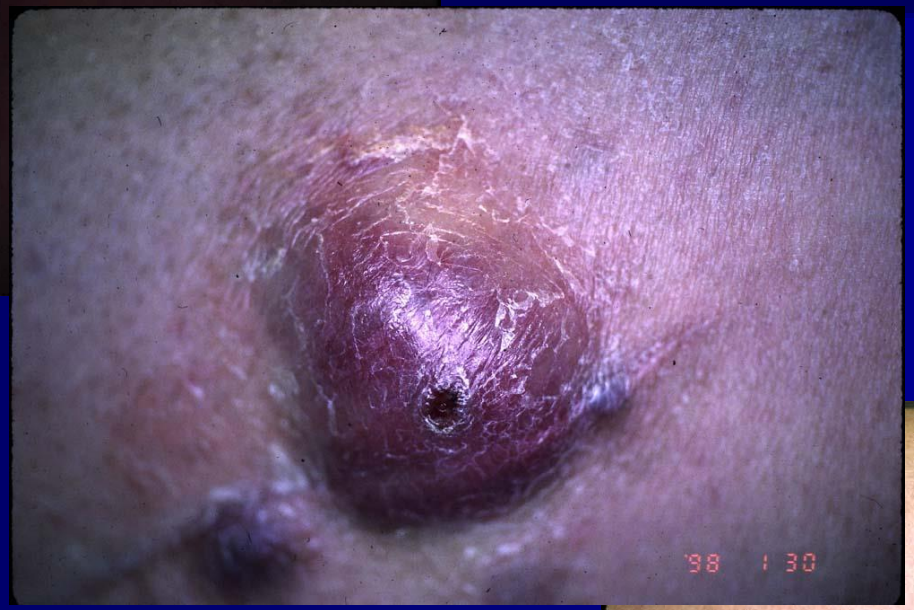
Metastatic Melanoma

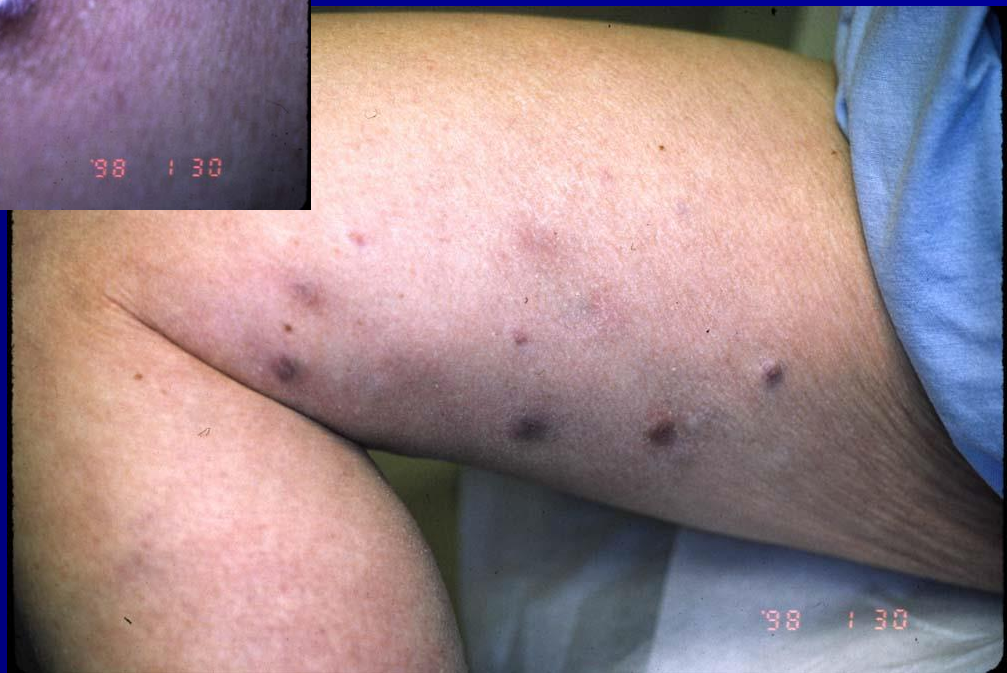




