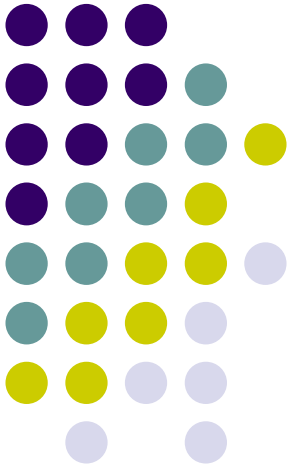
Malignant melanoma clinical aspects

Dr. Battyáni Zita



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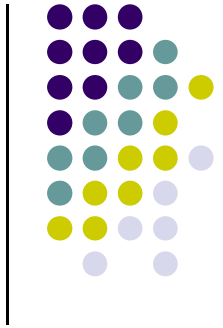
Malignant melanoma



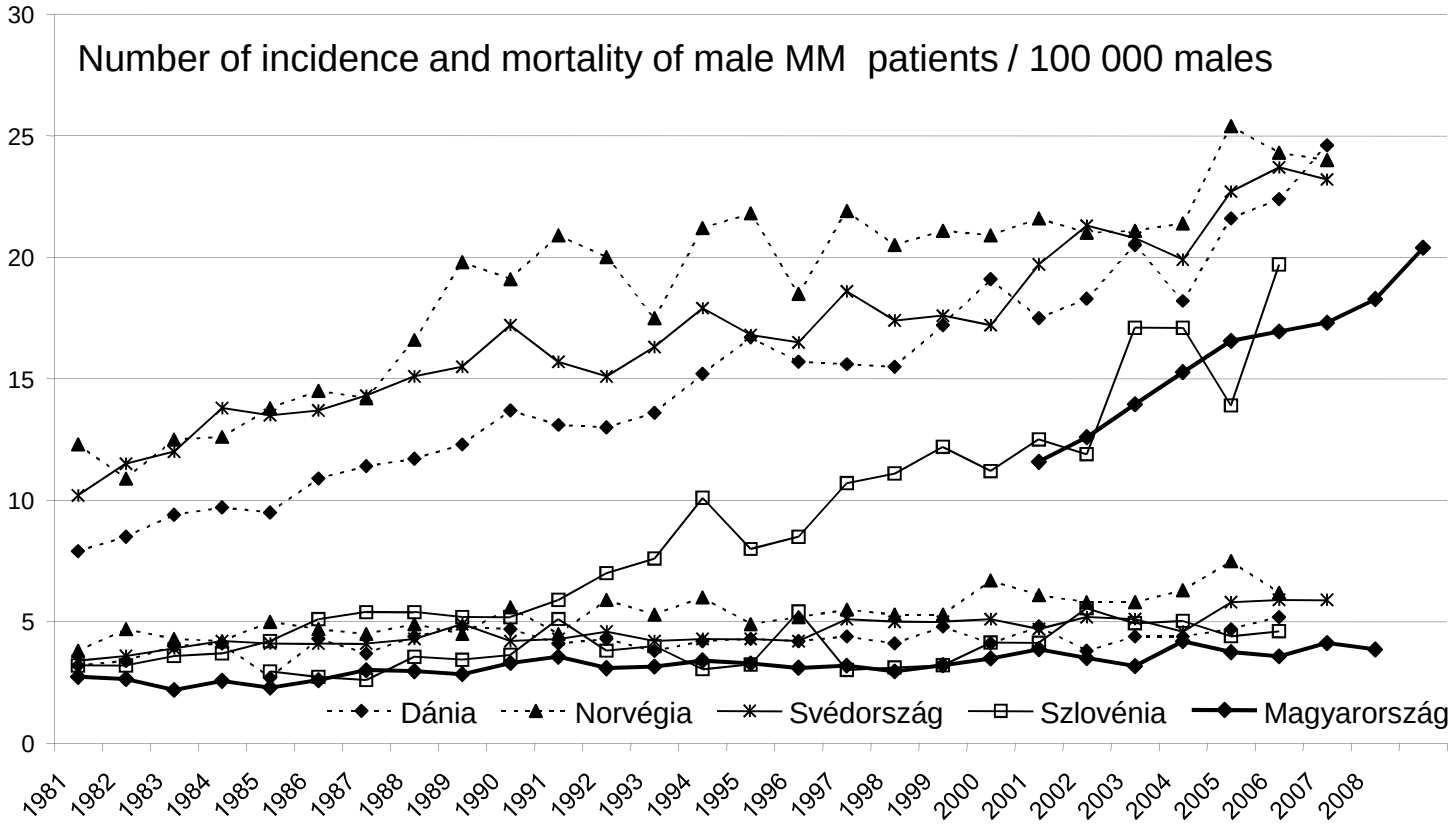
- Definition:
  - arise from melanocytes
  - the most serious oncological problem
  - incidence and mortality rise
  - affects relatively younger population
  - great tendency to early metastasis
  - the only treatment is the early recognition and the surgical excision
  - advanced tumor responds poorly

Epidemiology

- Incidence dramatically increases

  - Australia: 50/ 100 000
  - Europe: 15-20/ 100 000
  - Mexico 40 /100 000 (above 2000 m)
  - Hungary 2110 / year (2009)

Incidence of Malignant melanoma in Hungary 2008 (male)



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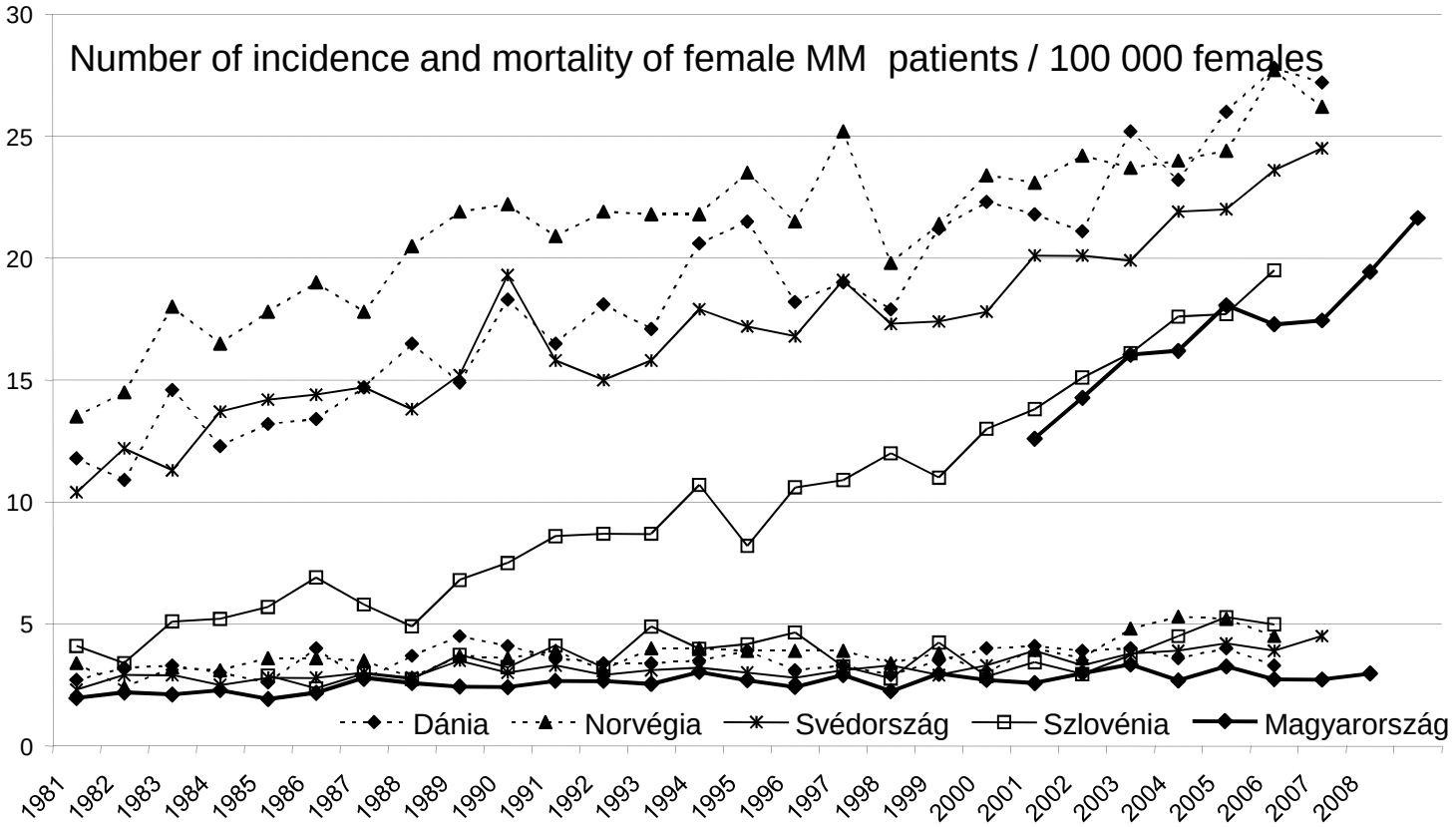
Hungarian Cancer Inst. 2009.

Incidence of Malignant melanoma in Hungary 2008 (female)



29.April 2010.

Hungarian Cancer Inst. 2009.

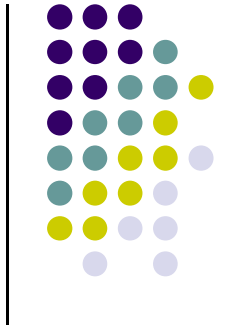
Epidemiology

- F>M
- Age affected

  ~40-60 years (increased 20-30 y)
- Among blacks is very rare, mainly localized

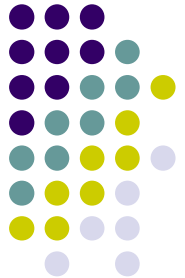
  subungual, on palm, soles and mucosa

Epidemiology



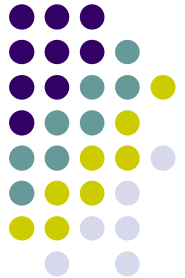
- Life time risk in USA
  - 1935 1:1500
  - 1980 1:250
  - 2000 1:70
  - 2010 1:50
- Life time risk in Australia
  - 2000 1:60

Etiology and pathogenesis



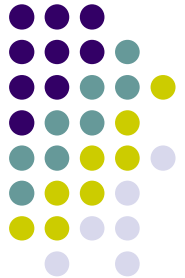
- The exact cause is unclear
- Genetical and environmental factors
- 10% show familial occurence
- Iatrogenic or acquired immunosuppression
  - Melanoma risk increased 3x

Etiology, pathogenesis



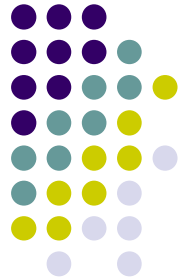
- UV irradiation- UVA-pirimidin dimers
  - Single, high dose exposition
  - Sunburns, mainly in childhood
    - >3 sunburns, melanoma RR increased 3x
- Presence of nevi
  - 25-40% of melanoma arise from nevi
  - > 50 nevi melanoma risk is 5X higher
  - Atypical or dysplastic nevi, dysplastic nevus syndrome
  - Giant congenital nevi
  - Mechanical irritation and repeated damages

Etiology, pathogenesis



- Chromosomal alterations:
  - 9p21- cell cycle regulation (CDK2A)
  - BRAF és RAS mutation
  - Raf-MAPK kinase-ERK (RAF-MEK-ERK)
  - PI3K/**PTEN**/AKT pathway (leads to apoptosis blockade)
  - Interaction between tumor cells and stroma

Etiology, pathogenesis

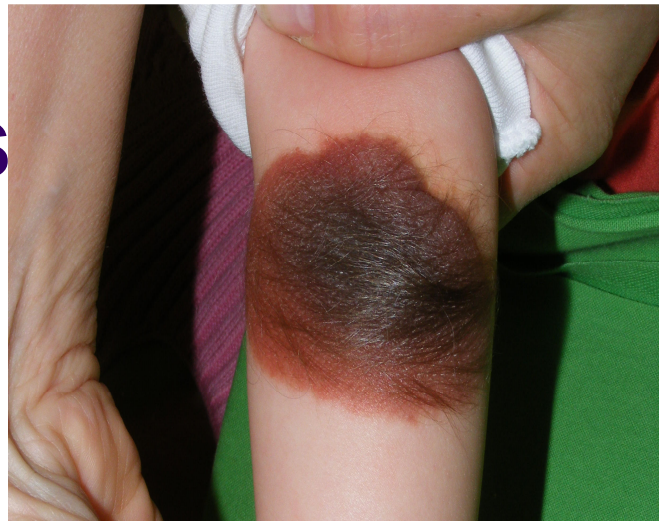


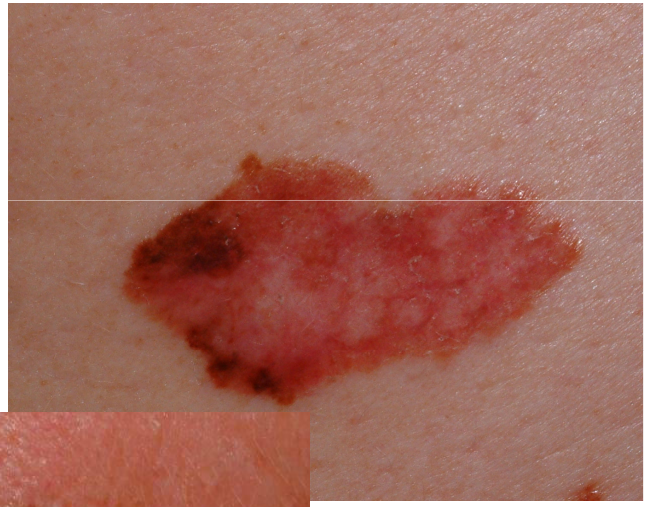
Familial incidence,

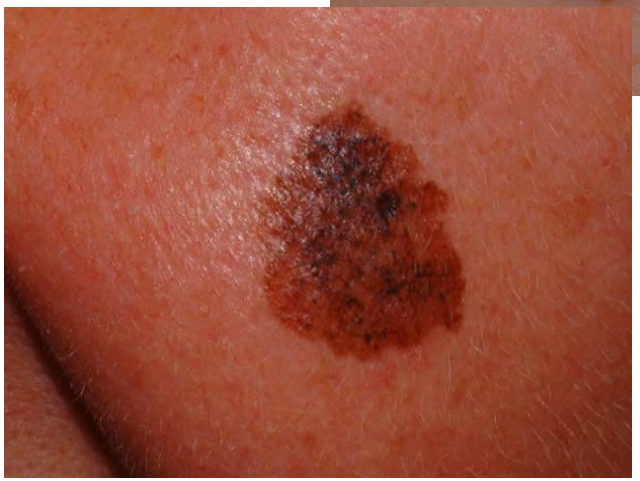
- Red hair and freckles in skin types I-II,
- both parents have melanoma the child risk for melanoma 100%
- 10% of melanoma are familial

