Advances in Melanoma

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Conflicts

- None

Melanoma

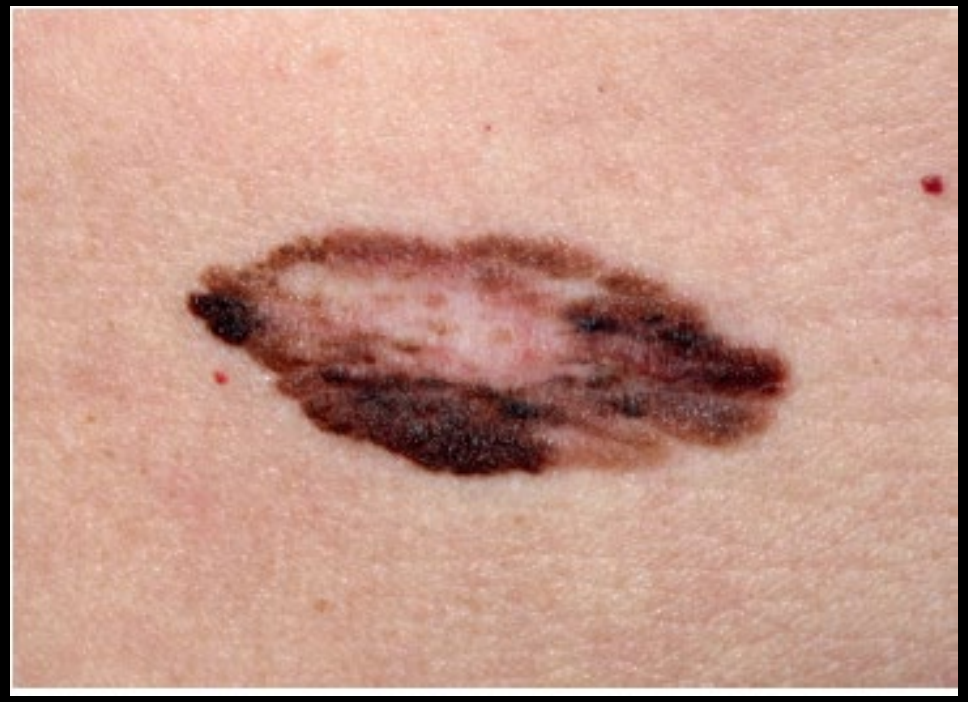
Epidemiology and Clinical Presentation

Introduction

- Melanoma represents a malignant tumor that arises from melanocytes
- Due to its metastatic potential, it leads to >75% of skin cancer deaths
- The incidence rates of melanoma have increased over the past four decades by three- to five-fold, whereas mortality rates began to stabilize in the early 1990s
- Early detection of *in situ* and early invasive cutaneous melanomas by dermoscopy has led to an improvement in diagnostic accuracy
- Early-stage melanomas are often curable by surgical excision
- For metastatic melanoma, immunotherapies (e.g. ipilimumab) and targeted therapies (e.g. vemurafenib) can be tried

Epidemiology

- Melanoma is derived from melanocytes, most commonly cutaneous
  - Can be mucosal e.g. oral, conjunctival, vaginal, uveal tract of eye and leptomeninges
- Majority are brown/black in color
  - others are pink to skin-colored or amelanotic



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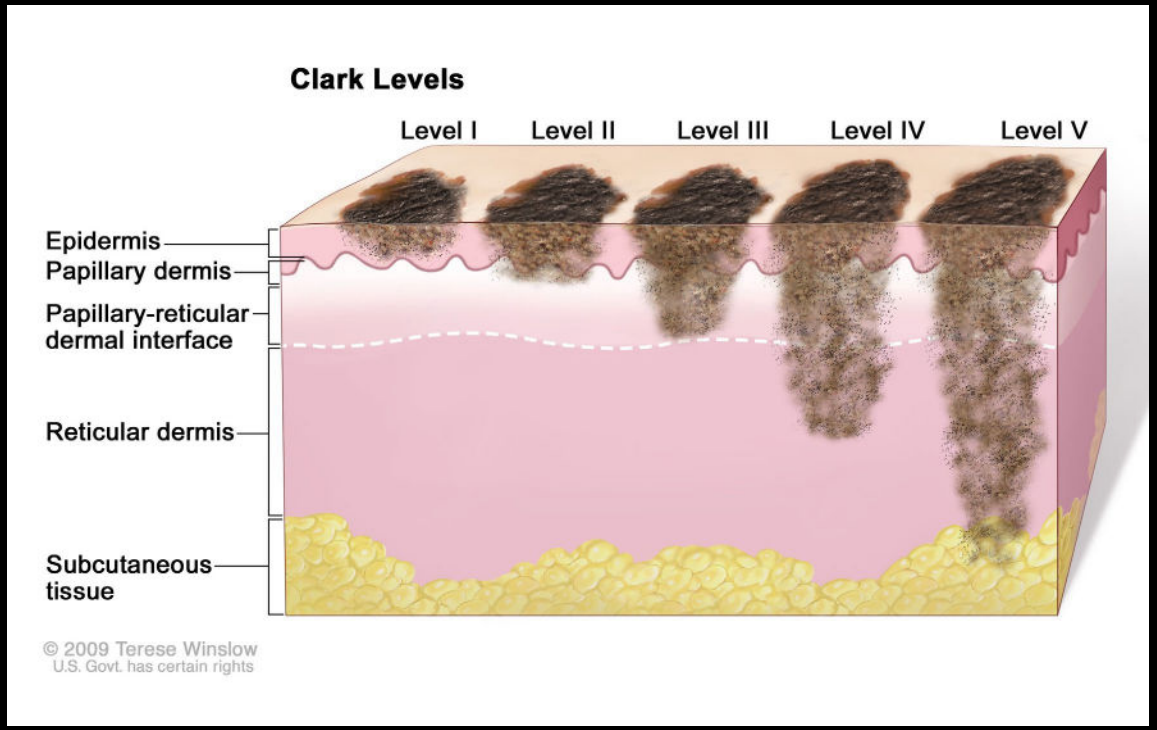
Epidemiology

- Very low prevalence in skin of color
  - Most commonly acral subtype
- Melanoma represents the most rapidly increasing cancer in white populations
- Lower rates in Mediterranean countries and higher rates in Scandinavian countries
- Highest incidence rate in Australia/New Zealand

Epidemiology

- Vertical tumor thickness (Breslow Depth) is the most important local prognostic factor in primary cutaneous melanoma
- Diagnosis of thinner tumors yields stable/decreased mortality rates, despite increasing incidence rates
- Percentage of thicker melanomas increases with age



National Cancer Institute, cancer.gov

Risk Factors For Cutaneous Melanoma: Genetics

- Germline genetic mutations/polymorphisms may predispose individuals to developing melanoma
  - Both rare high penetrance genes and very common pigmentation genes for fair-skinned individuals predispose individuals to develop melanoma
- CDKN2A is a major high-penetrance susceptibility gene locus associated with familial melanoma
  - 2% cutaneous melanoma specifically attributed to this germline mutation
  - CDKN2A linked to increased pancreatic cancer risk
- MC1R mutations associated with lighter skin phenotype
- SNPs in TYR, TRYP1, SCL45A2 associated with increased melanoma risk

Risk Factors For Cutaneous Melanoma Phenotypic Risk Factors Reflecting Gene/Environment Interactions

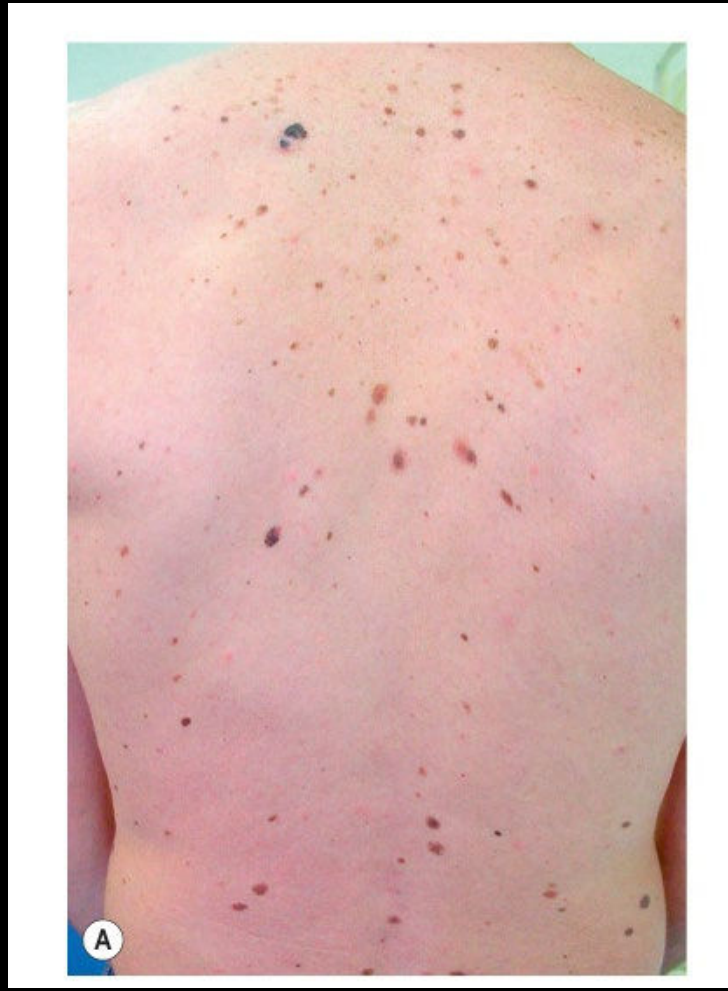
- Strongest independent risk factors for cutaneous melanoma development reflect both genetic susceptibility and environmental exposure
- Development of melanocytic nevi, atypical melanocytic nevi, and solar lentigines are independent risk factors for melanoma
  - indicate UV exposure/DNA damage
  - can serve as formal precursors of melanoma