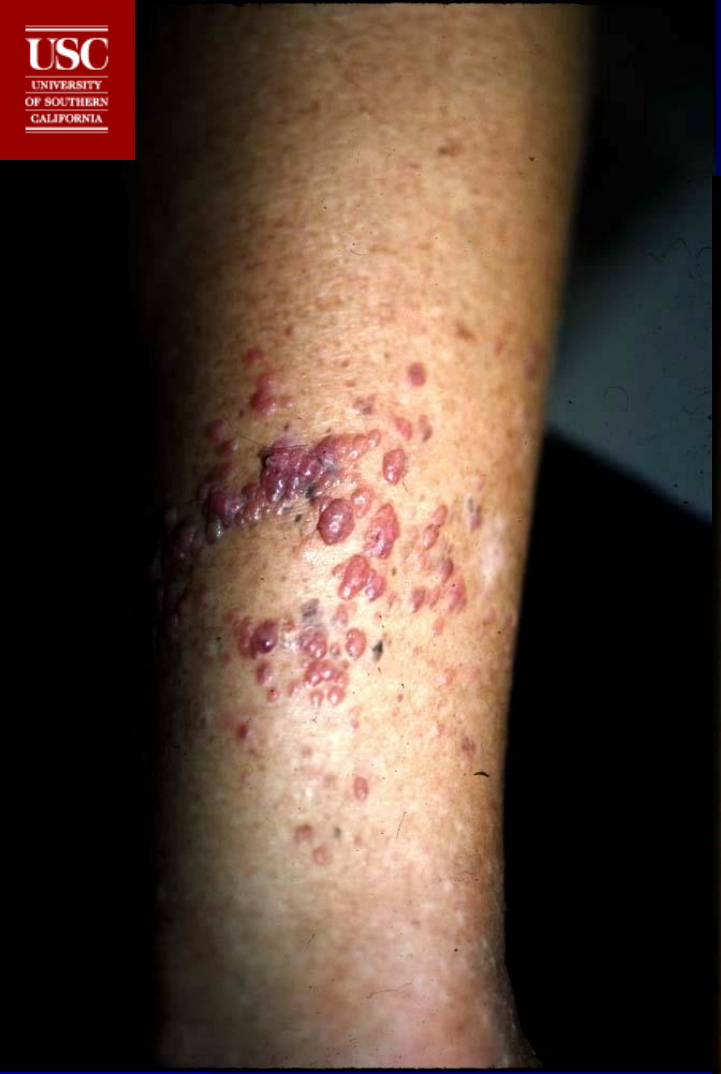
Metastatic Melanoma

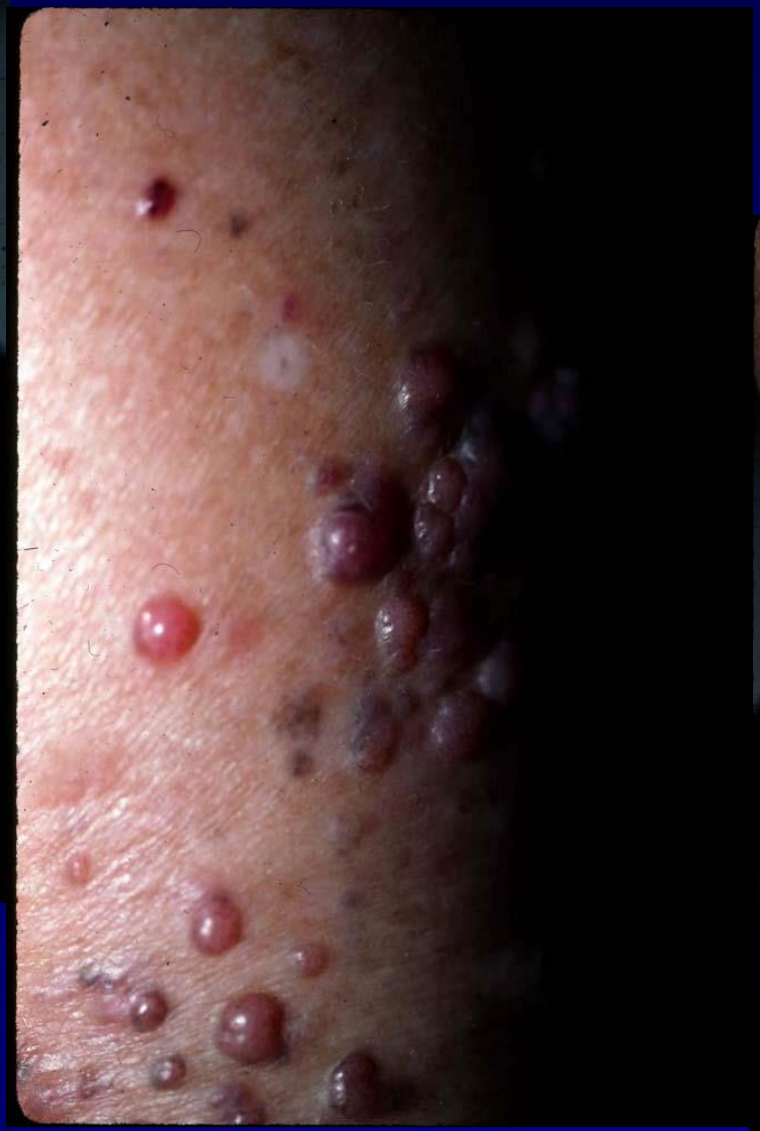