Precursor lesions

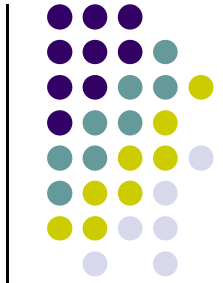
- Congenital nevi
  - mainly giant and deeper type
- Dysplastic nevi
- *In situ* melanoma (lentigo maligna)
- Without precursor lesion, de novo







Clinical form of malignant melanoma



- Lentigo maligna melanoma 1%
- SSM 70%
- Nodular melanoma 21%
- Acrolentiginous melanoma 5%
- Non classifiable 3%

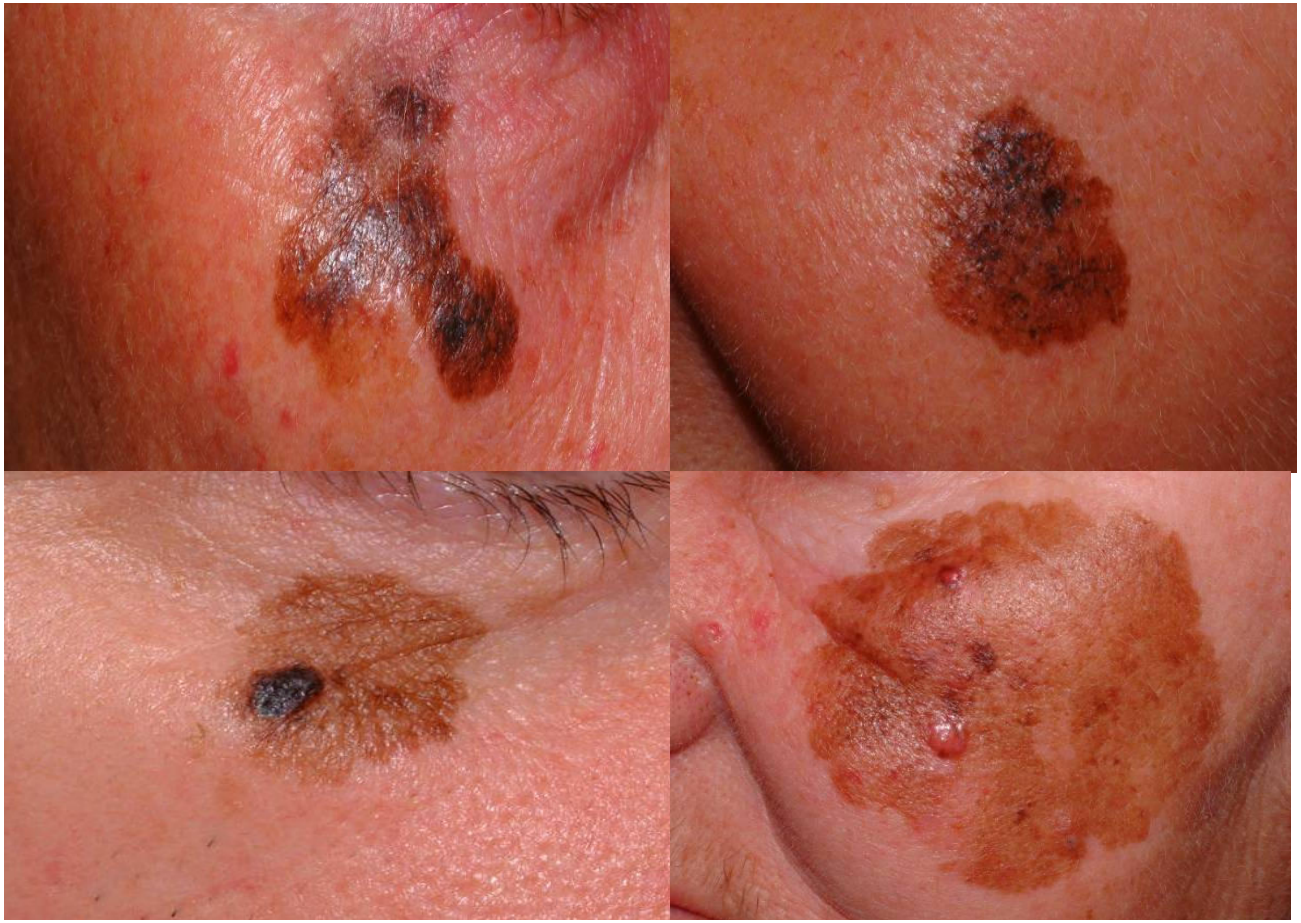
  (mucosal, amelanotyc, desmoplastic)

Lentigo maligna melanoma 1%

The most favorable prognosis

Grows very slowly

Mainly on the face of elderly patients,

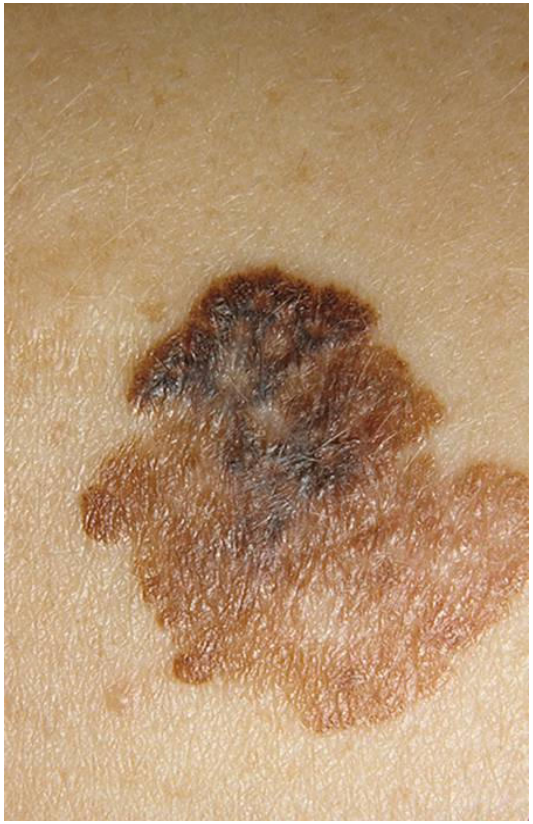


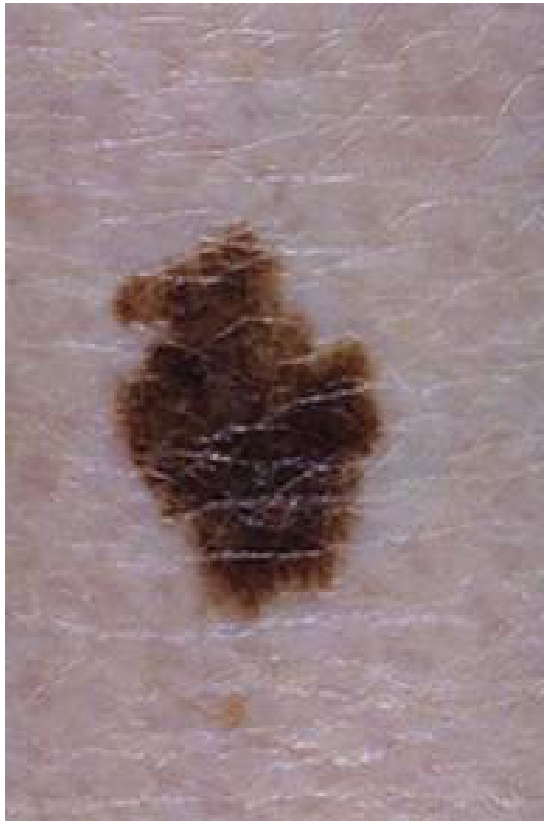
Superficial spreading melanoma (70%)