Risk Factors For Cutaneous Melanoma: Number of nevi

- Light skinned populations have higher melanocytic nevus counts than darker-skinned populations
  - Light skinned populations have increased risk of melanoma correlating with increased number of melanocytic nevi
- Superficial spreading and nodular melanoma development has strongest association with melanocytic nevi counts
- Lentigo maligna melanoma development has strongest association with skin type and hair color

Risk Factors For Cutaneous Melanoma: Atypical Melanocytic Nevi

- Independent risk factor for sporadic melanoma
- Maximum reported relative risk for melanoma is as high as 32 fold when 10 or more atypical melanocytic nevi are found
- Five or more atypical melanocytic nevi associated with clearly higher relative risk of melanoma development



Andrews' Diseases of the Skin by James et al.

Risk Factors For Cutaneous Melanoma: Environmental Risk Factors, UV radiation

- 80% melanomas develop in intermittently sun-exposed regions,
  - both intermittent sun exposure and sunburn history are identified as risk factors
- However, melanoma development is not all about UV radiation
  - The anatomic distribution of melanoma does not closely match sites of greatest cumulative sun exposure
  - Melanoma is most often in middle-aged adults and not elderly with most cumulative sun exposure

Risk Factors For Cutaneous Melanoma Environmental Risk Factors, UV radiation

- Sunburns in childhood and adolescence are significantly associated with melanoma development
  - duration of sun exposure stronger risk factor than the occurrence of sunburns
- Both UVB and UVA radiation are associated with the development of cutaneous melanoma, but UVB exposure serves as strongest risk factor
- However, total number of melanocytic nevi is identified as the most important risk factor for cutaneous melanoma

Risk Factors For Cutaneous Melanoma: Environmental Risk Factors, Sun Protection

- In 2009, WHO categorized tanning beds as a human carcinogen
- Tanning bed exposure before age 35 is statistically significantly associated with melanoma development
  - Suberythema doses of UVR can cause DNA mutations
  - There is a significant misunderstanding that avoidance of sunburns and use of sunscreens are sufficient to prevent skin cancer
- Encourage sun avoidance between 10 am and 4 pm, hats, non-transparent clothing (UPF)

Types of Primary Melanomas

- From most common to least common:
  - Superficial spreading melanoma
  - Nodular melanoma
  - Lentigo maligna melanoma
  - Acral lentiginous melanoma
  - Unclassifiable melanoma

DIFFERENT TYPES OF PRIMARY CUTANEOUS MELANOMA			
Clinico-histopathologic subtype	**Abbreviation**	**Percentage**	**Median age**
Superficial spreading melanoma	SSM	57.4%	51 years
Nodular melanoma	NM	21.4%	56 years
Lentigo maligna melanoma	LMM	8.8%	68 years
Acral lentiginous melanoma	ALM	4%	63 years
Unclassifiable melanoma	UCM	3.5%	54 years
Others		5%	54 years

Table 113.3 Different types of primary cutaneous melanoma. Data from the German Central Malignant Melanoma Registry (N = 30 015).

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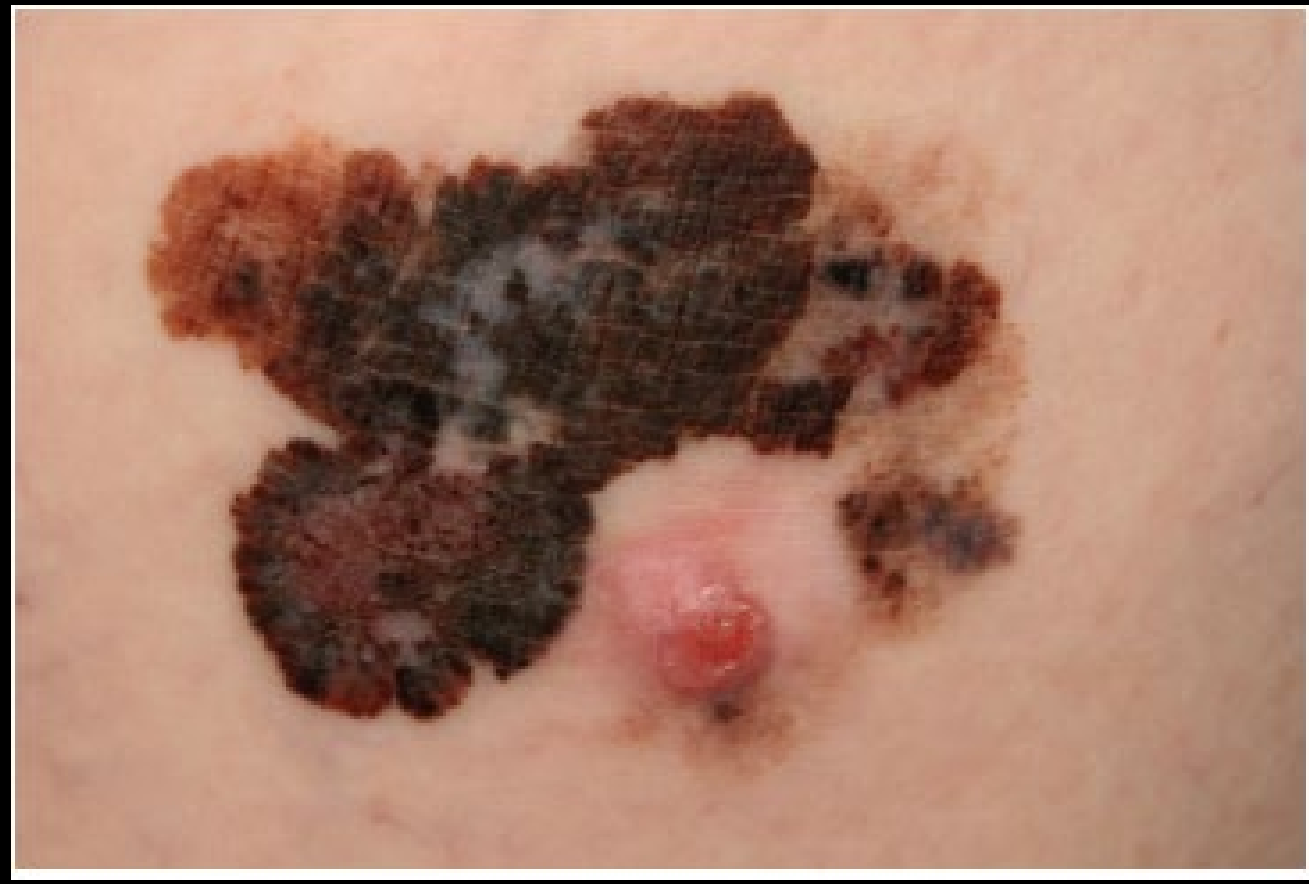
Types of Primary Melanomas: Superficial Spreading Melanoma

- Most common type in fair-skinned individuals
- Comprises 60-70% of all melanomas at any site
- Most commonly on the trunk of men, legs of women
- 2/3 present with regression, including networkless areas on dermoscopy
- Initially, characterized by horizontal growth
- ½ occur in pre-existing nevus