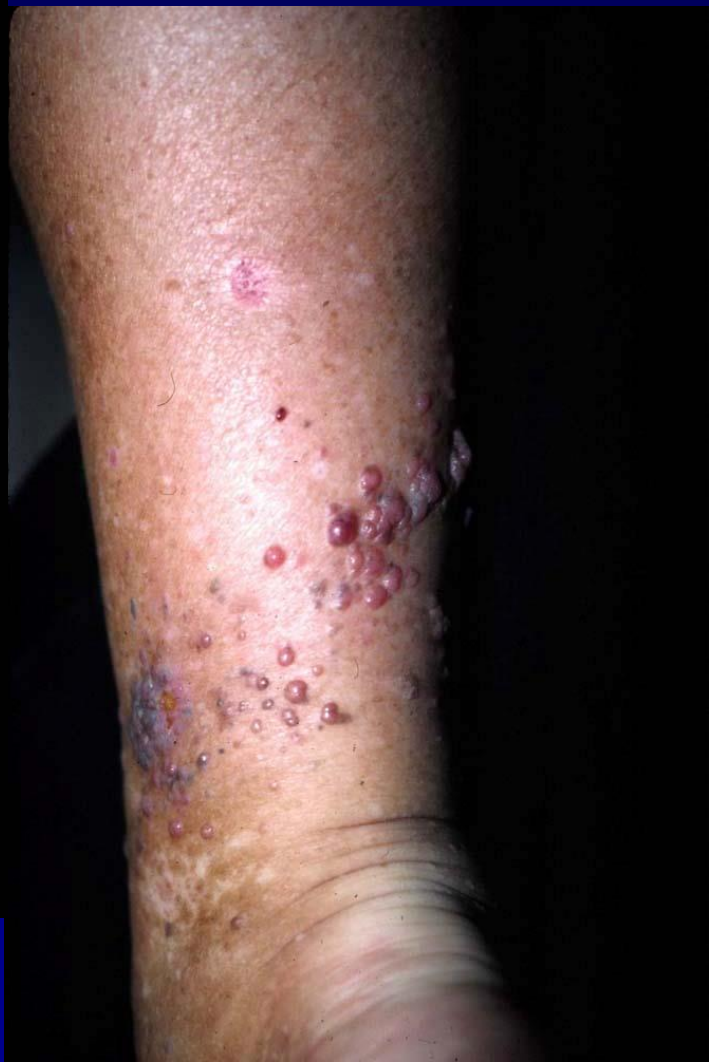




Metastatic Melanoma