Favorable prognosis

Long horizontal growth phase

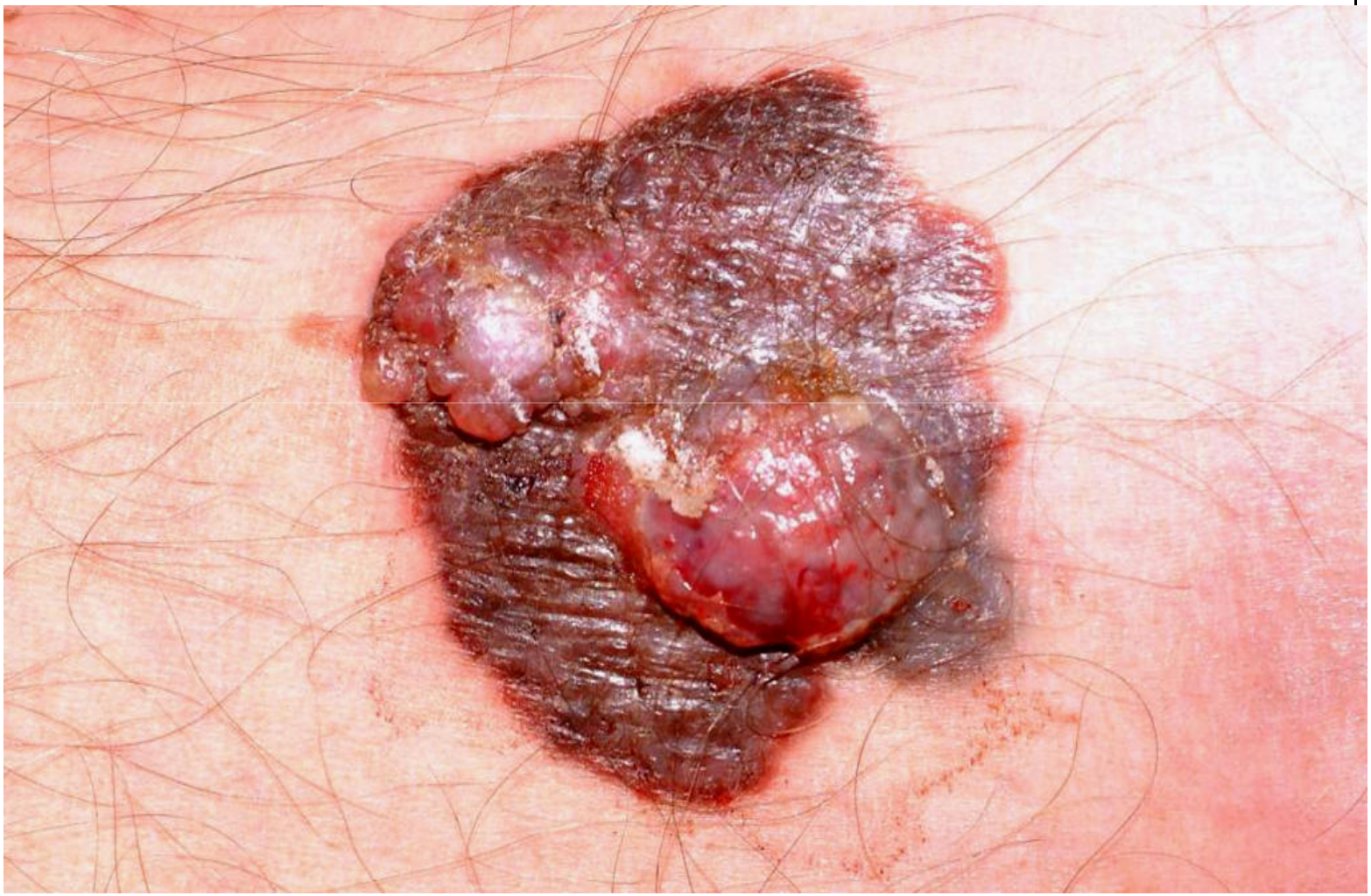
In vertical phase bad prognosis





SSM with vertical growth

The prognosis is worse

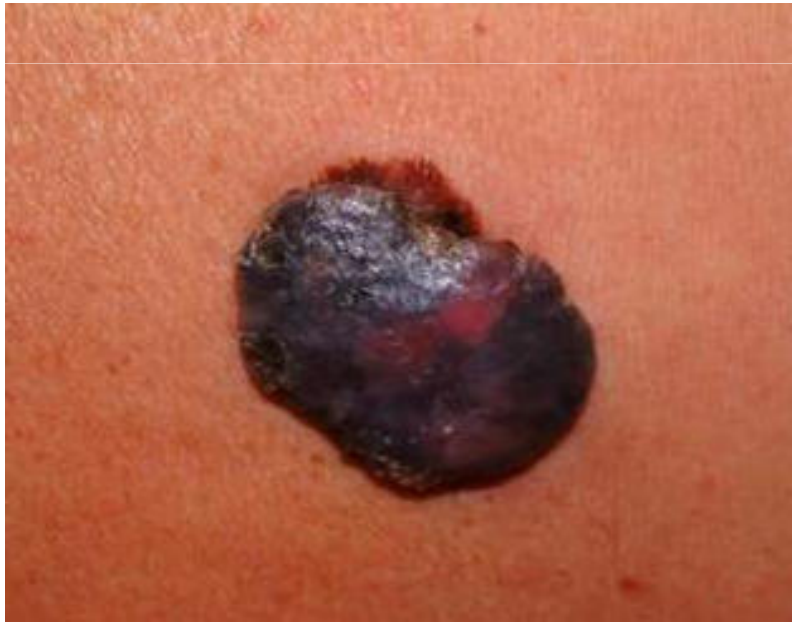


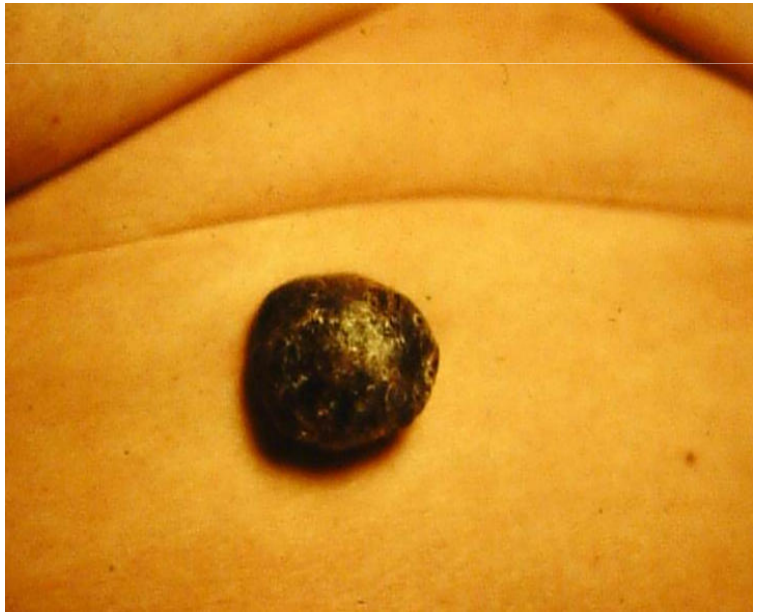
Nodular melanoma 21%

The 2nd most frequent type

Early tendency to vertical growth

Gives early metastases

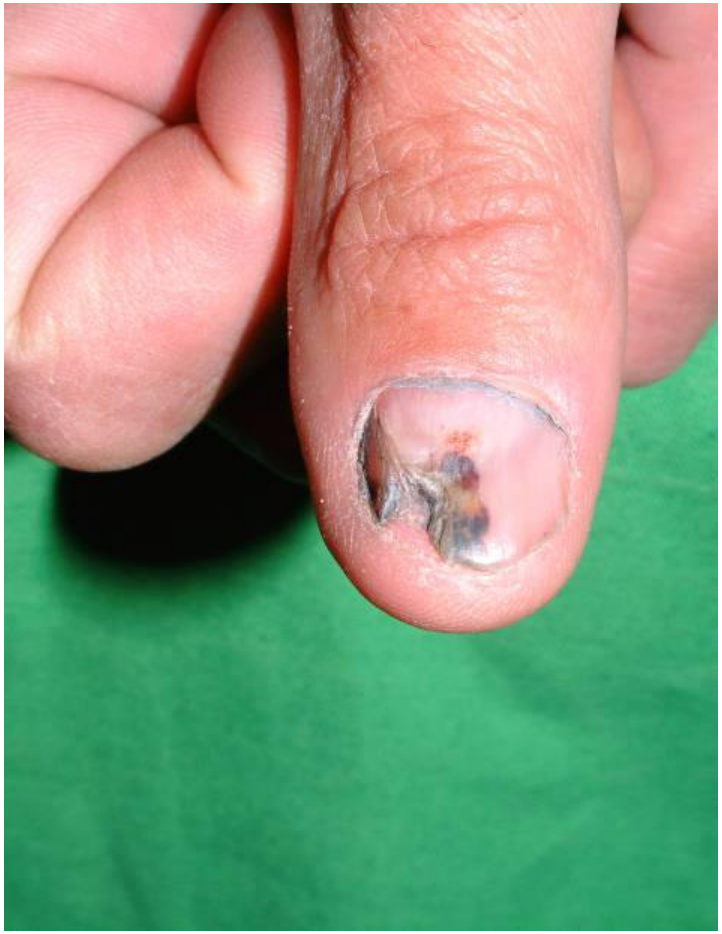


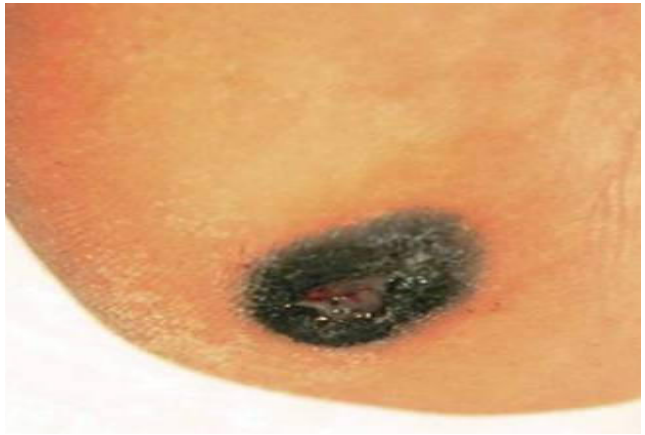