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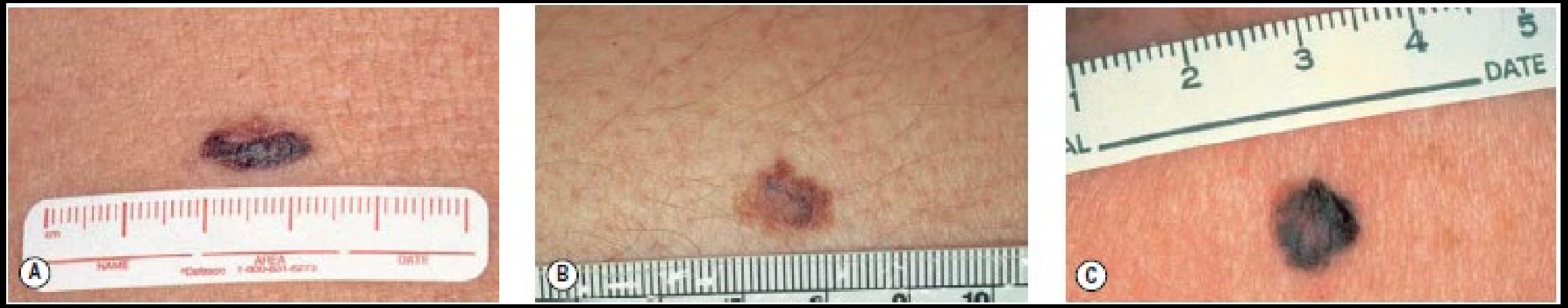
Superficial Spreading Melanoma: Clinical images



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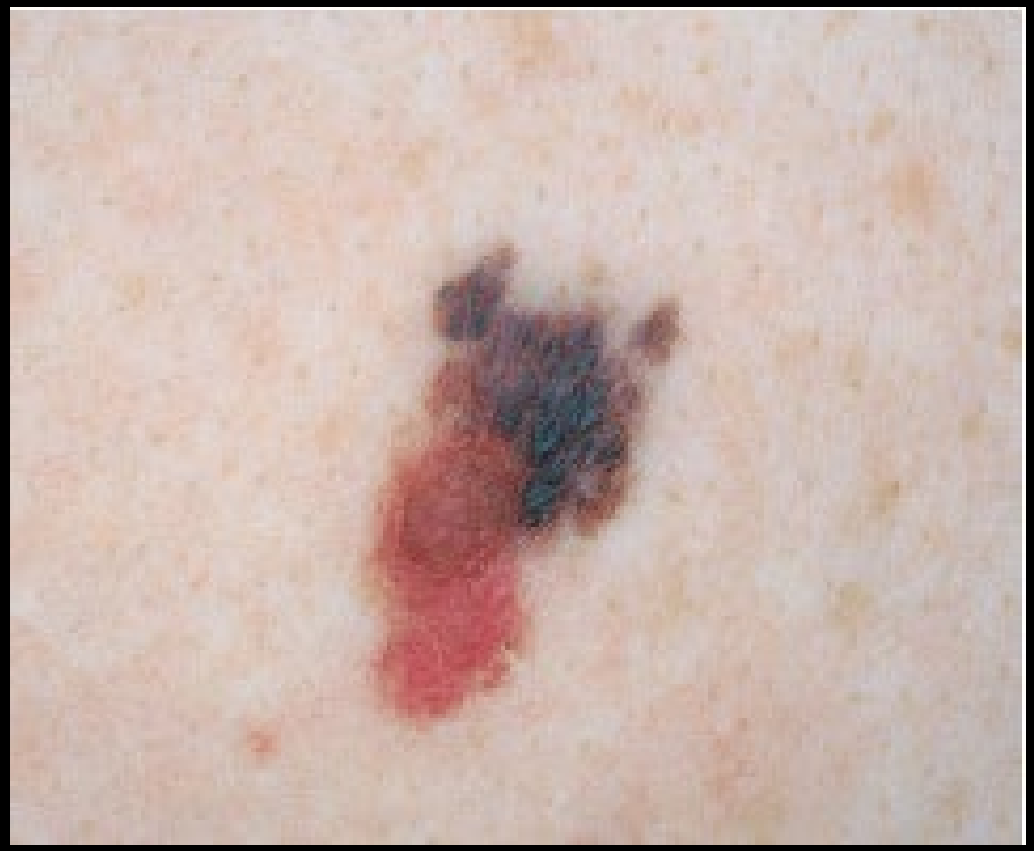
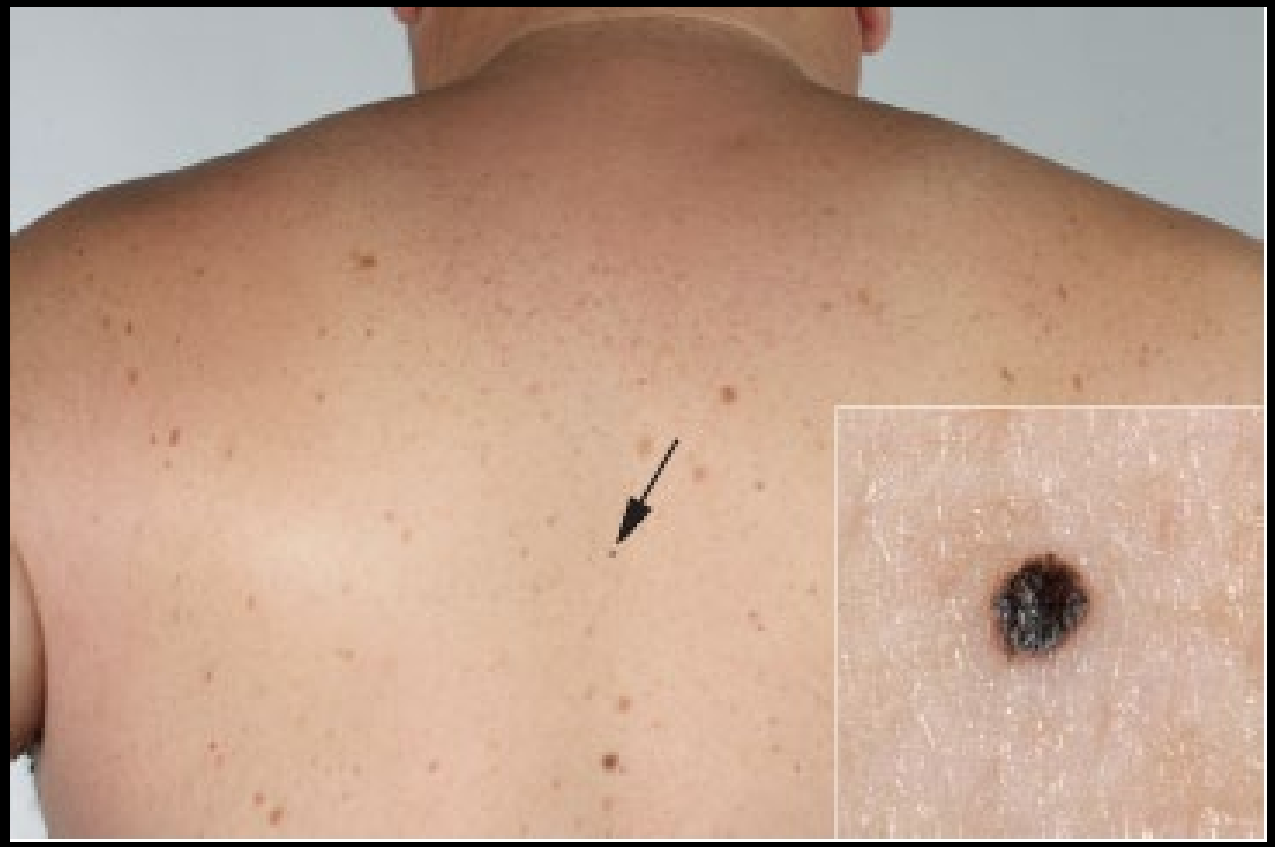
Superficial Spreading Melanoma: Clinical Images