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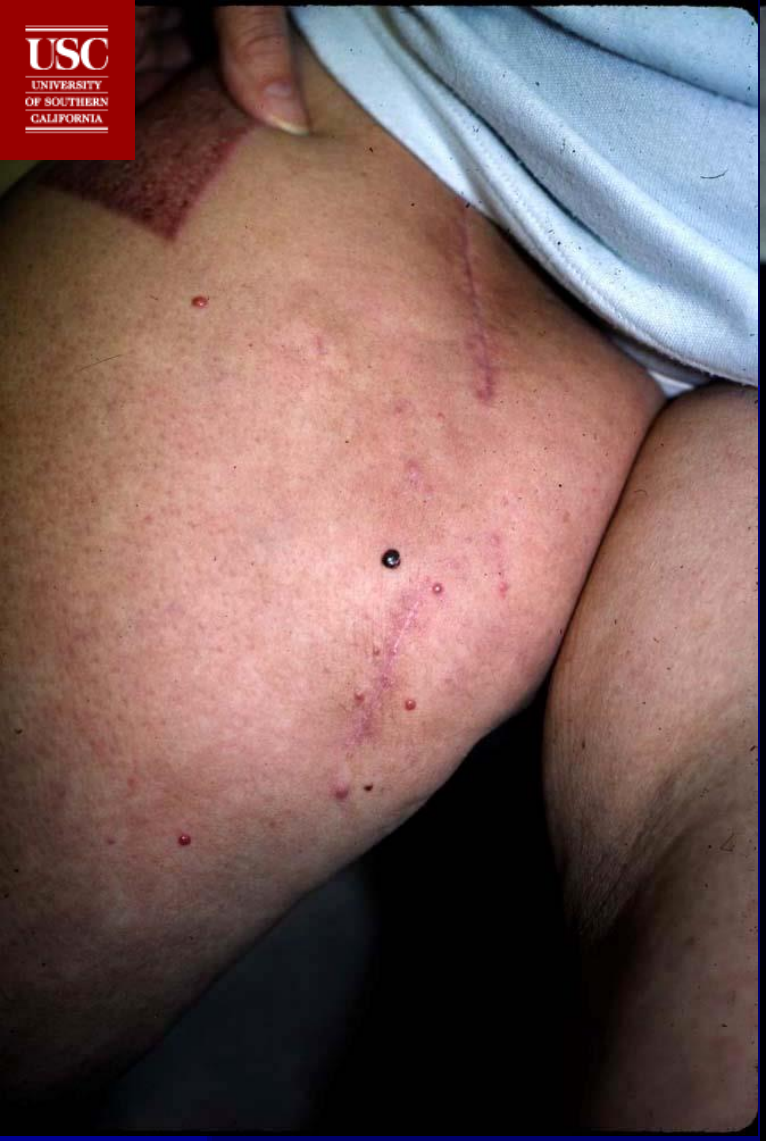