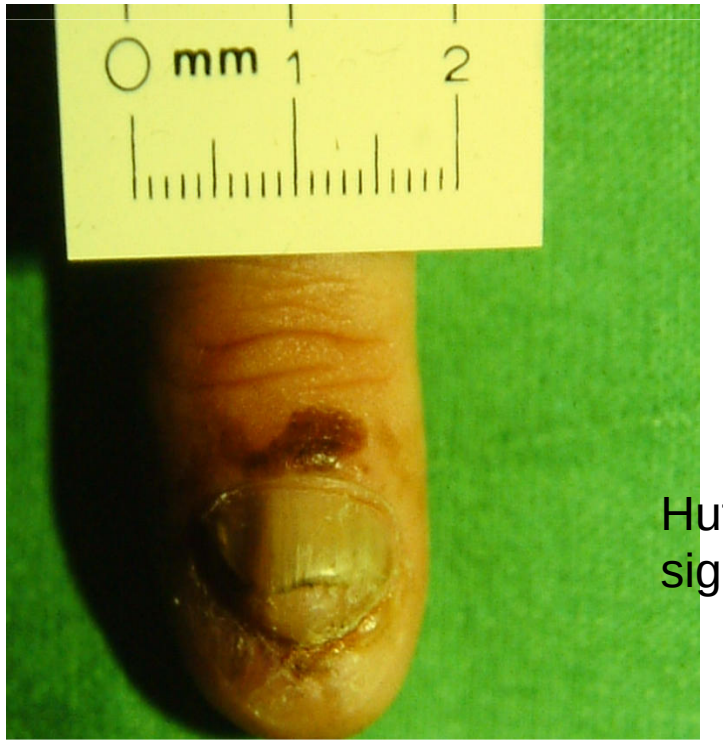
Acral lentiginous melanoma 5%

Palms, soles, subungual

Poor prognosis

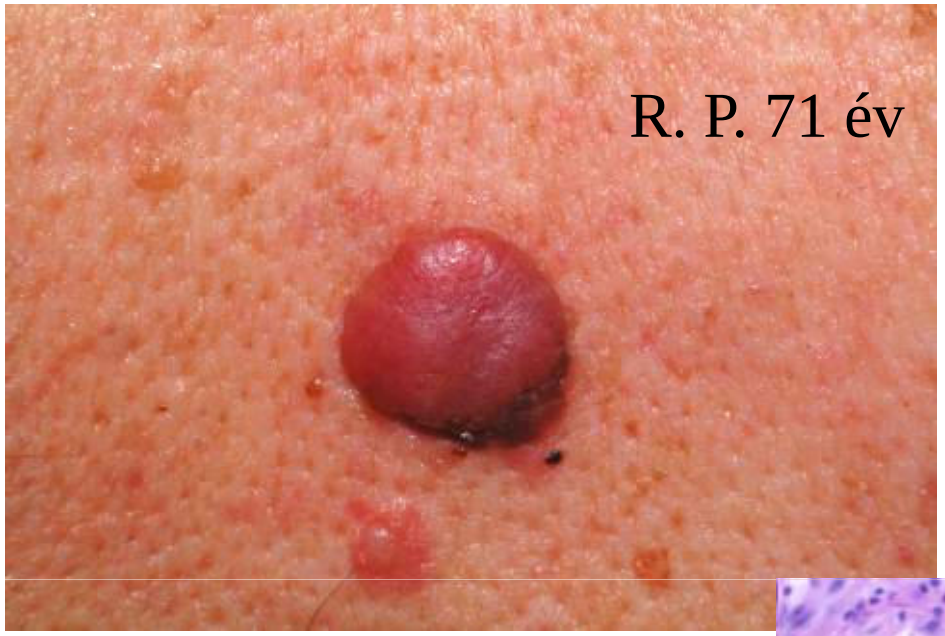


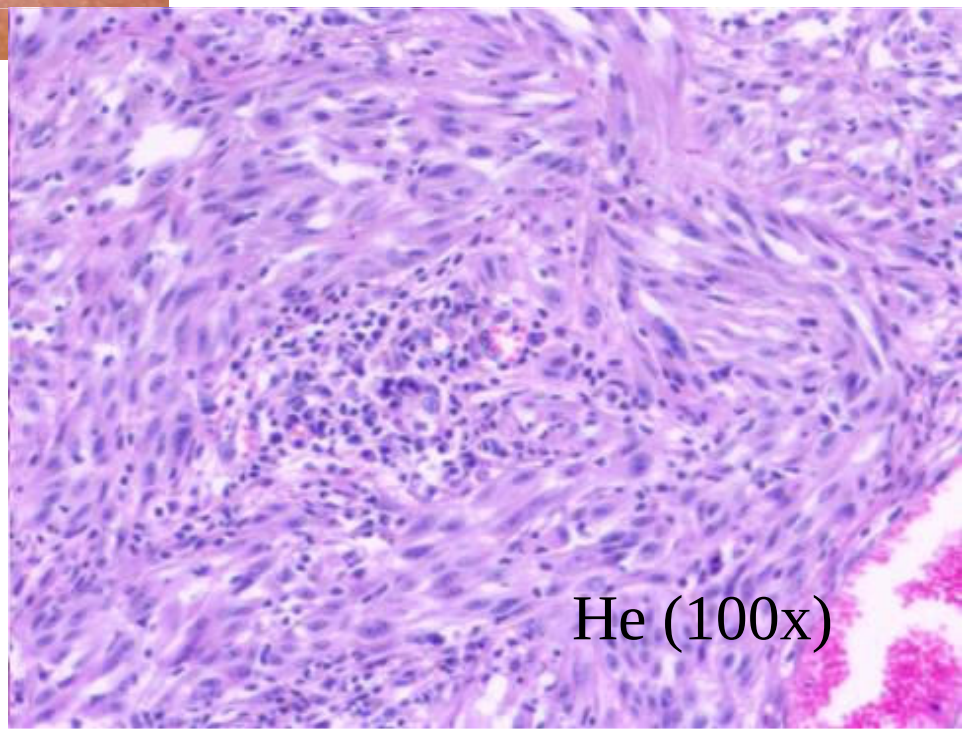




Hutchinson sign

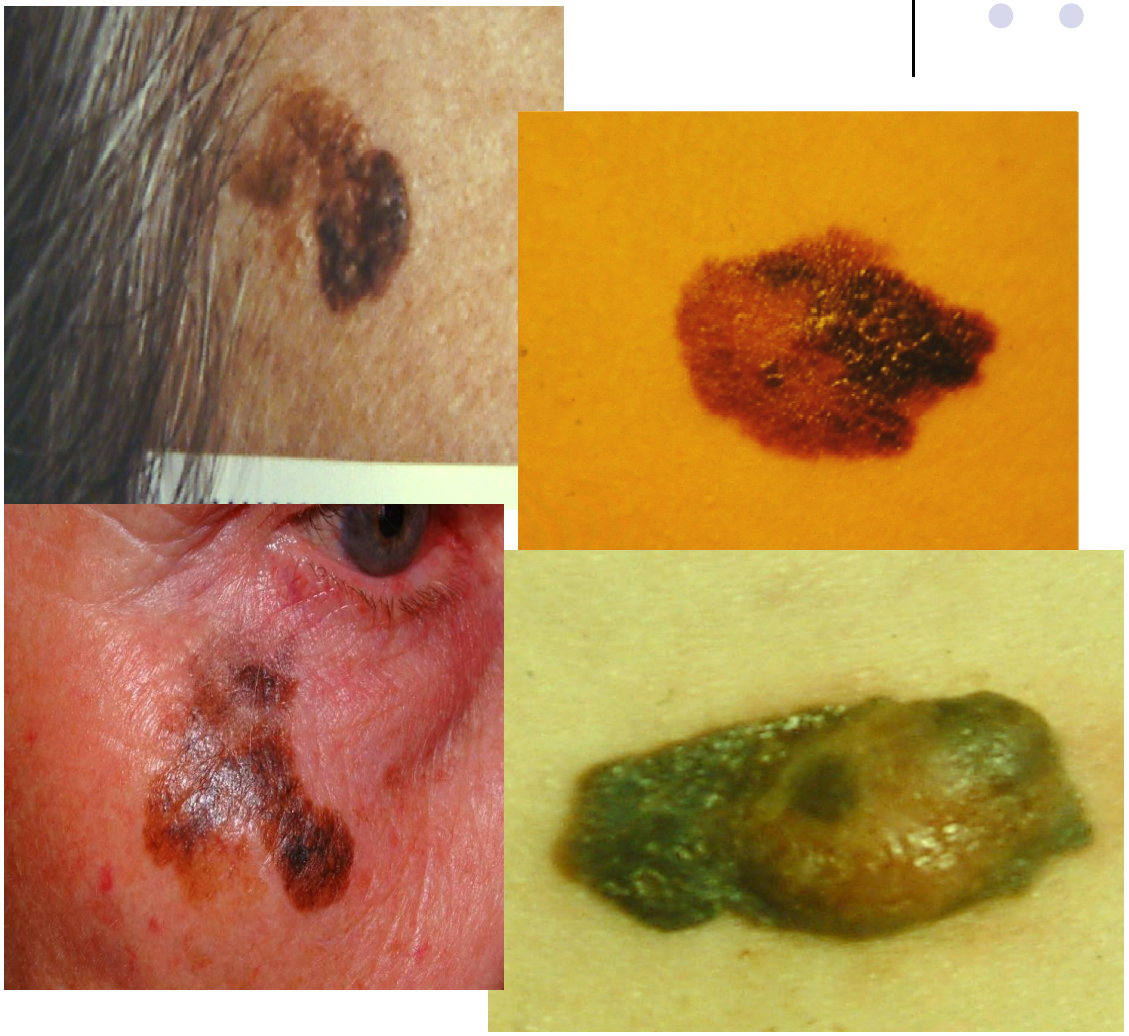
Amelanotic melanoma



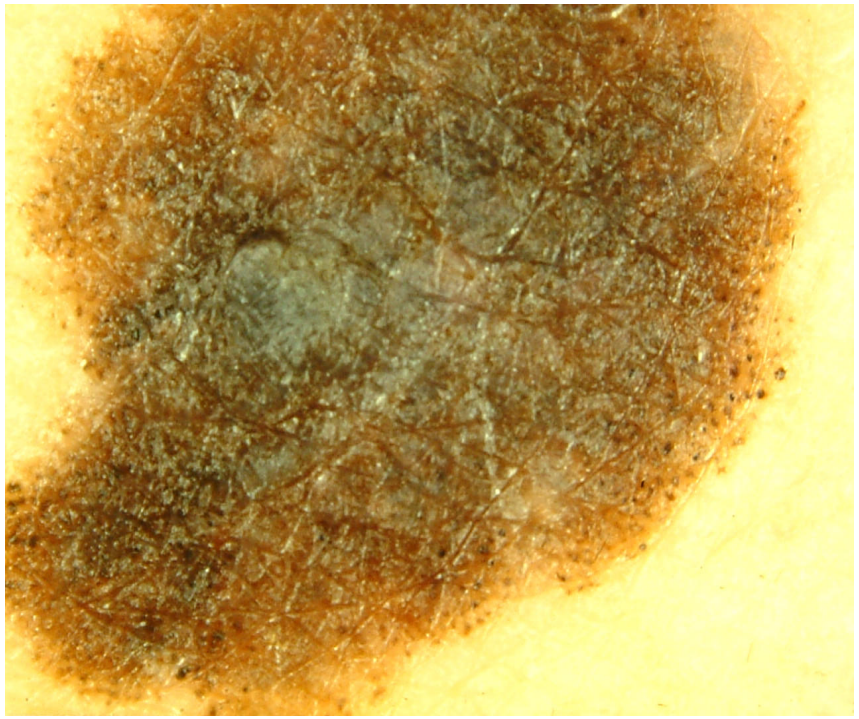


Suspicion of malignant changes

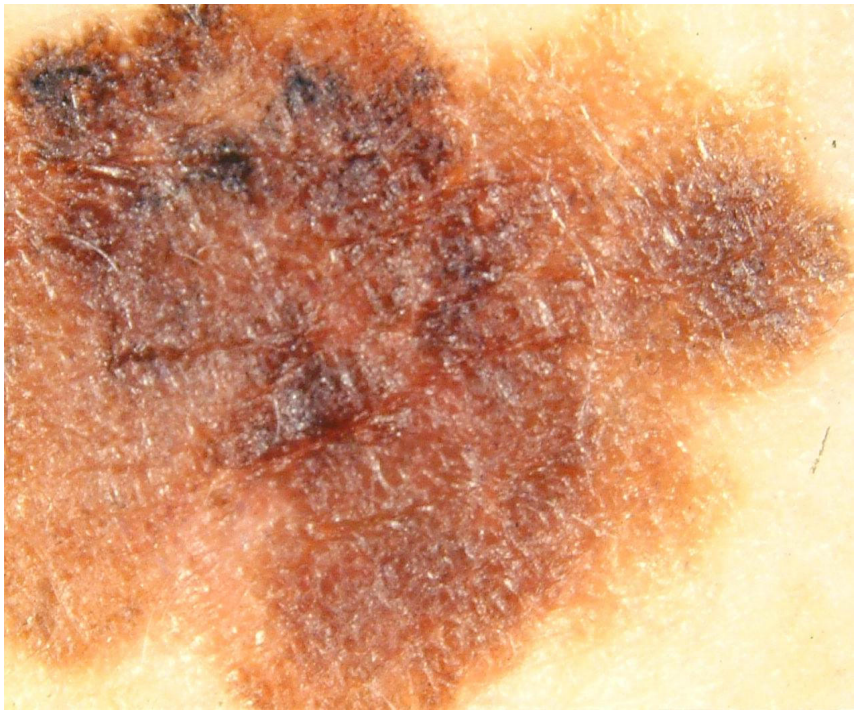
- Asymmetry
- Border (irregular)
- Color (multiple)
- Diameter(>6mm)
- Elevation