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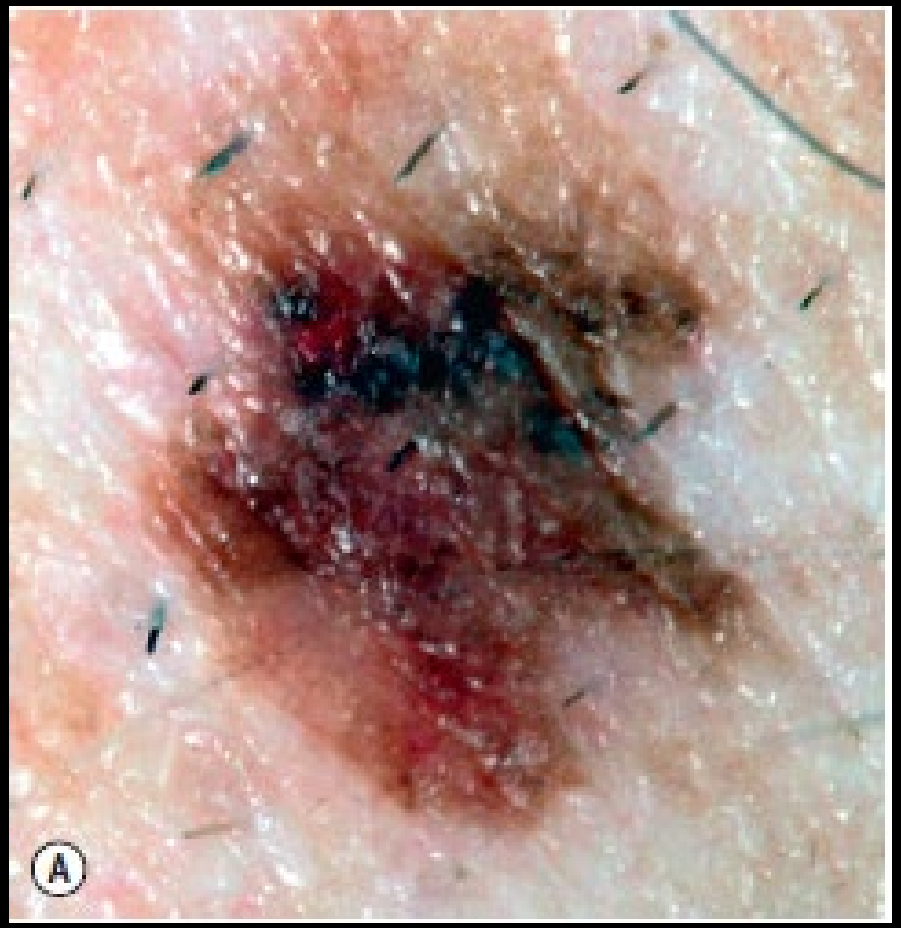
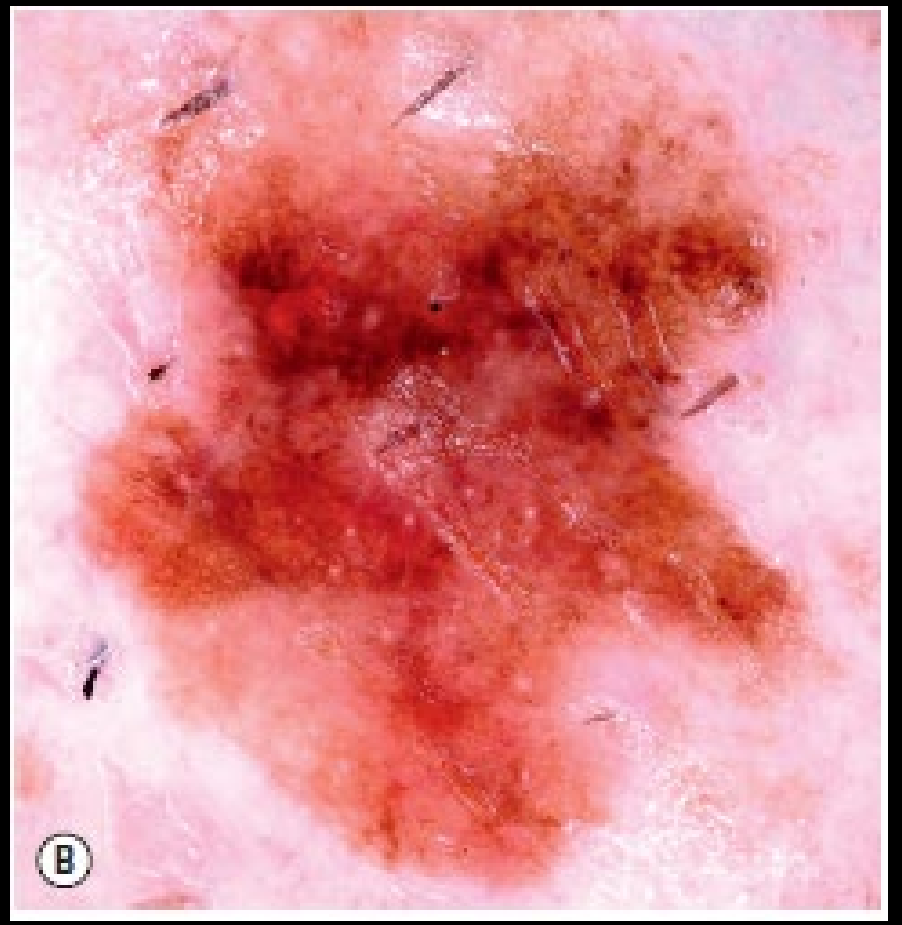
Superficial Spreading Melanoma: Clinical Images



“Little Red Riding hood sign”: erythema around melanoma



Dermoscopy of SSM

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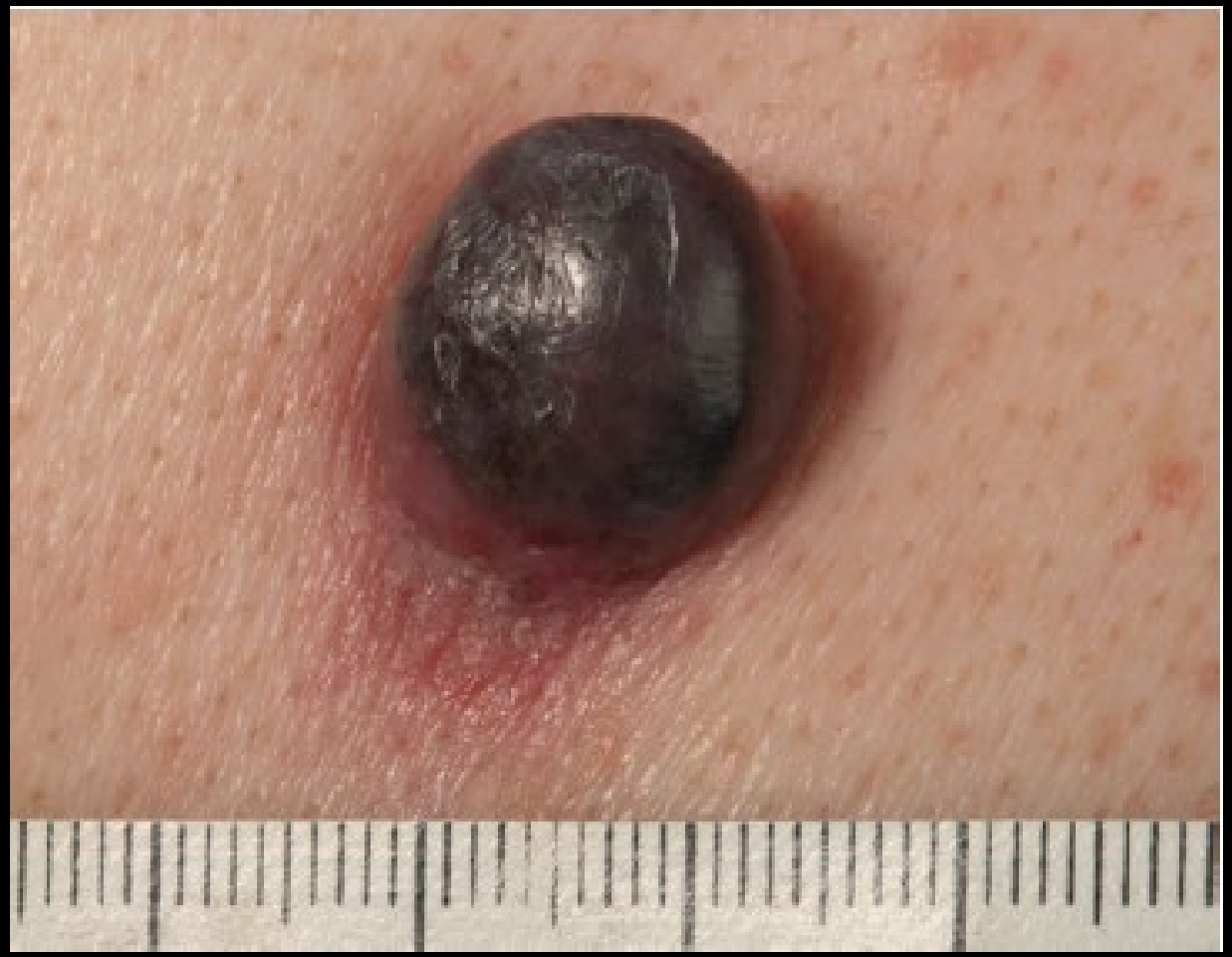
Types of Primary Melanomas
Nodular Melanoma