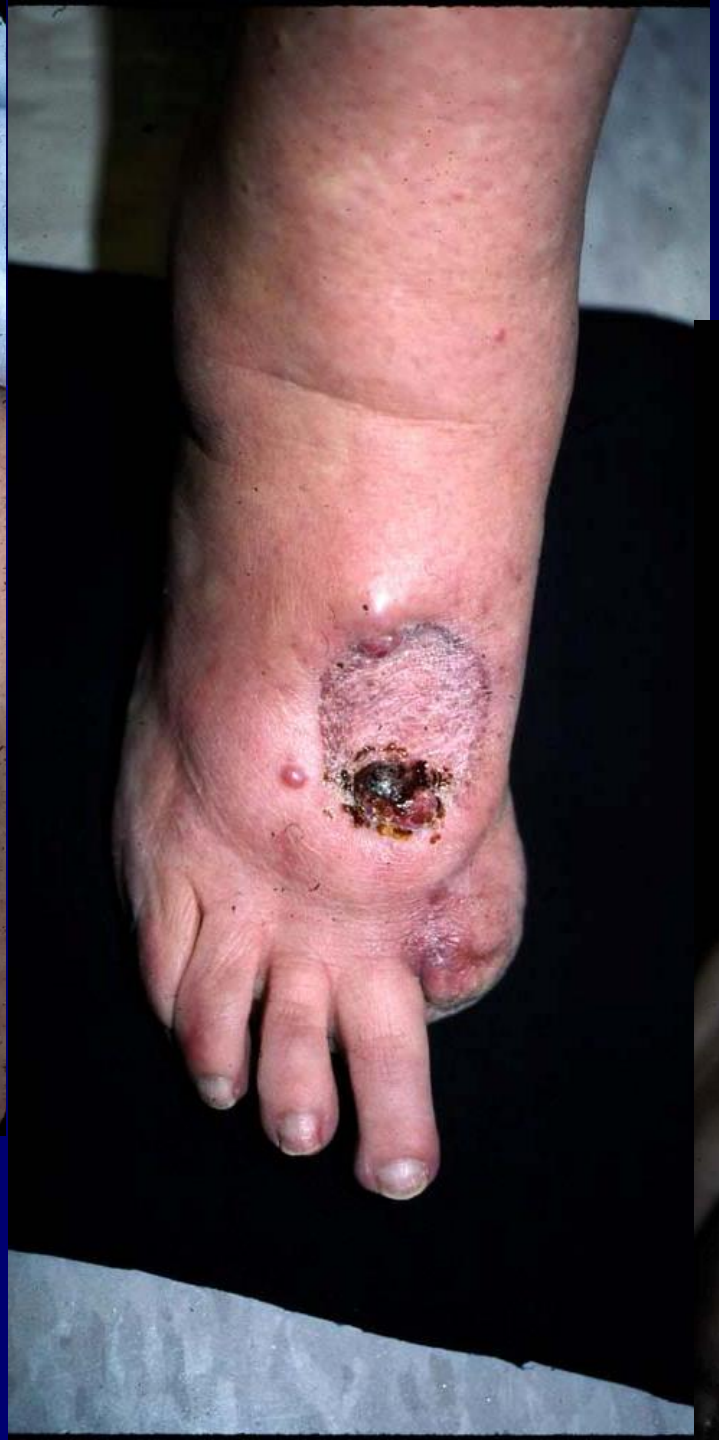
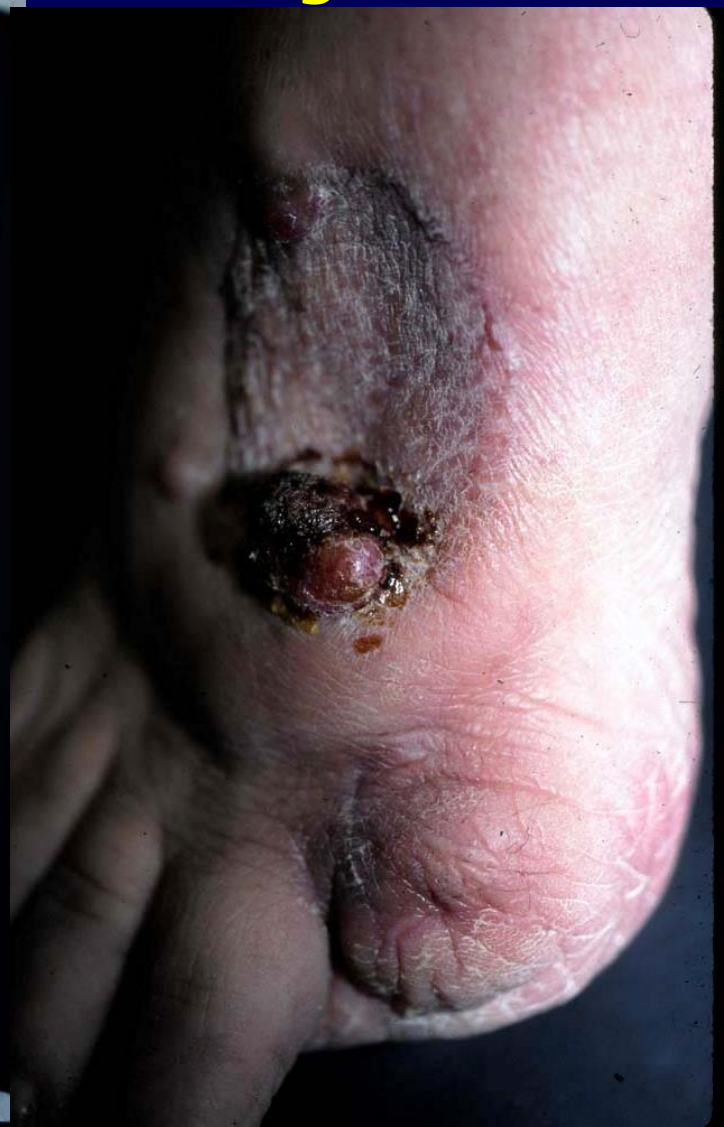
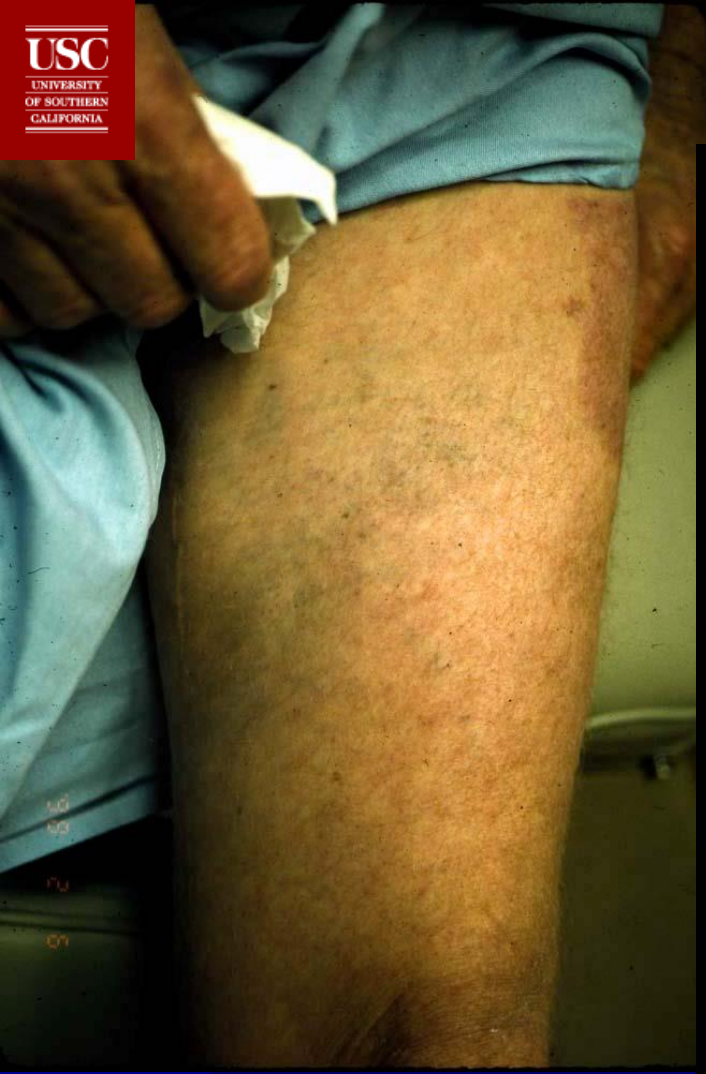