Malignant melanoma Dermoscopy

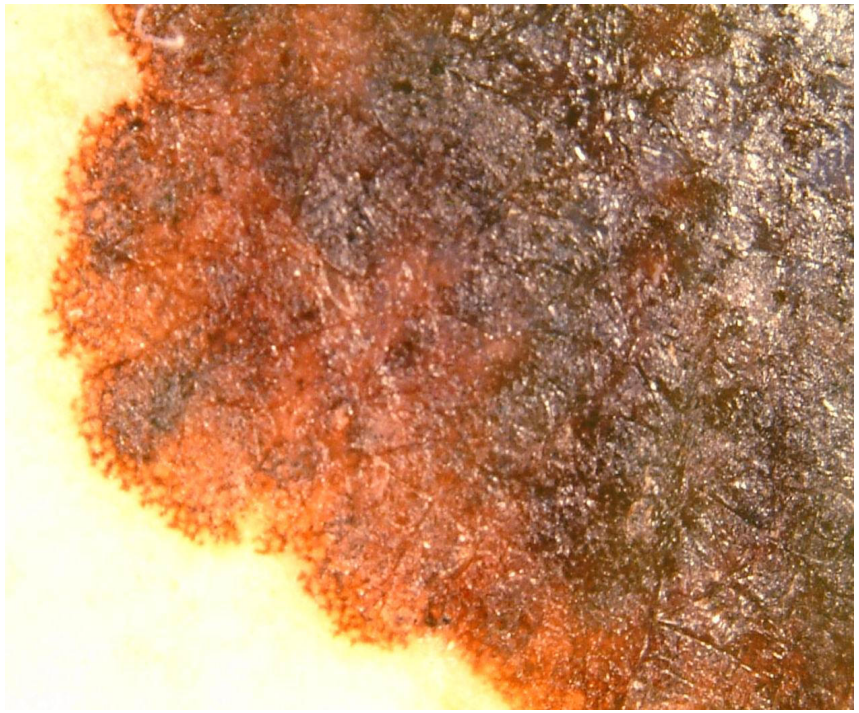


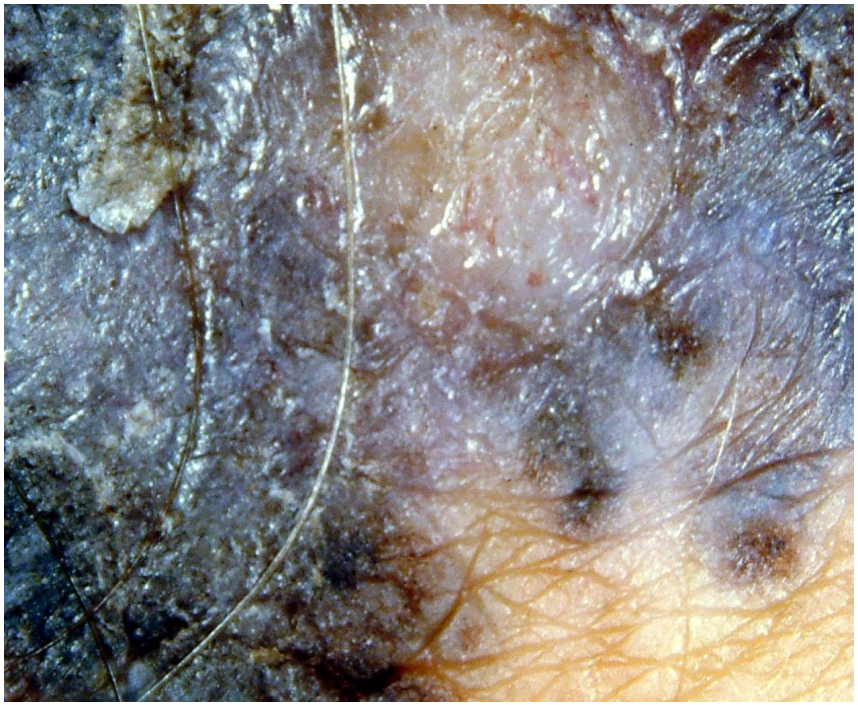
Irregular pigment dots



Multiple colors

Malignant melanoma dermoscopy



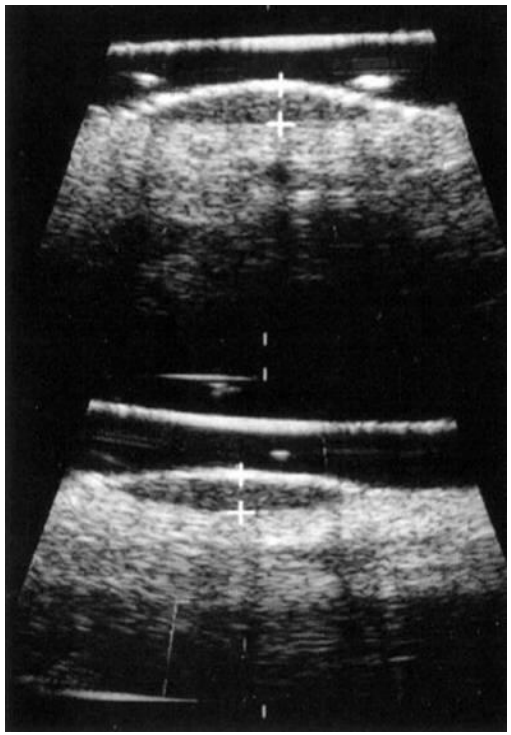


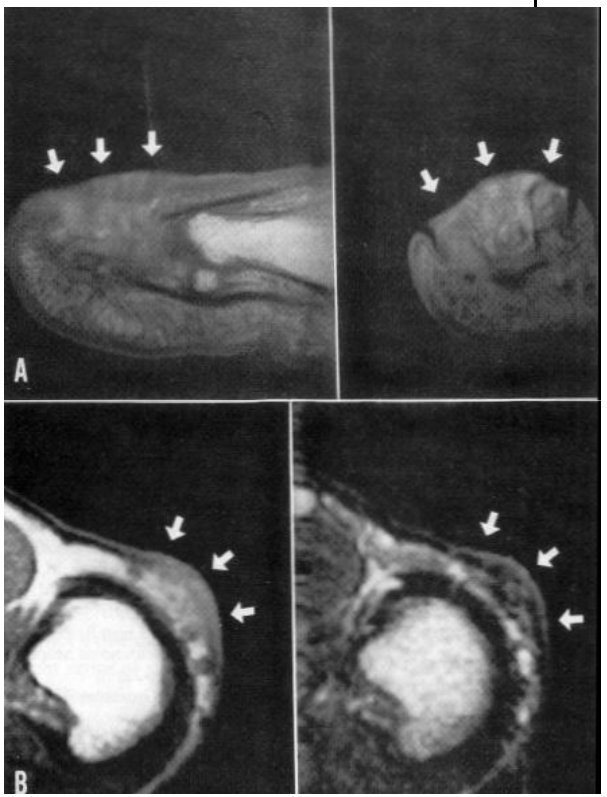
Irregular pigment streaks

Bluish black color, with milky glass shadows

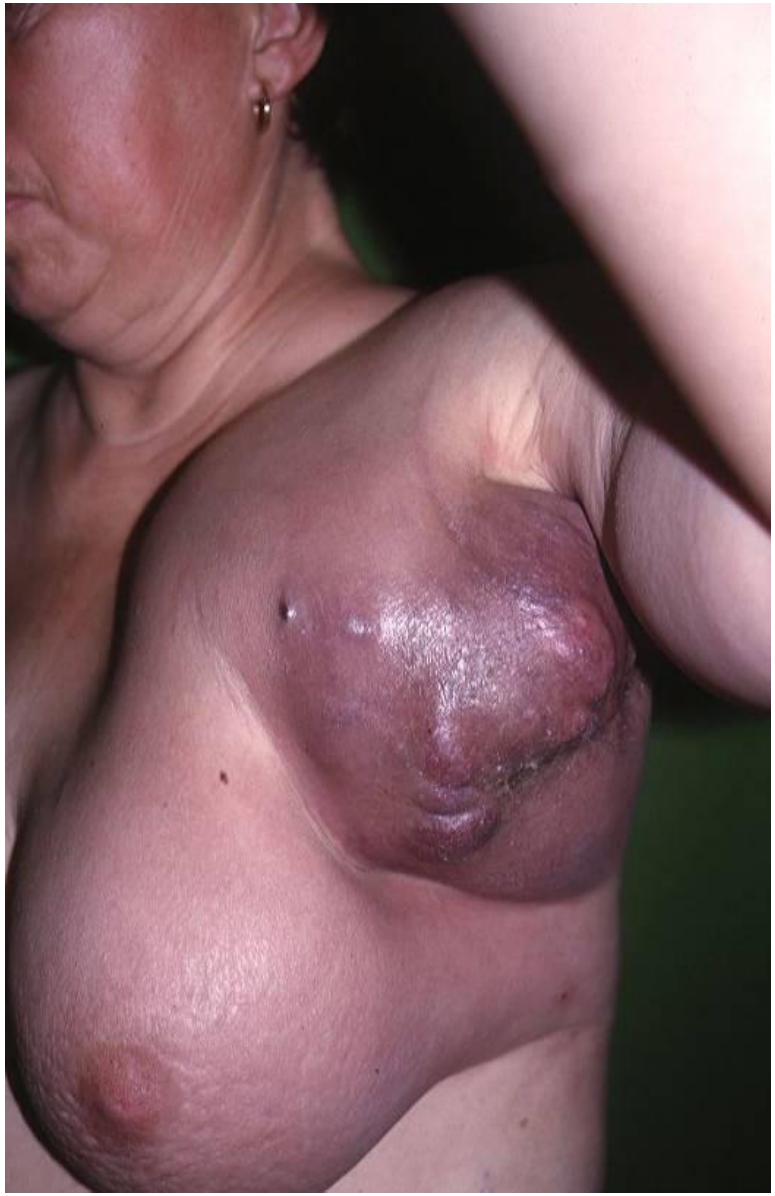
The new diagnostic possibility

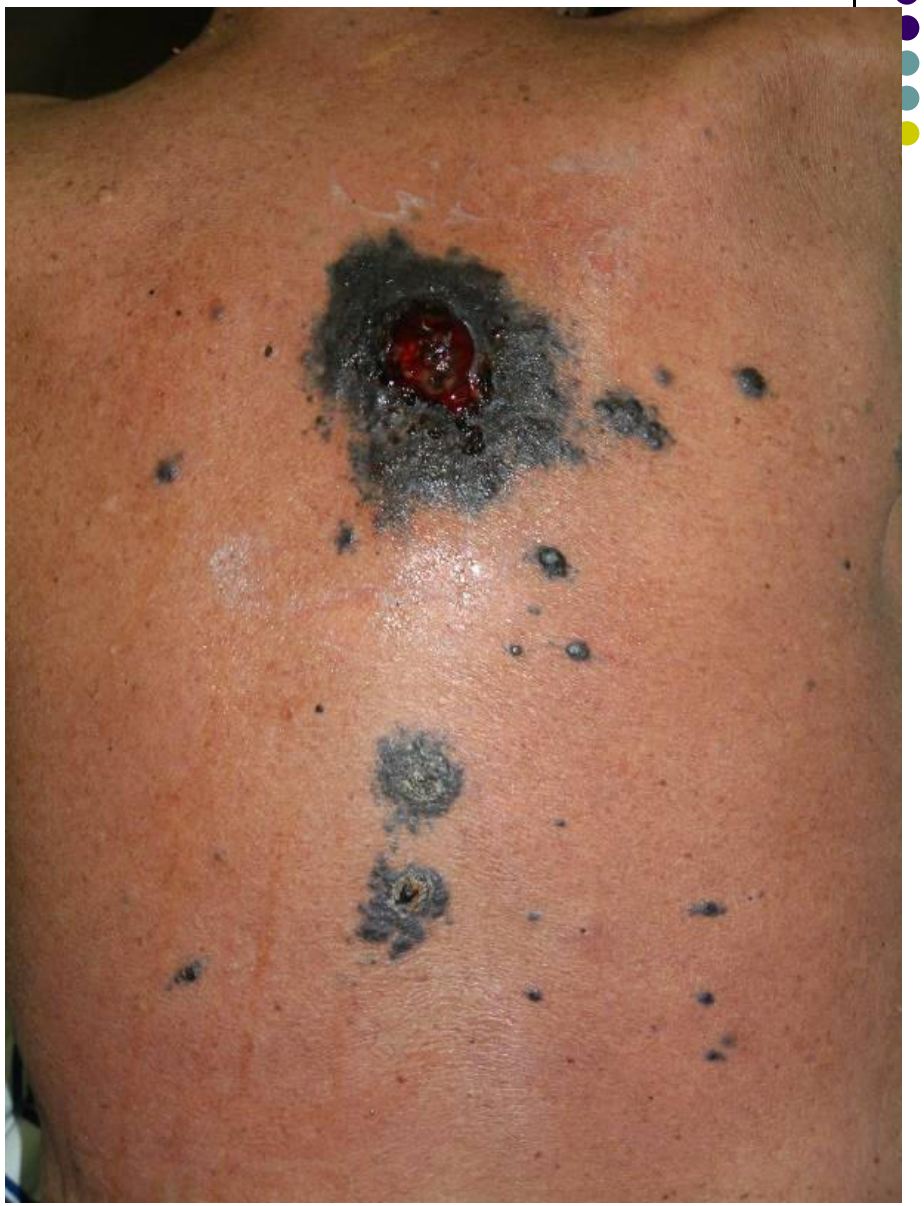
- Digital dermoscopy - dermoscopy
- 22 MHz ultrasound investigation
- MRI





By lymphatic way





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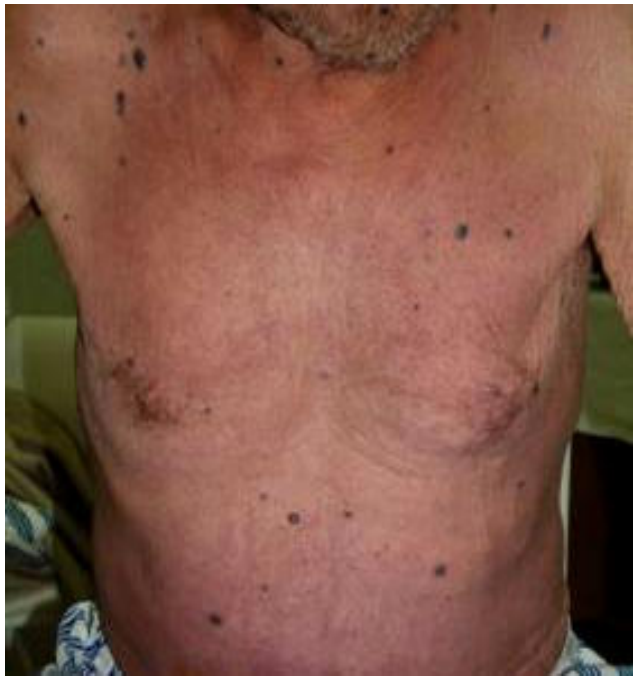
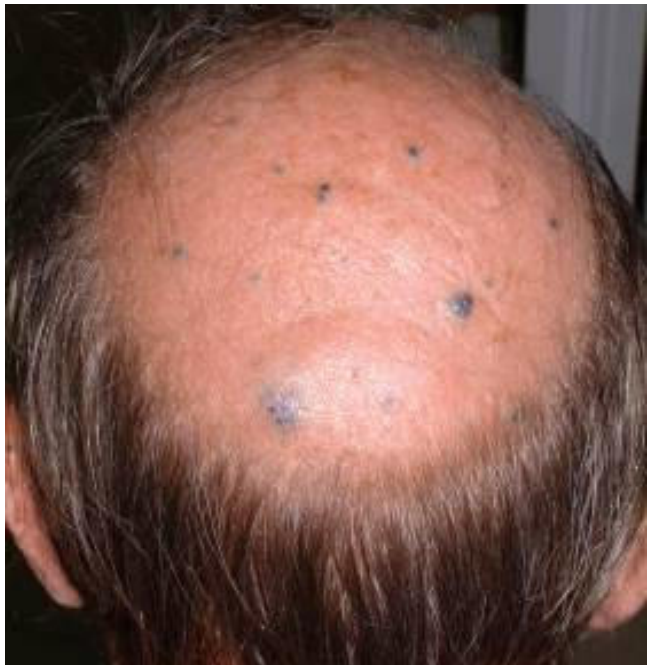
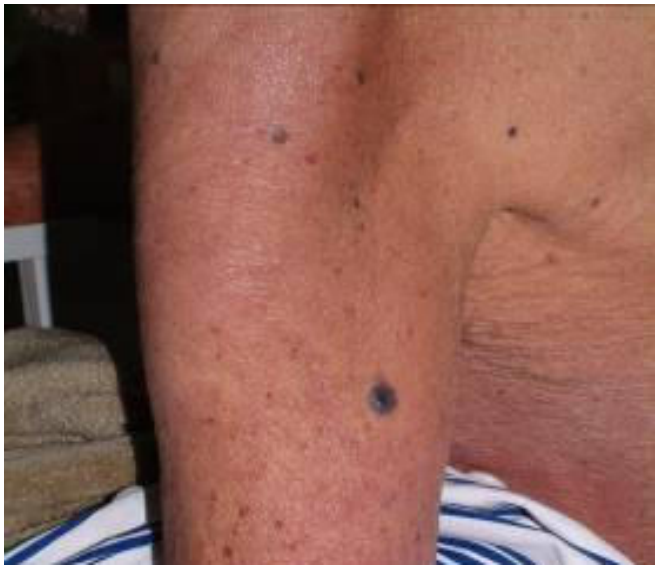
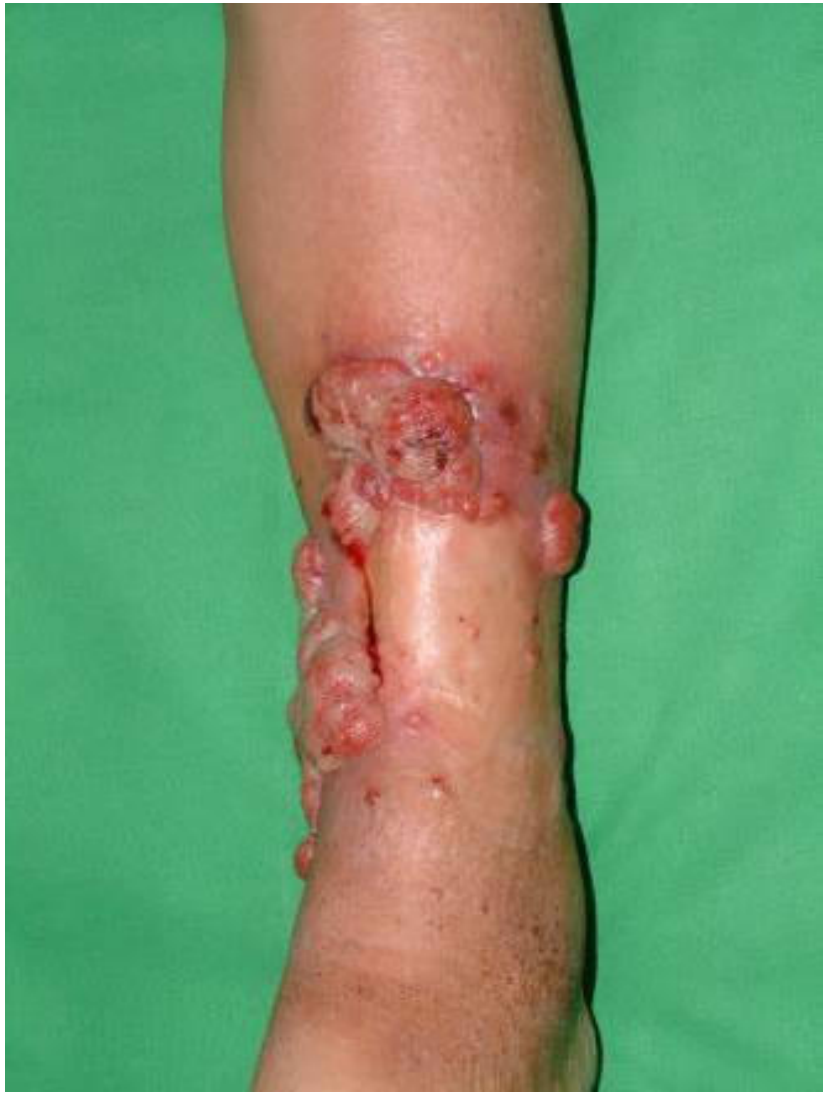