- 2nd most common type in fair-skinned individuals
- Most common in 6th decade of life
- 15-30% all melanomas, occurs on any body site
- Most frequently on neck, head, and trunk
- More prevalent in men
- Can be blue to black
- may ulcerate or bleed
- Rapid vertical growth phase tumor
- Thicker more advanced stage at diagnosis, poorer prognosis



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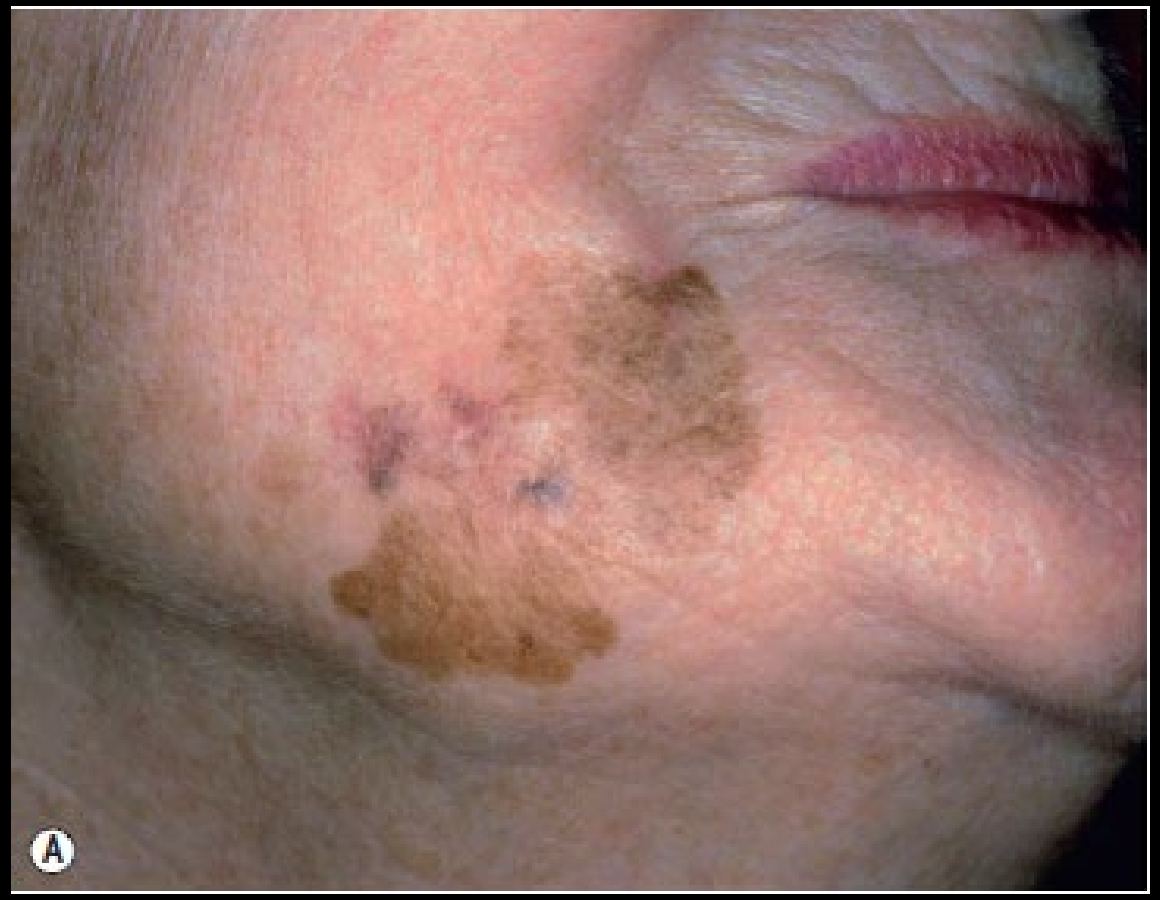
Types of Primary Melanomas
Lentigo Maligna Melanoma (LMM)

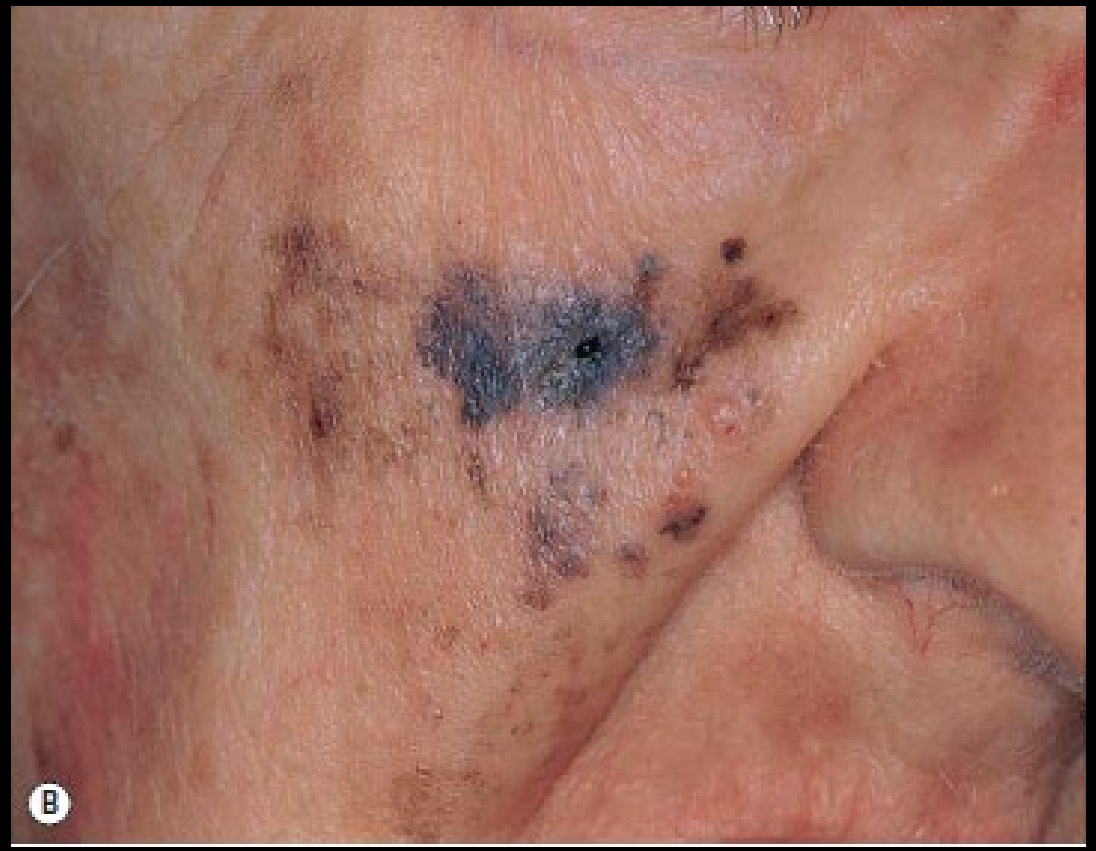
- Represents 10% of cutaneous melanomas
- Most frequently diagnosed in 7th decade of life
- Usually located on chronically sun-damaged skin, most commonly on face
  - Usually nose or cheek
- Slowly growing, asymmetric brown to black macule with color variation and irregular indented border
- Invasive LMM arises in precursor lesion termed lentigo maligna (LM)
  - LM represents an in situ melanoma in sun-damaged skin)
  - 5% of LM progresses to invasive LMM
- Dermoscopy: Hyperpigmented follicular openings on facial skin, circle in circle, irregular pigmented dots around follicles, rhomboidal structures

Types of Primary Melanomas
Lentigo Maligna Melanoma

Lentigo maligna



Lentigo maligna melanoma



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Lentigo Maligna Melanoma: Clinical Images