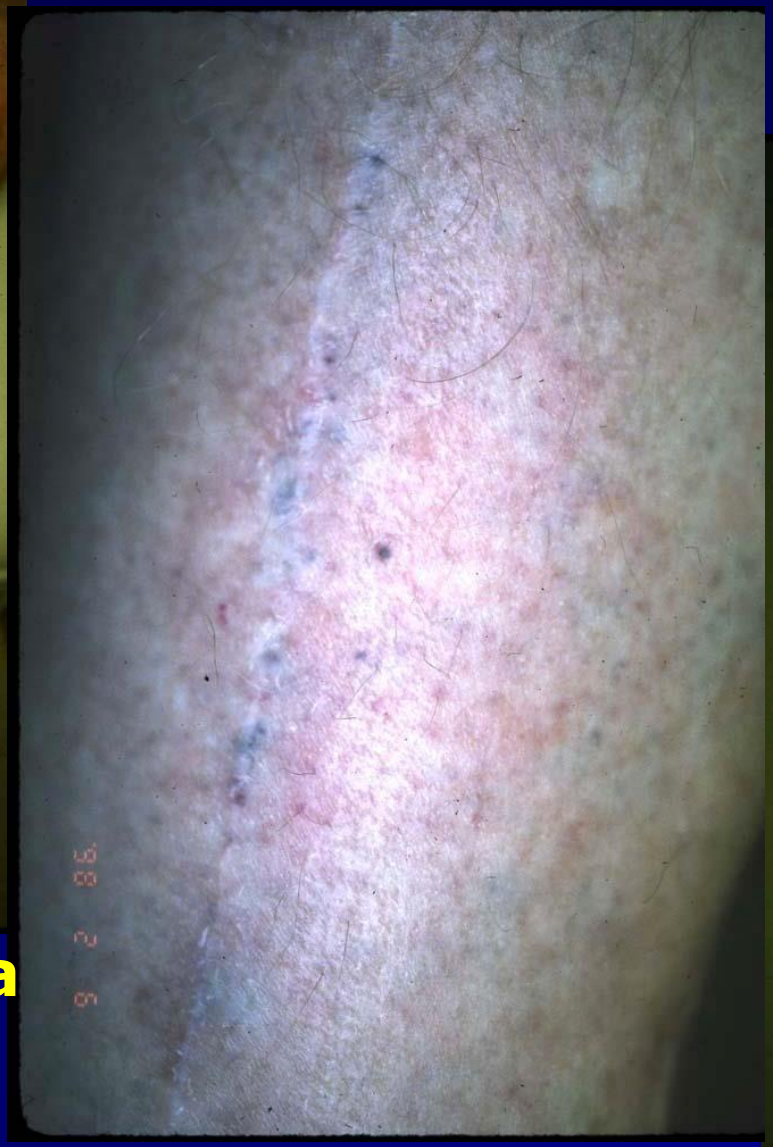
Metastatic Melanoma on skin graft