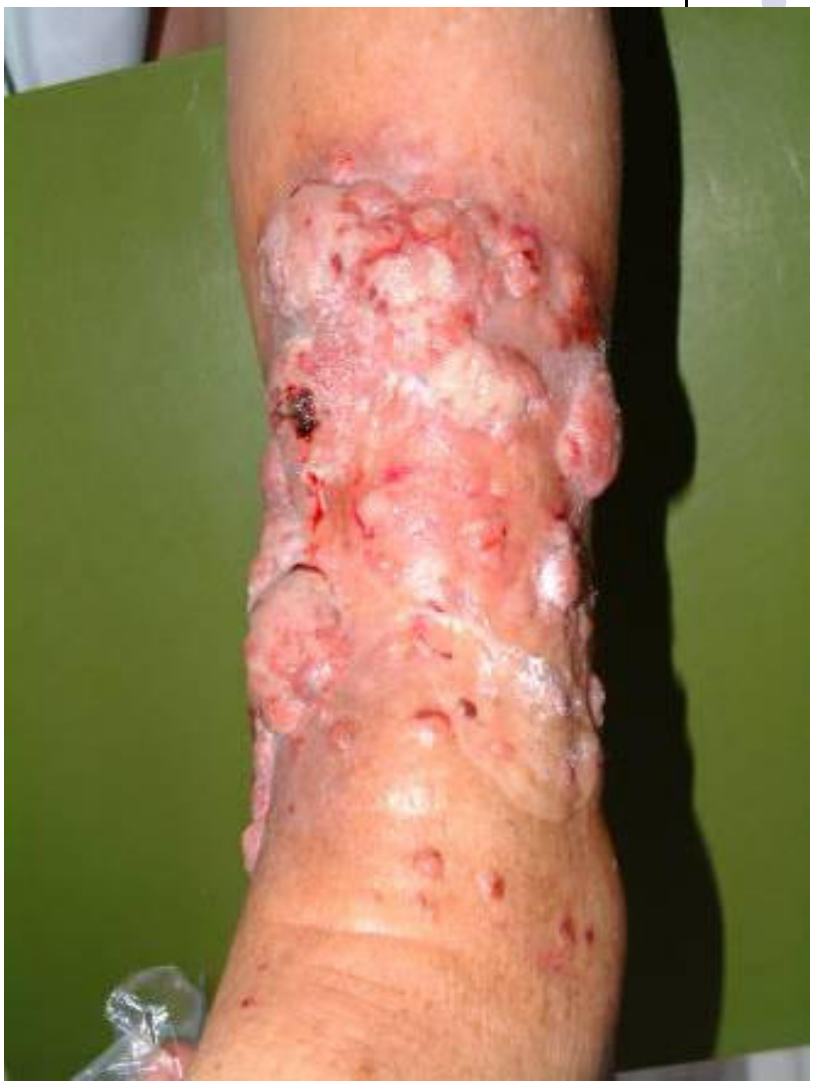




By hematological way

- Pulmonal
- Cerebral
- Liver
- Skin





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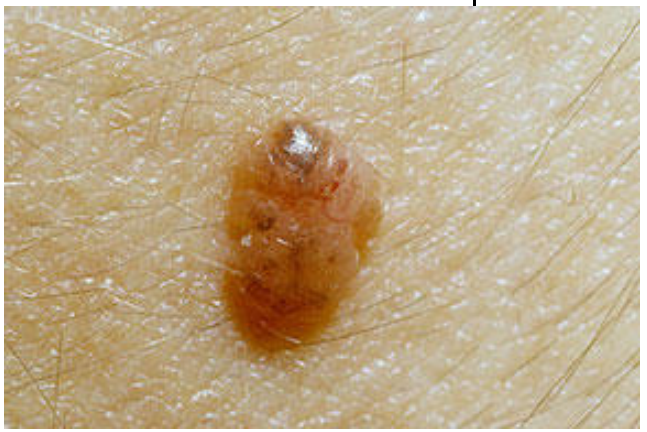
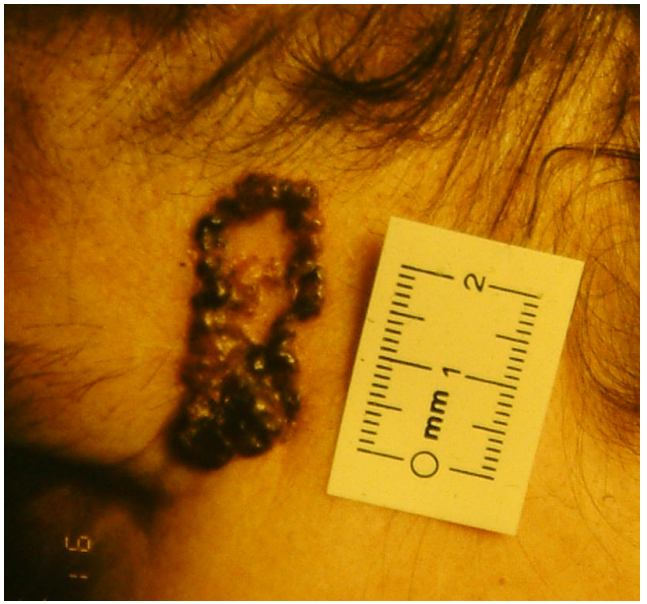
Differential diagnosis

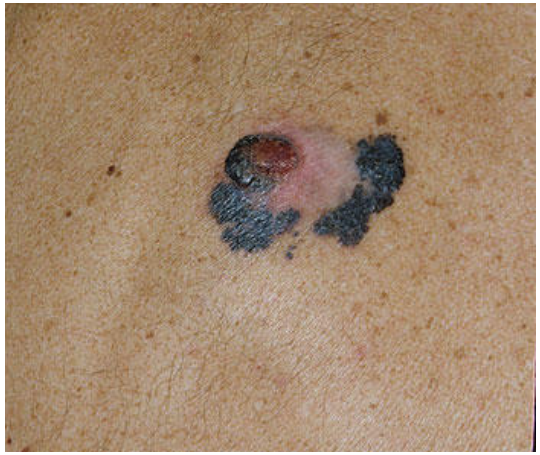
- Nevi
- Dysplastic nevi
- Pigmented basal cell carcinoma
- Verruca seborrhea
- Pyogen granuloma
- Hemangioma

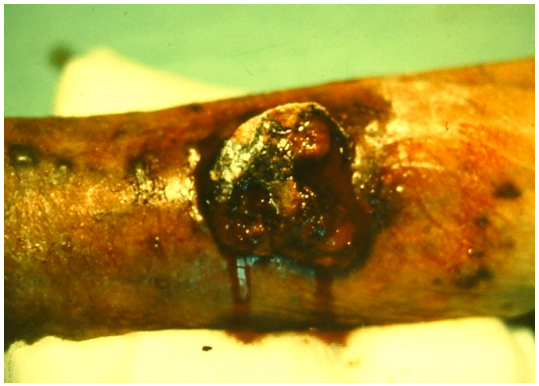




Clinical prognostic factors of melanoma

- Clinical type (LMM, SSM, ALM, NM)
- Tumor location (extremities, BANS region)
  - BANS: back, arm, neck, scalp
  - Multi-directional lymph drainage
- Age of patients (prognosis worsens with age)
- Sex (male is unfavorable)
- *Worse prognosis*
- Ulceration
- Regression
- Bleeding

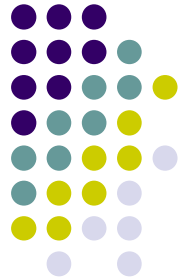




Histological prognostic factors

- Tumor thickness
- *(Invasion level-)* mitotic rate <; > 1/mm^2
- *(Number of mitoses HPF)*
- Micro-ulceration (important in stage I-II-III)
- Lymphocytes infiltration (lack of infiltration)
- Satellites, in transit metastases
- Vascular invasion

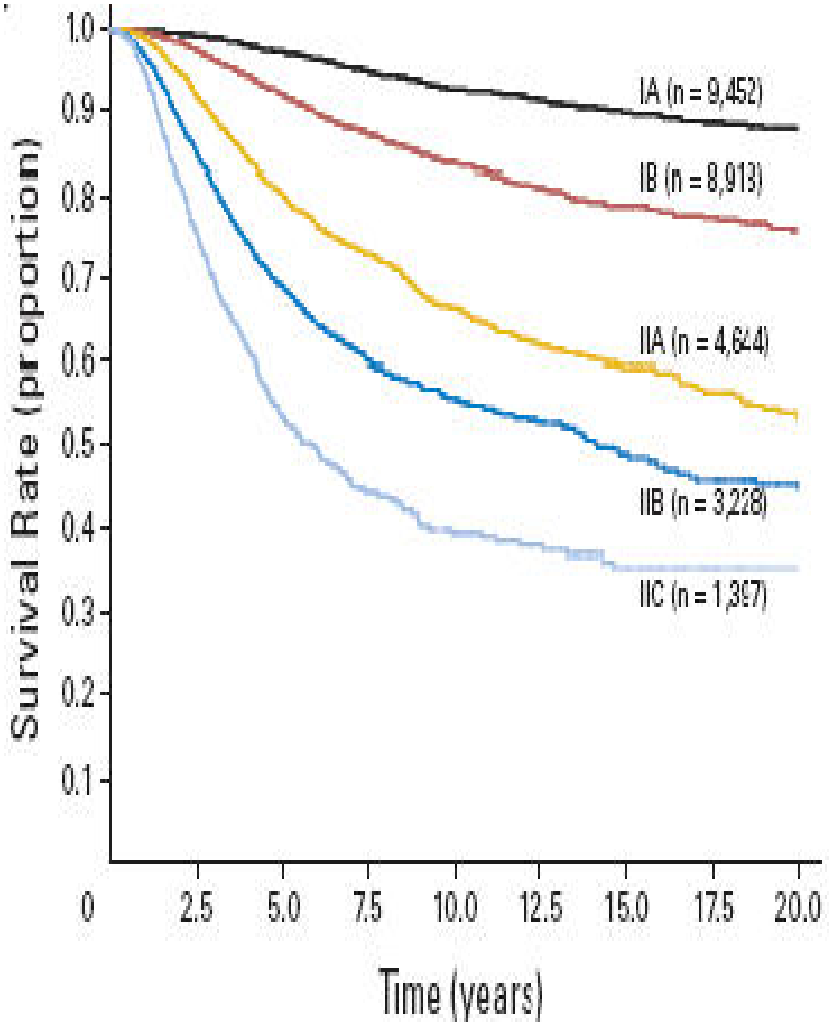
New findings and definitions in the new version of staging

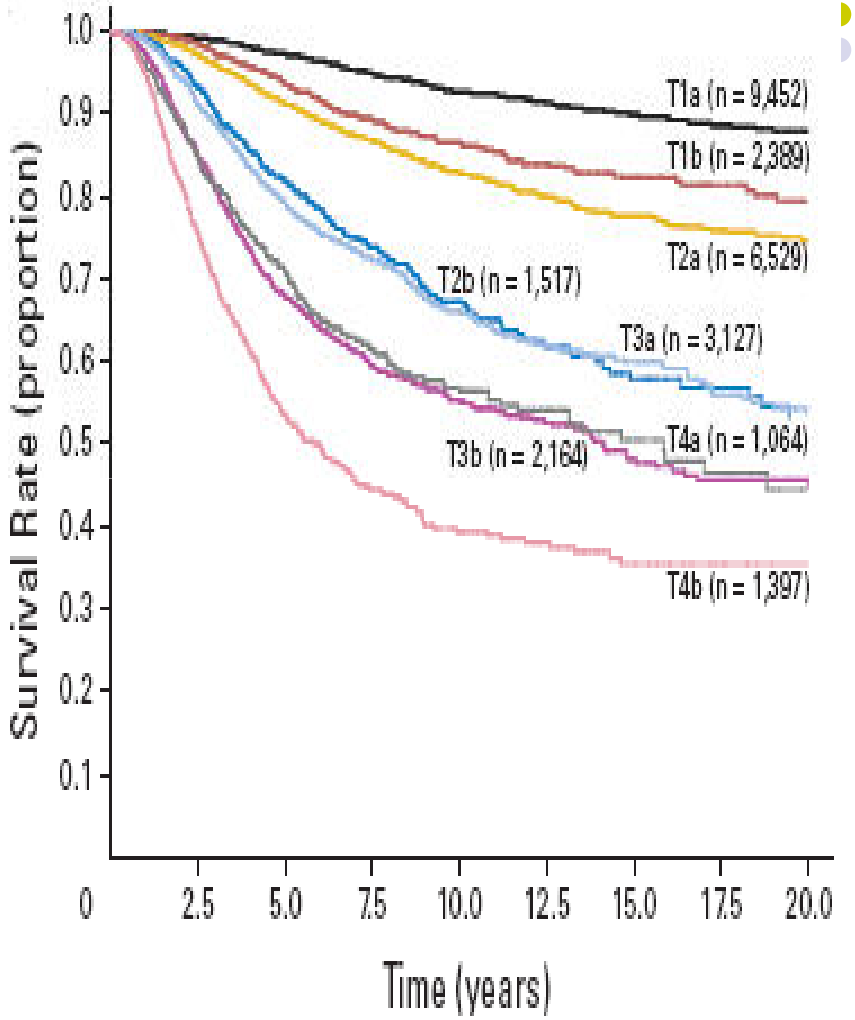


Stage I and II

- In patients with localized melanoma most dominant factors
  - Tumor thickness
  - Mitotic rate (mitosis/mm^2)
  - Ulceration

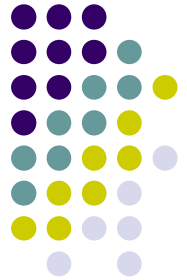
Survival rate comparing the different T categories and stage I and II





Balch CM .J Clin Oncol. 27:6199-6206 2009.

New pronostic parameter The mitotic rate

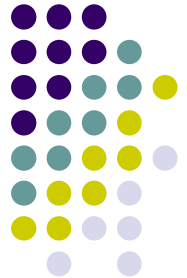


- Mitosis/mm^2 mitotic rate <; > $1/mm^2$

- Mitotic rate replaces level of invasion as a primary criterion for T1b melanoma

Balch CM .J Clin Oncol. 27:6199-6206 2009

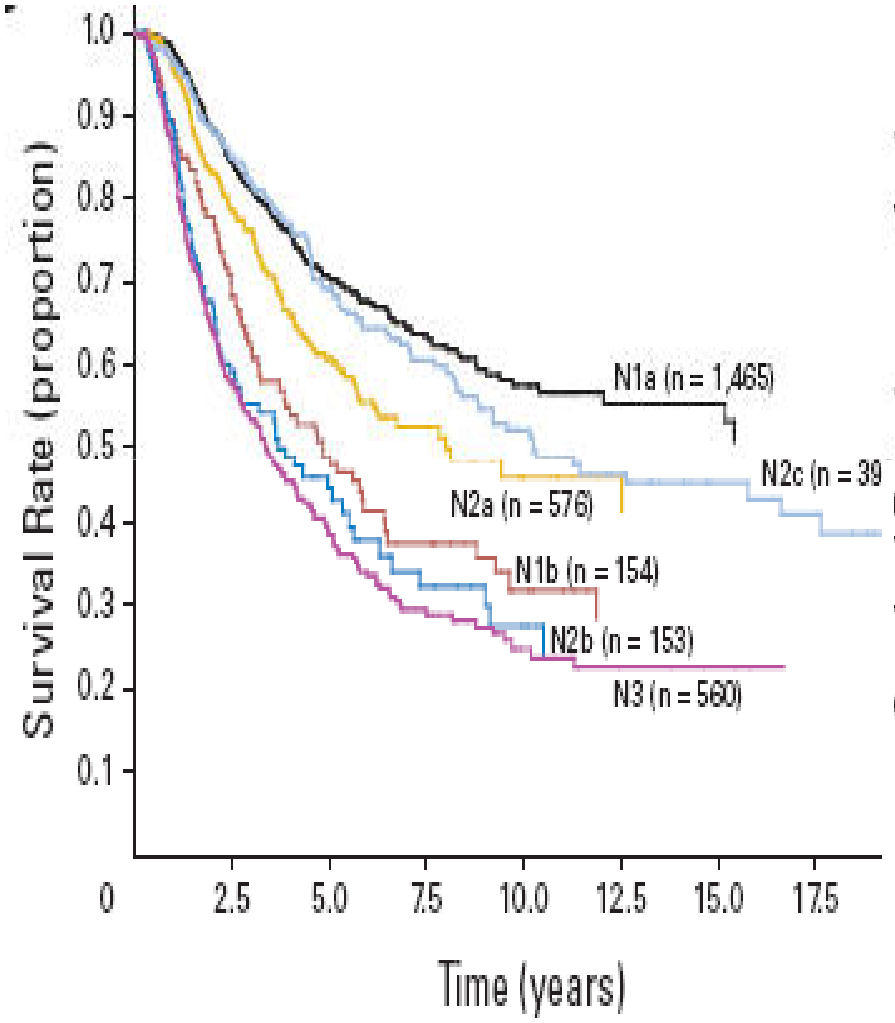
New findings and definitions in the new version of staging Stage III.