Lentigo maligna melanoma on nose

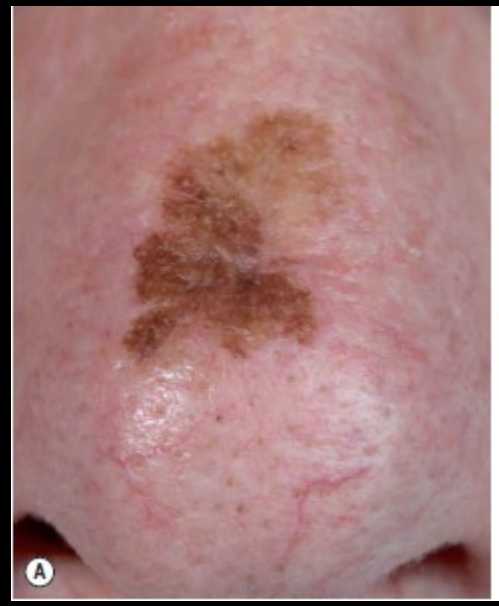
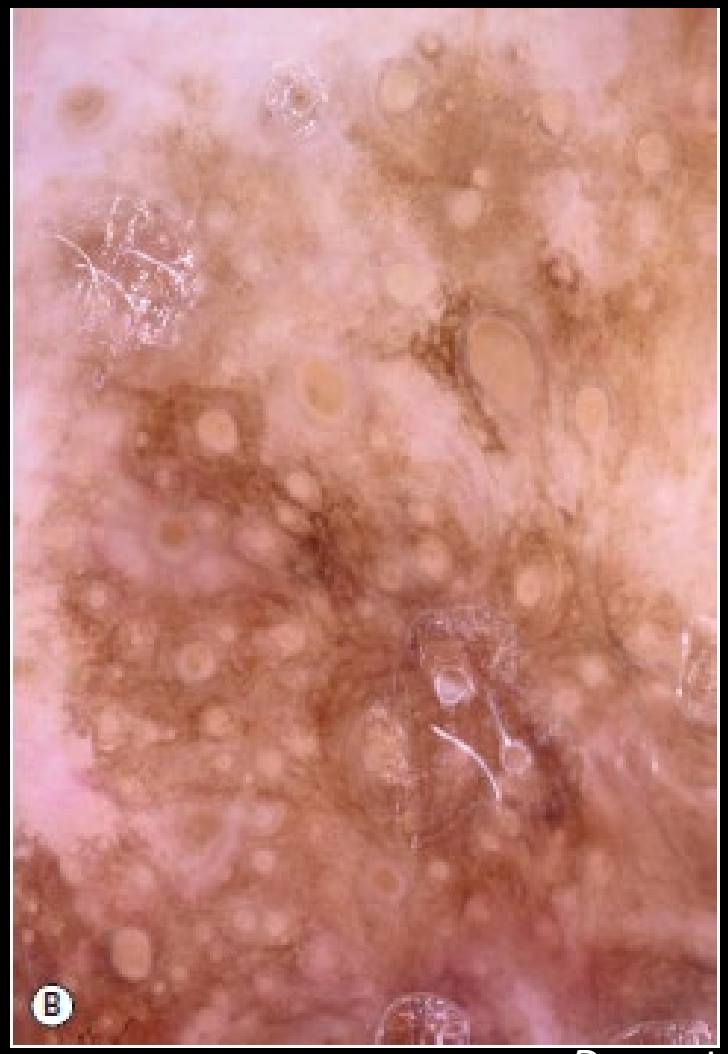


Fig. 113.16 Lentigo maligna melanoma (LMM). A A pigmented lesion on the dorsal nose, with irregular borders, light to dark brown pigmentation and marked asymmetry. **B** Dermoscopy demonstrating annular structures corresponding to follicular openings surrounded by melanoma cells ("circle in a circle").

Dermoscopy image



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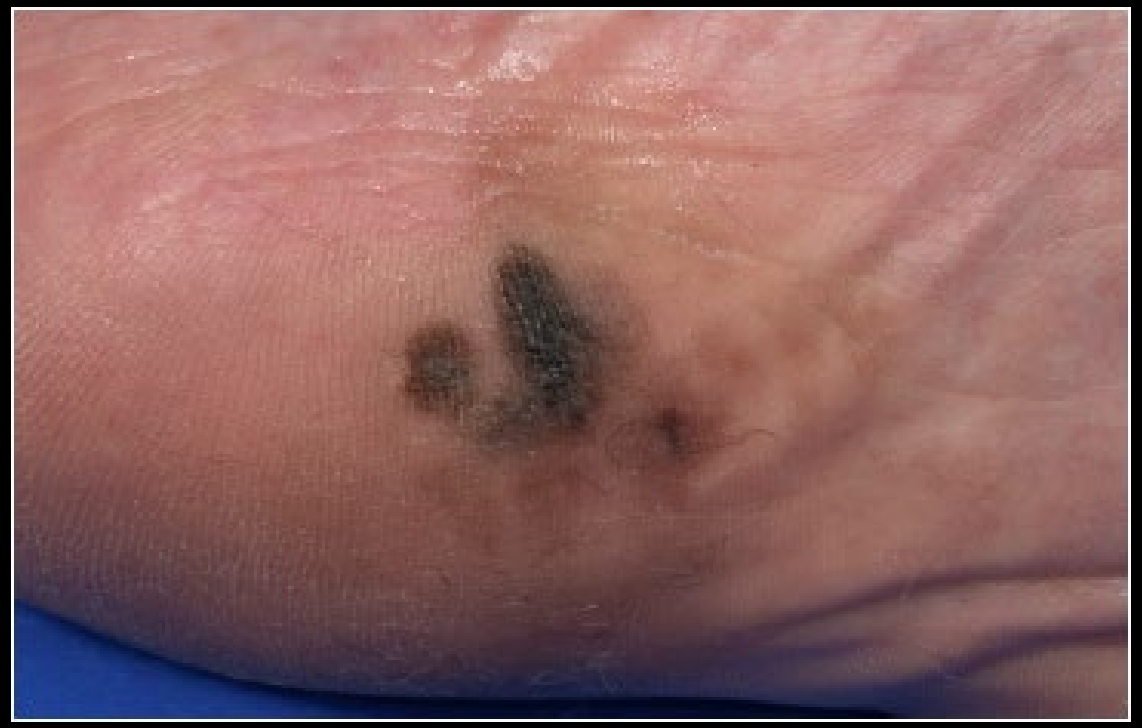
Types of Primary Melanomas
Acral Lentiginous Melanoma (ALM)

- Relatively uncommon
- Most frequently in 7th decade of life
- Located on Palms and soles and around nails
- Represents 5% of all melanomas
- Incidence is similar across all racial/ethnic groups
  - Most common melanoma subtype in darker-skin phenotypes, representing 70% of melanomas in blacks and 45% of melanomas in Asians



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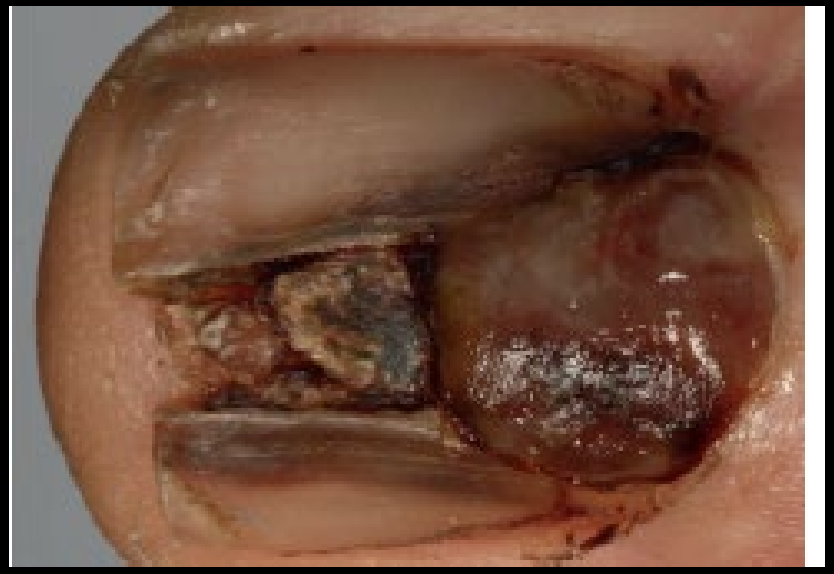
Types of Primary Melanomas
Acral Lentiginous Melanoma

- Presents as asymmetric brown to black macule with color variation and irregular borders
- Disproportionate amount diagnosed at advanced stage
- Physicians should have elevated threshold to biopsy due to increased morbidity with surgery at acral sites