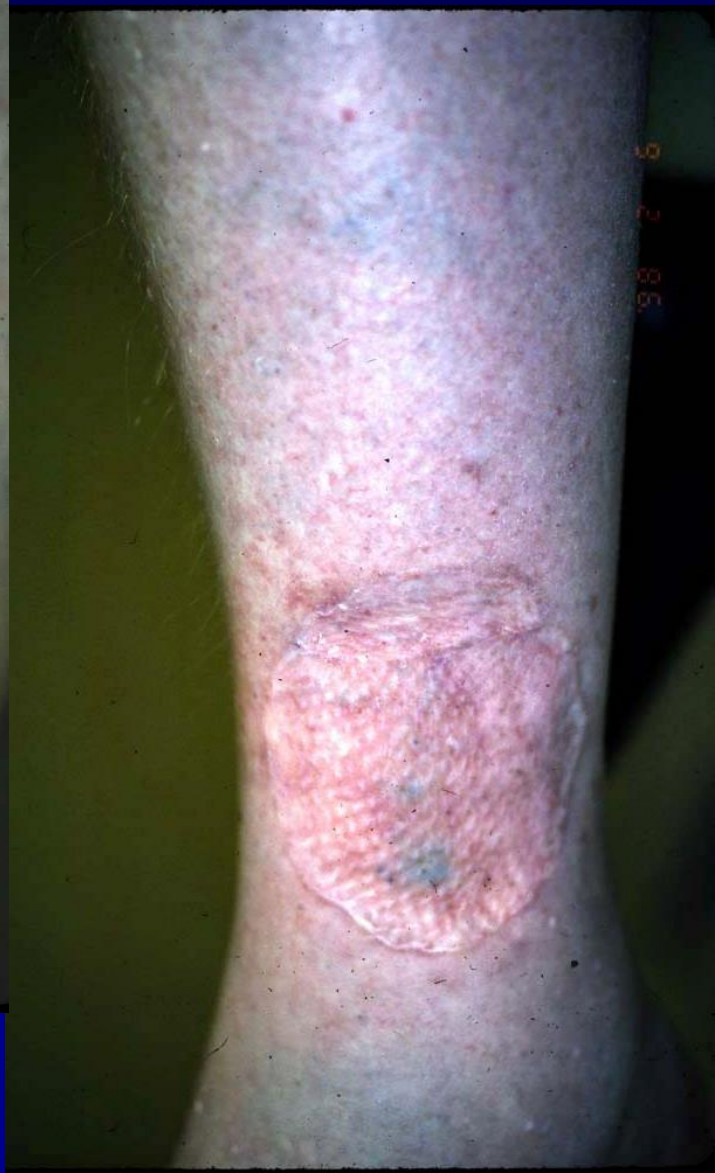












Metastatic Melanoma along blood vessels and under the graft

MELANOMA

What You should do before it happens

PREVENTION

- *Avoid the Sun between 10Am-3PM*
- *Sunscreen/Sunblocker*
- *Sun blocker clothings, hat and cap.*
- *Don't be a sun-worshiper!*
- *Stay in the shade*

The Grace Lines

Sun-induced Wrinkles !

The Grace Lines

Sun-induced Wrinkles !

Sun! Sun! Sun!

The ~~Grace~~ Lines

Sun-induced Wrinkles !

Sun! Sun! Sun!