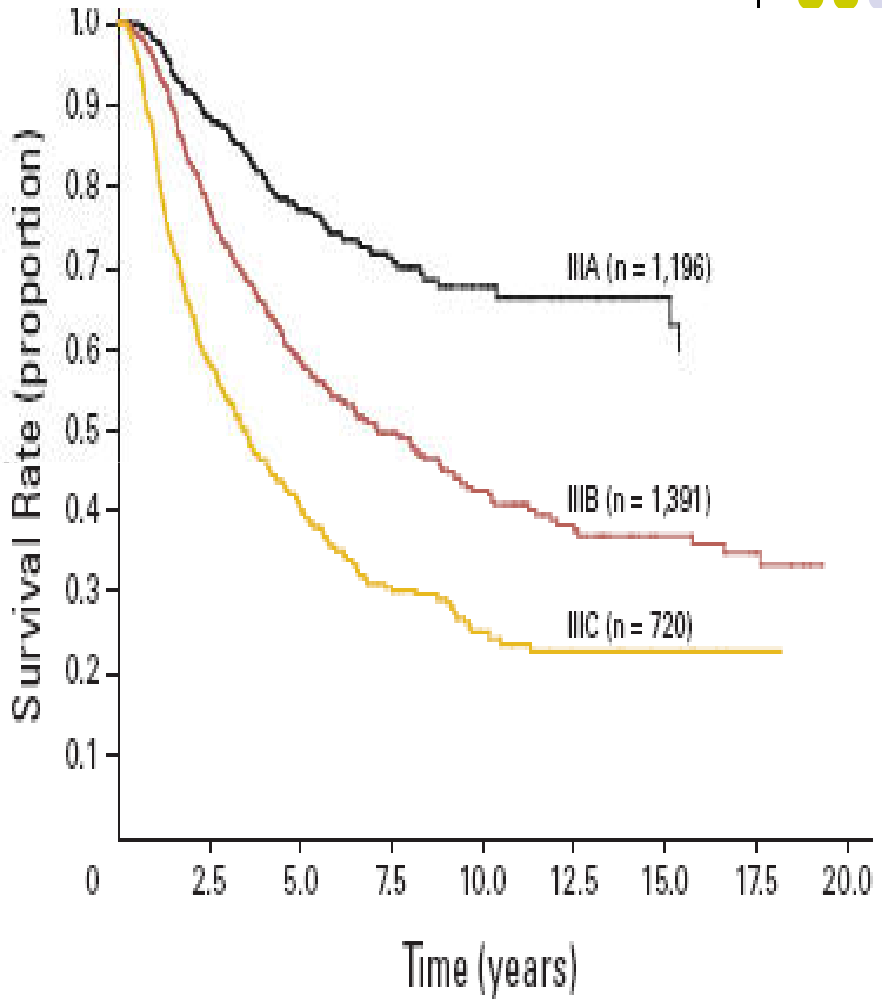


- Determinant by patients with regional metastases
  - Number of metastatic nodes
  - Tumor burden
  - Ulceration of the primary melanoma
- All patients with microscopic nodal met., regardless of tumor burden classified as *Stage III.*
- Micro metastases detected by immunohistochemistry are specifically included (HMB45, Melan-A/MART)

Balch CM .J Clin Oncol. 27:6199-6206 2009

Survival rate comparing the different N categories and stage III

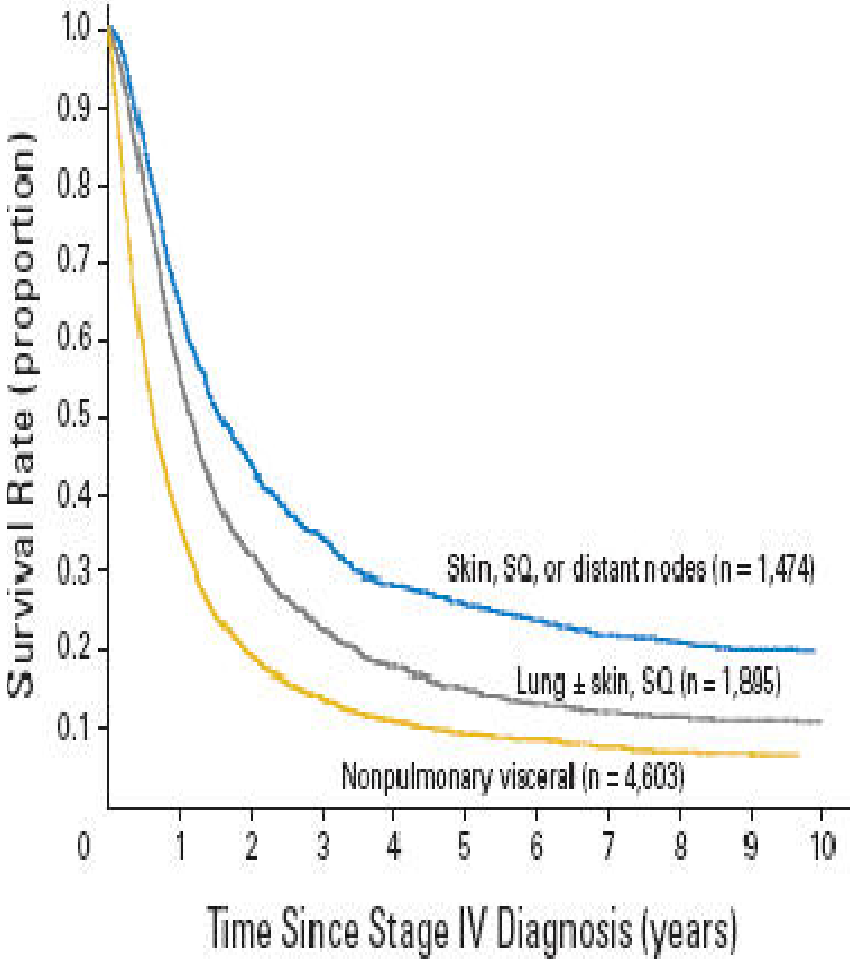




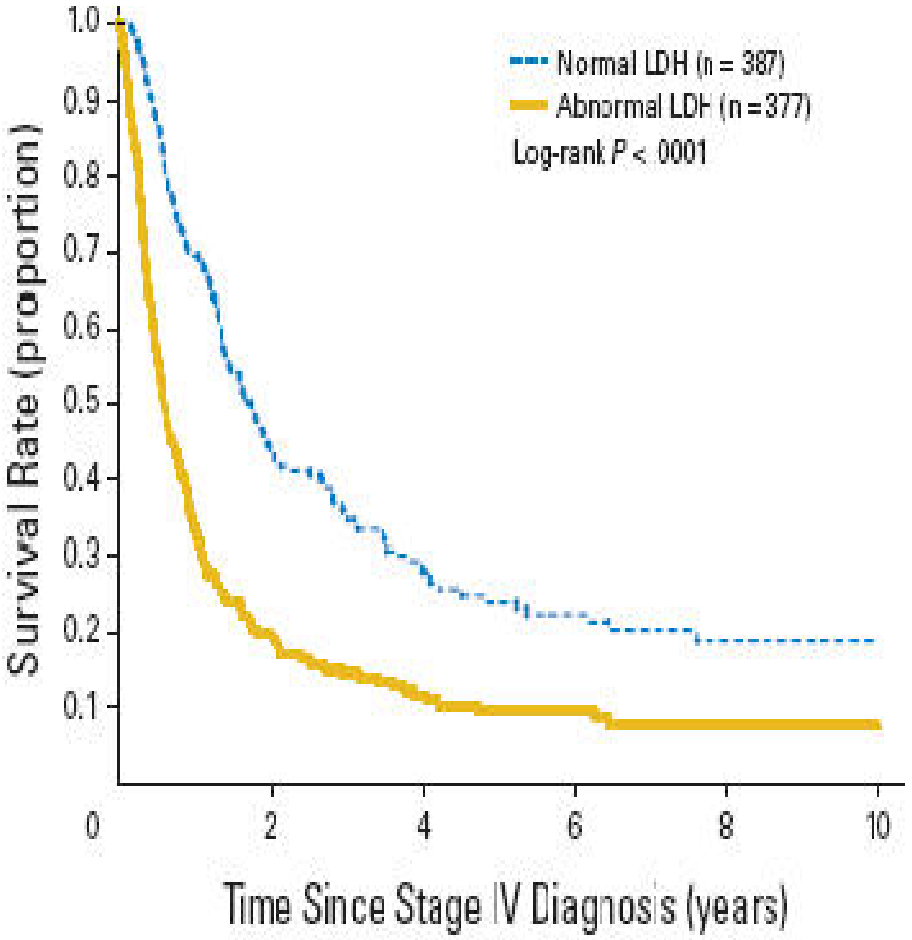
Balch CM .J Clin Oncol. 27:6199-6206 2009.

Survival curves with metastatic melanoma

at distant site

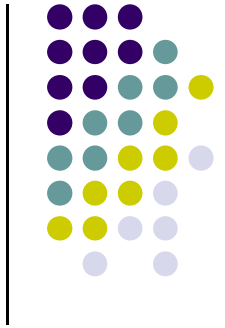


and serum LDH level



Balch CM .J Clin Oncol. 27:6199-6206 2009

Disseminated metastases
Stage IV.



- The determinant is the location of metastases
- Level of se LDH
- se S100
- Circulating tumor cells

NEW 7th TNM classification AJCC 2009.
pT

pT	Tumor thickness	Ulceration
T1	≤ 1,0 mm	a: without ulc. (*Clark II/III)* mitosis<1/mm^2
		b: with ulc. or (*Clark IV/V)* mitosis<1/mm^2
T2	1,01 – 2,0 mm	a: without ulc .
		b: with ulc .
T3	2,01 – 4,0 mm	a: without ulc.
		b: with ulc.
T4	> 4,0 mm	a: without ulc.
		b: with ulc.

Balch CM .J Clin Oncol. 27:6199-6206 2009

TNM classification pN

	Number of metastatic lymph node		Tumor mass lymph nodes
N1	1	lymph node	a: micromet b: macromet.
N2	2-3	lymph node	a: micromet. b: macromet c: in transit/satellita met. without lymph nod
N3	≥ 4	lymph node lymph node conglomerate or in transit/satellita metast. with lymph node metast.	

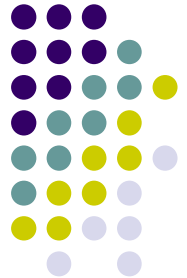
TNM classification pM

	Sites	LDH
Mo	No distant metastasis	not applicable
M1a	Distant skin, subcutaneous nodal metastasis	normal
M1b	Lung metastases	normal
M1c	All other visceral metastases Any distant metastases	normal elevated

Anatomic stage Groupings for cutaneous Melanoma

Clinical staging				Pathologic 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	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
II.A	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	II.B	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
II.C	T4b	N0	M0	II.C	T4b	N0	M0
III.	Any T	N>N0	M0	III.A	T1-4a	N1a, N2a	M0
				III. B	T1-4b	N1a, N2a	M0
					T1-4a	N1b, N2b	M0
					T1-4a	N2c	M0
				III. C	T1-4b	N1b, N2b	M0
					T1-4b	N2c	M0
					AnyT	N3	M0
IV	Any T	An N	M1	IV.	Any T	Any N	M1

The role of histology in the diagnosis of malignant melanoma



- Melanocytic vs. non melanocytic lesion
- Benign vs. malignant pigmented lesion
- In situ vs. invasive tumor
- Characteristics of primary tumor
  - Histological type of melanoma
  - Tumor thickness
  - Mitotic rate
  - Ulceration
  - Lymphocytic infiltrations
  - Vascular or lymphatic invasion
- Specification of the lymph node status

Treatment of malignant melanoma
Primary tumor pT

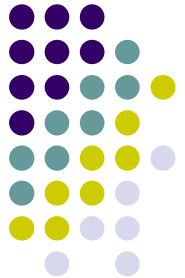
- Plastic surgical excision
  - Electric knife
  - To fascia of muscle
  - Safety margin depends on the tumor thickness
    - In situ melanoma (pT_{is}) 0,5 cm
    - 1-2 mm (pT1-2) 1,0 cm
    - >2 mm (>pT3) 2,0 cm

INCISIONS BIOPSY PROHIBITED

Loco-regional management

- Sentinel lymph node biopsy
  - Indispensable
  - Together with primer tumor surgery
  - or within 2-3 weeks later
  - general anesthesia
- Indications:
  - tumor < 1mm, ulceration, >1 mitosis/mm^2 (lev. IV/V) regression (pT1b)
  - tumor >1 mm (pT2)
- Regional lymph node dissection Stage III.
  - by histological positive sentinel lymph node
  - palpable or detectable lymph node

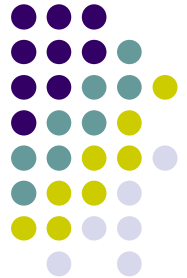
Uncertain diagnosis of MM



- Excision with 5 mm safety margin
- Histological examination
- Further surgical treatment
  - Depends on the tumor thickness