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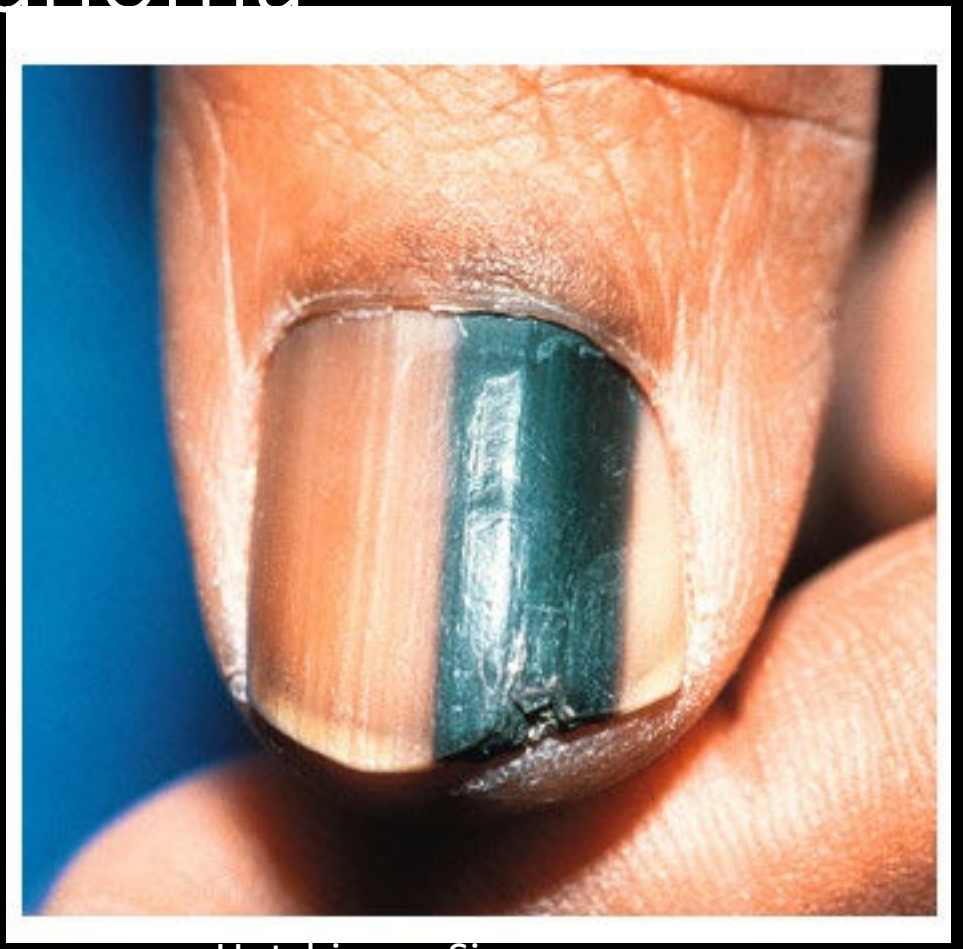
Types of Primary Melanomas
Acral Lentiginous Melanoma

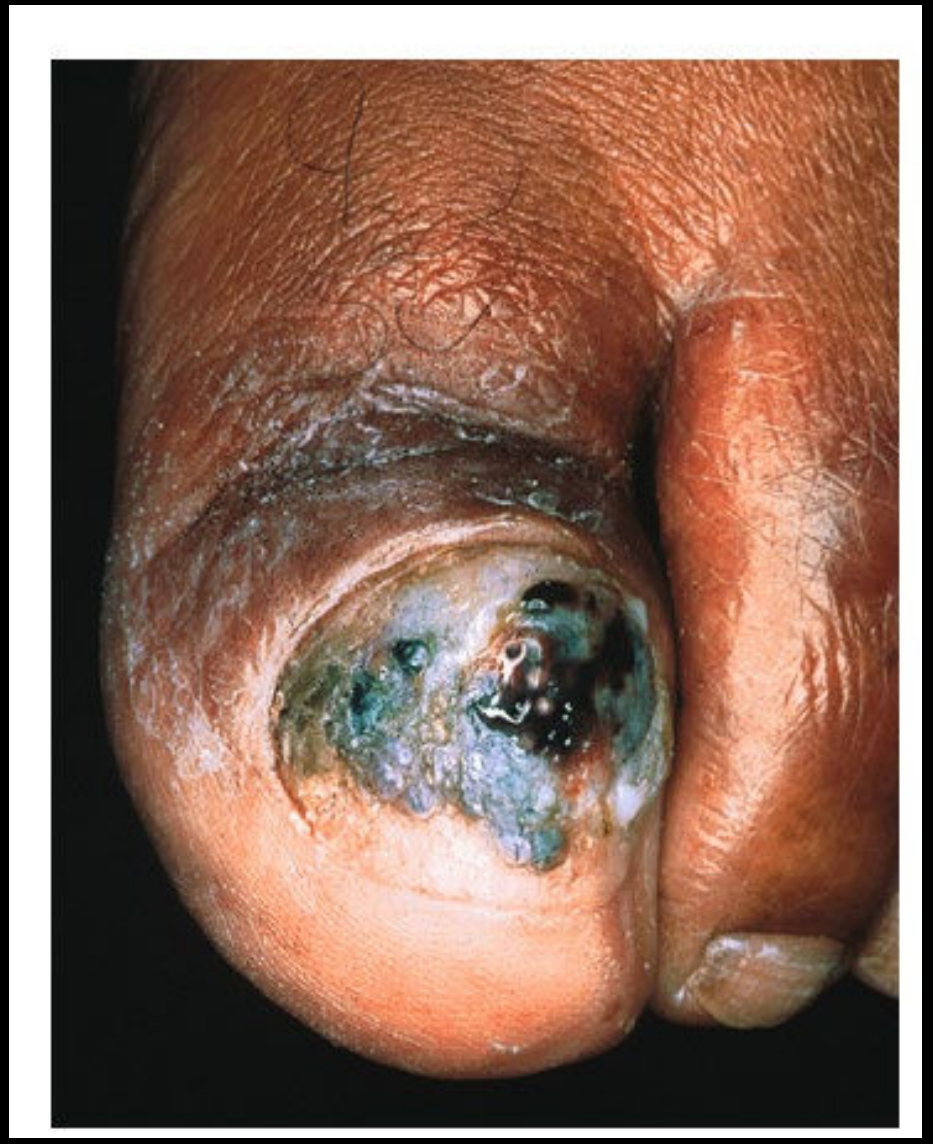
- **Hutchinson sign:** pigment beyond the lateral or proximal nail fold/on hyponychium
- Longitudinal melanonychia should be biopsied if darkly pigmented, irregular, or >3 mm width
- ALM, displays KIT activating mutations, making the tumor sensitive to KIT-inhibiting drugs e.g. imatinib



Hutchinson Sign

Andrews' Diseases of the Skin by James et al.

Acral melanoma: clinical images



Ulcerated and nodular component

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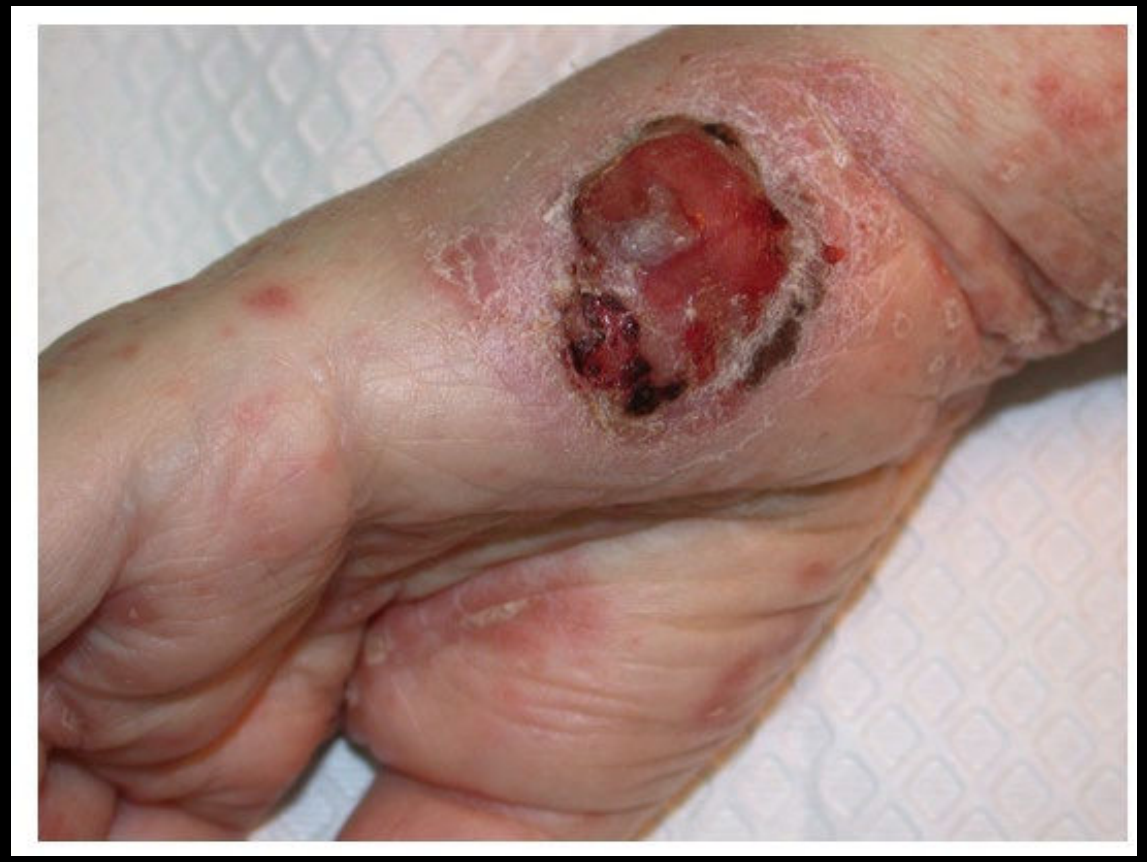
Other Melanoma Variants
Amelanotic Melanomas