Age spots/Liver spots-

Lentigo Simplex or Solaris

The Grace Lines

The Best Sunscreens

Helioplex

Active photobarrier complex

Mexoryl SX

MELANOMA

What You Could Do

MEDICAL [for Advanced MM]

- *r*IFNα*2b* s/p Surgery: toxic/costly
- *r*IFNα*2b + IL-2* s/p Surgery: toxic/costly
- Chemotherapy:
  - *DTIC* [dacarbazine] alone,
  - *Dartmouth* [cisplatin,carmustin,DTIC,tamoxifen],
  - *CVD* [cisplatin, vinblastine, DTIC]
- Aldara cream *(5% imiquimod)* for MM in situ

MELANOMA TREATMENT

What's New Treatment

- Yervoy *(ipilimumab)*: *anti-CTLA-4 monoclonal antibody for Stage IV*
- Zelboraf *(Vemurafenib): anti-BRAF ; for Stage IV*
- Tafinlar *(Dabrafenib): anti-BRAF V-600-E;*
- Mekinist *(Trametinib): Anti-MEK*

**All extend the survival 3-4 months longer*

MELANOMA *2002 Staging System*

[Balch CM et al. J Clin Oncol 2001; 19: 3635]

- Stage 0: in-situ
- Stage IA: ≤1 mm w/o ulcer
- Stage IB: ≤1 mm w ulcer or 1.01~2 mm w/o ulcer
- Stage IIA: 1.01~2 mm w ulcer or 2.01~4 mm w/o ulcer
- Stage IIB: 2.01~4 mm w ulcer or >4 mm w/o ulcer
- Stage IIC: *>4 mm* w *ulcer*
- Stage IIIA: *1~3 LNs* w "micro"meta, *w/o ulcer*
- Stage IIIB: 1~3 LNs w "micro"metastasis w ulcer, or
  1~3 LNs w "*macro*" metastasis, or
  in-transit met(s)/satellite(s) w/o metastatic LNs
- Stage IIIC: 1~3 LNs w "macro" metastasis w ulcer, or
  ≥4 LNs, or matted LNs, or
  in-transit met(s)/satellite(s) w metastatic LNs
- Stage IV: distant meta in (a) skin, SQ, LNs; (b) Lung; and
  (c) other viscera, or distant met(s) w elevated LDH

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Prognosis - Second Melanoma

- Among patients who had melanoma
  10% would have a 2nd in 5-10 yrs

- A 2nd melanoma will occur in:
  In the 1st year (60%)
  At the same anatomic site (50%)
  JAMA 2005; 294: 1647

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Prognostic Factors

- While MM already developed

- *Thickness* (and Level) of melanoma
- *Ulceration* of melanoma
- *Age* (*60 yrs*) & *Sex* (*male*) of patients
- *Site* of melanoma (*Axial vs. Limbs*)

Balch et al. CA Cabcer J Clin 2004, 54:131

- *Tumor-infiltrating lymphocytes (TILs)*
- *Mitotic rate (> 6/mm^2)*
- *Vertical growth phase*
- *Sentinel lymphnode (DFS,DMFS & OS)*
- *LDH for Stage IV/Metastasis*
- *Tumor regression (no inter-observer concordance)*

MELANOMA

Prognosis - Bad Markers

- *C-myc oncogen*:
- *TA90-IC* (a 90-kDa glycoprotein immune complex)
- *MIA* (Melanoma-inhibiting activity)
- *S-100 beta & LDH*: makers for *metastasis*

MELANOMA

Dx & Rx

Prognosis

10 Yr Survival based on the thickness of MM

- <1 mm: >90%
- <2 mm: ~75%
- <4.0 mm: ~60%
- > 4.0 mm: ~50%

10 Yr Survival based on the No. of LN

- One LN: 55%
- 2– 4 LNs: 40%
- > 4 LNs: 26%

- *In general, 5-yr survival in patients with metastasis is 10%*

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Dx & Rx
Appraisal of Evidence

MELANOMA

Follow-up

Thickness	*F/U*
In-Situ	1/y up to 10y
.01-1.00mm	2/y for the 1st 3y, then 1/y up to 10y
1.01-2.00mm	3/y for the 1st 3y, then 1/y up to 10y
2.01-4.00mm	4/y for the 1st 3y, 2/y for the 4thy, then 1/y up to 10y
>4mm/LN+	4/y for the 1st 3y, 3/y for the 4thy, then 1/y…..
Metastasis	6/y for the 1st 3y, 4/y for the 4th & 5thy, then 2/y…1/y…

W/U — *Hx & PE [each visit]; Sentinel LN for MM ≥1mm; LDH,CXR [every 1-2 yr] ;CT, MRI, PCR [depends]*