INCISIONS BIOPSY PROHIBITED

Adjuvant interferon α treatment

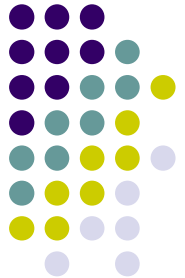


Interferon alpha 2a, 2b

- Effects
  - Antiproliferative
  - Immunomodulatory
  - Inhibition of angiogenesis
  - Increase MHC1 antigen expression
  - CD4+ T cells infiltration into melanoma
- Response rate 15% (5% CR)
- Median response duration 6-9 month

(Agarwala SS. 1996)

Adjuvant treatment of melanoma



- Indication
  - II. A, B,C, (pT2b, pT3, pT4)
  - III.A,B,C after tumor resection
- Mode the administration
  - Low dose: 3 x 3 MU/ week sc. for 18 months prolong the PFS (Grob. Phehamberger)
  - Intermediate dose 3x9-10MU/ week sc. 12 months
  - High dose

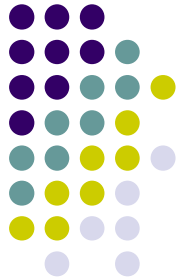
    20MU/m^2 iv. 5x/week 1 Month (induction)

    10 MU/m^2 sc. 3x/ week 11 Months (maintain)

    Significantly prolong the OS

    (Kirkwood)

Chemotherapy



- Indication: stage IV

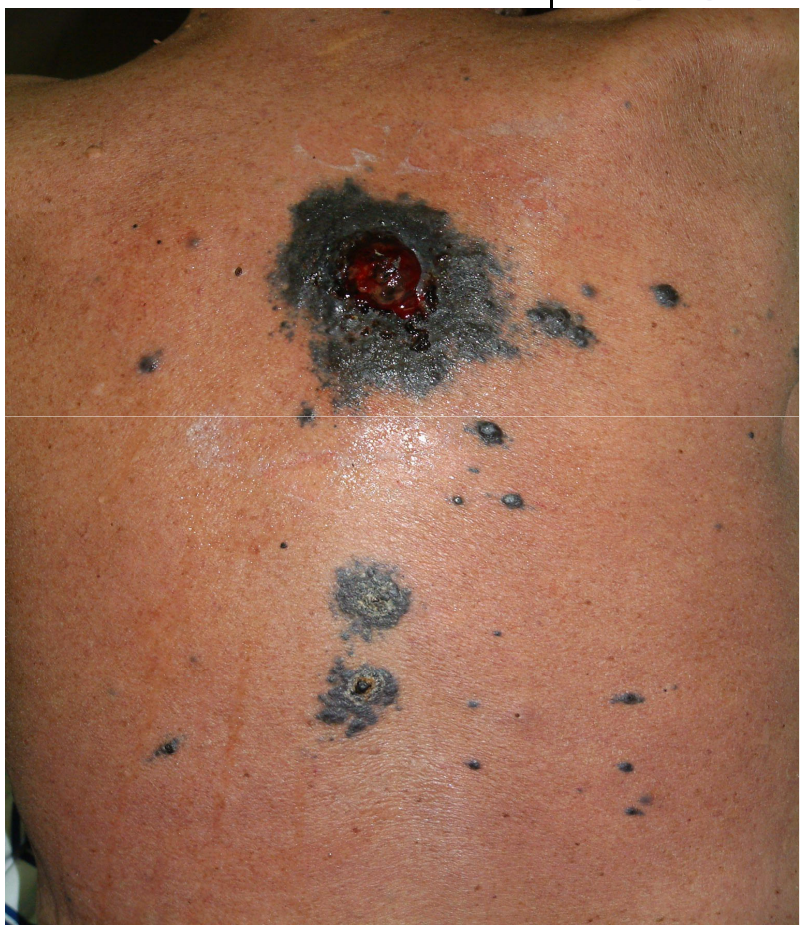
  5 years survival 6%

  main survival 7,5 months

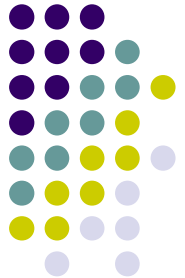
- Monochemotherapy
- Polychemotherapy

Monochemotherapy

- Distant metastases
- *Dacarbasin (DTIC)*
- Remission rate 10-25% (CR 5%)
- Median respons duration 5-6 month
  - < 2% survive 2 years (Comis R. 1976)



New drug :Temozolomid



- imidazotetrazine
- *equivalent* with DTIC for survival, response rate and toxicity,
- *superior* for progression free survival and quality of life
- Efficacy in CNS metastases
  - Better blood-brain barrier penetration than DTIC

(Middleton MR. 2000)

New drog :Fotemustin

- The most active nitrosourea in metastatic melanoma
- Cross the blood-brain barrier
- Response rate 20-25%
- CR 5-8%
- The first significant efficacy in brain metastases

(Khayat D 1994)

- Not universally available

Polychemotherapy

Many side effects, no better clinical efficacy as DTIC

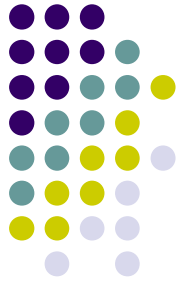
(Huncharek M. 2001 meta -analysis)

Bio-chemotherapy

don’t prolong OS

Falkson CI. 1998.

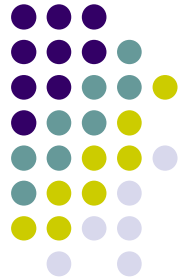
Immunotherapy IL2



- High dose treatment in stage IV melanoma
- Response rate 15-20%
- CR 4-6%
- 1998. FDA approved in unrespectable cases
- Severe toxicity
- Usage effective in selected patient groups
- Low - dose treatment is ineffective

(Atkins MB, 1997, 1999,)

Radiations treatment Stage III, IV

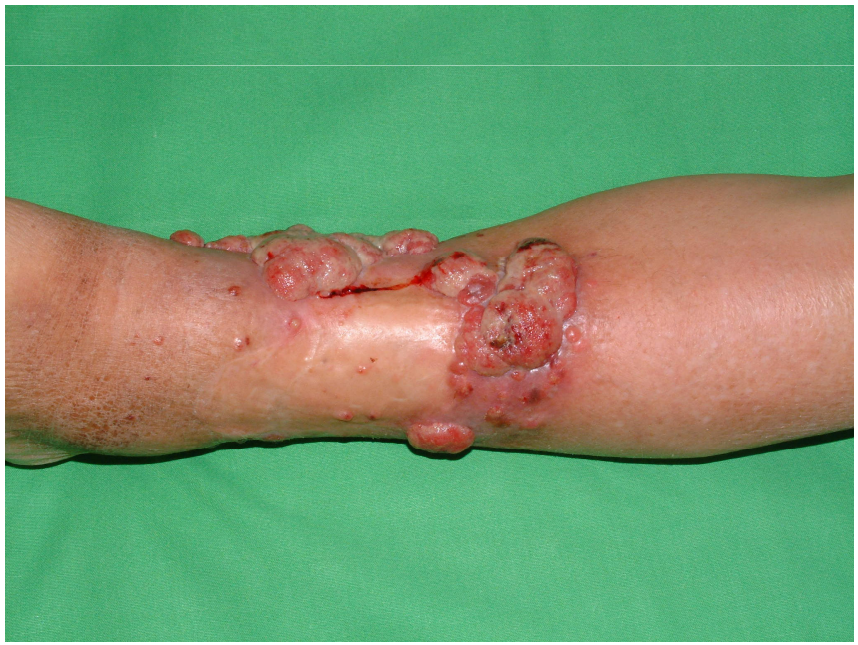


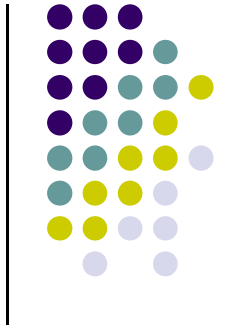
- Palliative treatment
  - Vascular invasion
  - Multiple lymph node metastasis with capsule involves
  - Cerebral metastases
  - Symptomatic treatment

- Treatment modalities
  - Whole brain irradiation
  - Stereo-taxis irradiation
  - After loading treatment
  - Electron radiation

Special treatment modalities

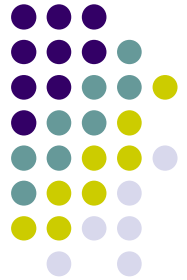
- hyperthermic Isolated limb perfusion,
  - In case of isolated limb metastases
- Chemo-embolisation of liver





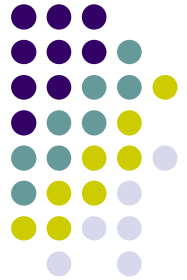
New treatment modalities and future

29.April 2010.



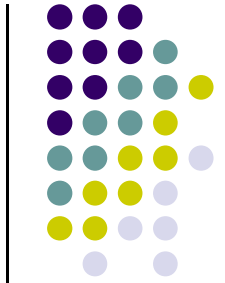
- Melanoma intrinsic drug resistant tumor
- Melanocytes acquire further mutation
- Multiple signal transduction pathways are aberrant(PIEK,MAP,nFkB
- Enhanced cell survival
- The targeted treatment , use small molecule inhibitors reducing the treatment resistance

New treatment modalities and future



- Anti CTLA-4 antobodies
- BRAF inhibitors
- Pro-apoptotic agents
- Anti-angiogenic treatment
- mTOR inhibitors
- Proteosoma inhibitor
- MEK inhibitors

Cytotoxic T- Lymphocyte Associated protein – 4 (CTLA-4)

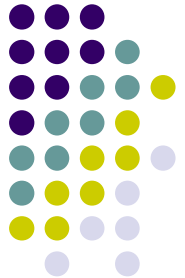


- CTLA 4 ag critical immuno-modulatory molecule
- Expressed on activated and other regulatory T- cells
- Dow-regulation of T cell activation

Anti CTLA-4

- Enhance T cell dependent immunity

Anti CTLA-4

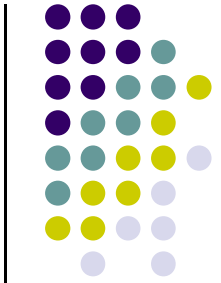


Monoclonal antibodies anti-CTLA-4

- ipilimumab
- tremelimumab

- Phase II/III trials
  - the median overall survival increased to 1 year of 25-35% for patients stage 3-4 (O'Day SJ. 2008)
  - The treatment related toxicity is significant with 43% grade III/IV, autoimmune –mediated manifestations, which appeared dose dependent (Phan GQ. 2003)

BRAF inhibitors
Sorafenib

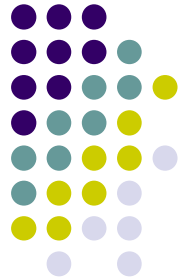


- Small molecule
- Multi tyrosin kinase inhibitor
- Inhibit cell proliferation by targeting MAPK pathway at level of RAF kinase
- Phase I/II trial well tolerated as single agent

(Eisen T. 2006Strumber D. 2007

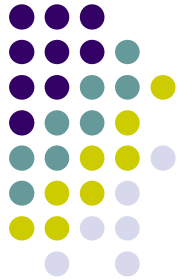
- Combination with DTIC or temozolomid encouraging in PFS (Eisen 2007, McDermott DF. 2008)

Anti-sens BCl2 Oblimerzen



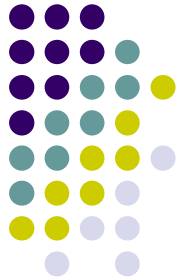
- Anti Bcl-2 antisense
- Phase III trial combination with DTIC
  - Response rate increasing
  - Improve PFS
  - Improve median OS- but not significant
  - Efficacy is higher in patients with normal level of LDH (Bedician AY. 2006)

Anti-angiogenic treatment



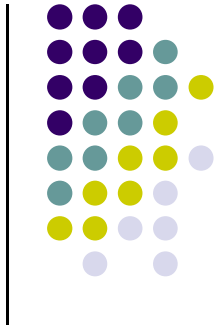
- Semaxanib
  - selective inhibitor of VEGFR-2
  - and Kit receptor kinase
  - In phase II trial is well tolerated (Peterson AC. 2003)
- Bevacisumab
  - Monoclonal antibody against VEGF-A
  - Block its binding to receptor
  - Phase II trial minimal toxicity and prolonged disease stabilization (Vaker KA: 2007)

mTOR inhibitors



- Inhibition of signal transduction pathways (PI3K/PTEN/AKT)
- CCL-779 hasn't sufficient antitumor activity as a single agent
- Phase I trial in combination with low dose INFα well tolerated, an potentially active
  - Direct antitumor
  - Antiangiogenic effect (Dutcher JP. 2003)

Proteosoma inhibitor Bortezomib

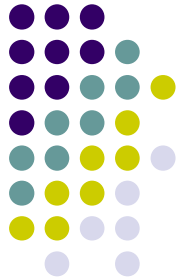


- Dipeptidyl boronic acid analog
- Potent and reversible proteosoma inhibitor
- Phase II trial shows infectivity and toxicity as singlee agent(Markovicz SN. 2005)

MEK inhibitors

- PD0325901 (Phase I.)
- AZD6244 (Phase II.)
- BRAF mutant melanomas may be sensitive to this agent
- Side effects retinal vein thrombosis (Dummer R. 2008)

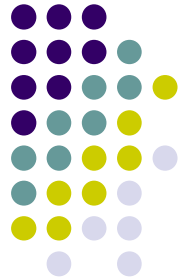
Thalidomide (lenalidomide)



- Immuno-modulatory
- Anti-angiogenic
- Anti-proliferative
- Pro-apoptotic properties
- Phase II trials shows
  - Low efficacy of TMZ, thalidomid and WBRT in treatment of CNS metastatic melanoma
  - DTIC+ thalidomid activity is insufficient

Take home message

- The only effective treatment the early detection and the appropriate surgical therapy
- The adjuvant treatment more effective in cases of micrometastases
- The high doseintrferon α regime prolong the OS
- The mono-chemotherapy indicated only in stage IV
- The new treatment modalities, the targeted therapy can ameliorate the prognosis of metastatic cases



"Malignant melanoma writes its message in the skin with its own ink and it is there for all of us to see. Some see but do not comprehend”

Dr Neville Davis,
Queensland surgeon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