- Vast majority of melanomas are pigmented
- All four histologic subtypes of melanoma can have amelanotic variants that largely defy clinical diagnosis
- Often biopsied due to suspicion of BCC
- ALMs amelanotic may be mistaken for warts or SCC
- Do not differ in prognosis or therapy



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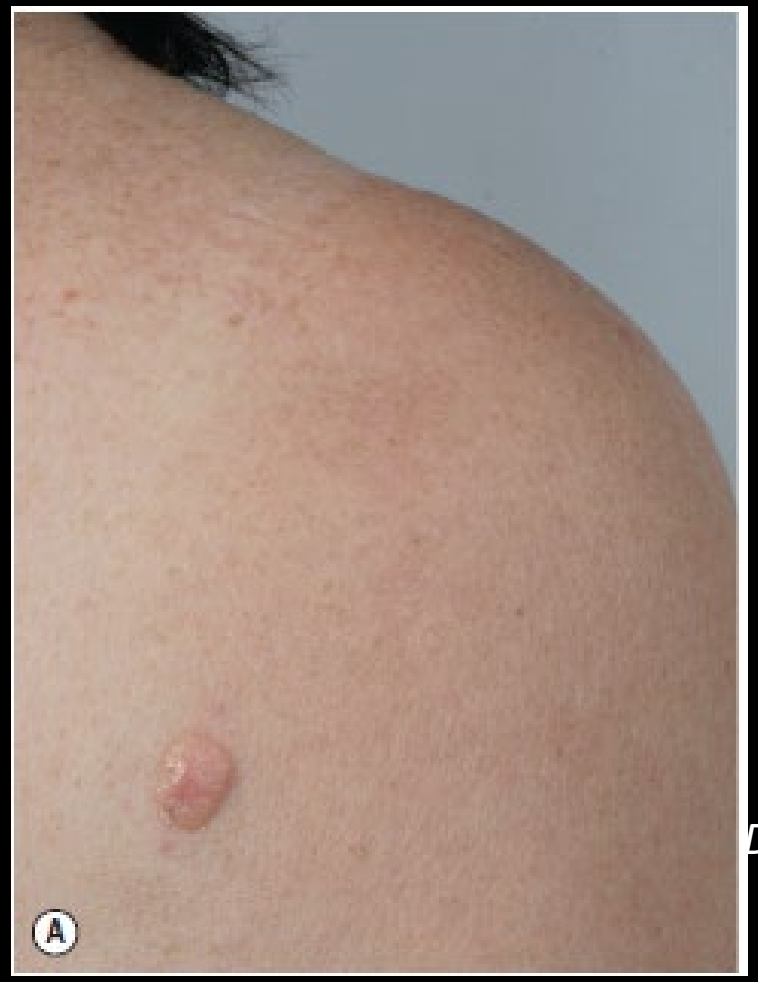
Other Melanoma Variants
Amelanotic Melanomas



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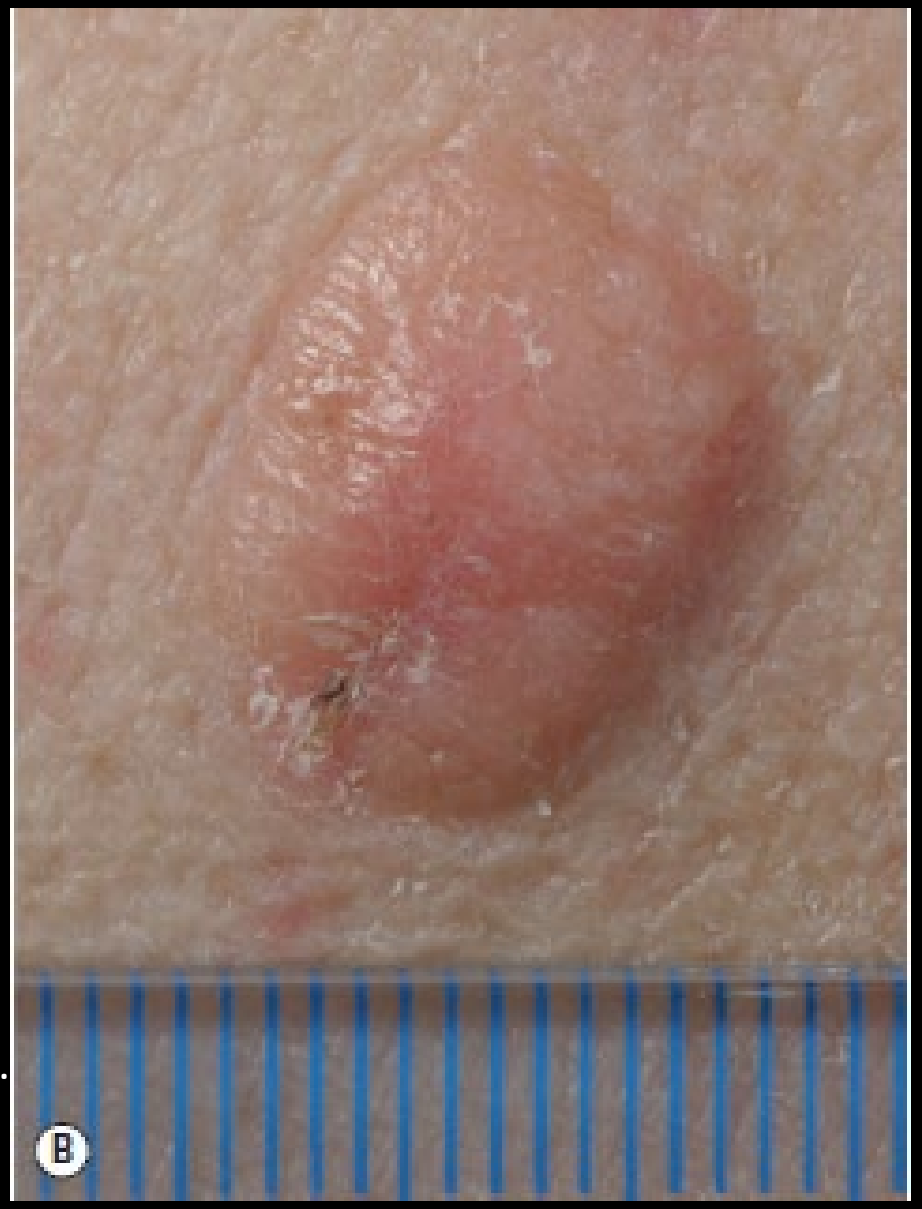


Melanoma and Pregnancy

- Hormones/growth factors stimulate melanocytes
- Yields increased pigmentation
- >10% women have darkening of melanocytic nevi in first 3 months
- However, no demonstration of development of melanoma or worsening in pregnancy
- Transplacental metastases are very rare
- Surgical excision and SLN are performed based on stage
- Ultrasound/MRI are okay but CT scans should be avoided
- Women with diagnosed high risk melanoma should wait 2 years before becoming pregnant again
  - 2/3 of recurrence occur during this window

Childhood Melanoma

- Very rare
- 2% of melanomas are present in population younger than 20 years of age
- 0.3% of melanomas are in those younger than 14 years
- Melanomas with Spitz features are more common in this age range
- Survival/prognosis is similar to adults and stage dependent

Staging of Melanoma

Traditionally, staging and clinicopathology factors answer two key treatment questions following diagnosis of cutaneous melanoma

Diagnosis of localized cutaneous melanoma

What's the risk of recurrence (follow up, imaging and referral decisions)?

Traditionally, tumor thickness, ulceration, and SLN status are used to make this decision

What's the risk for a positive SLN?

Traditionally, tumor thickness and ulceration are used to make this decision.

Assumed Lower Risk

Guideline-based treatment plans include:

- Low frequency clinical follow-up, primarily with dermatology
- No advanced imaging

Assumed Higher Risk

Guideline-based treatment plans include:

- High frequency clinical follow-up, including oncology
- Initiation of advanced imaging
- Consideration of adjuvant therapy
- Consideration of clinical trial enrollment

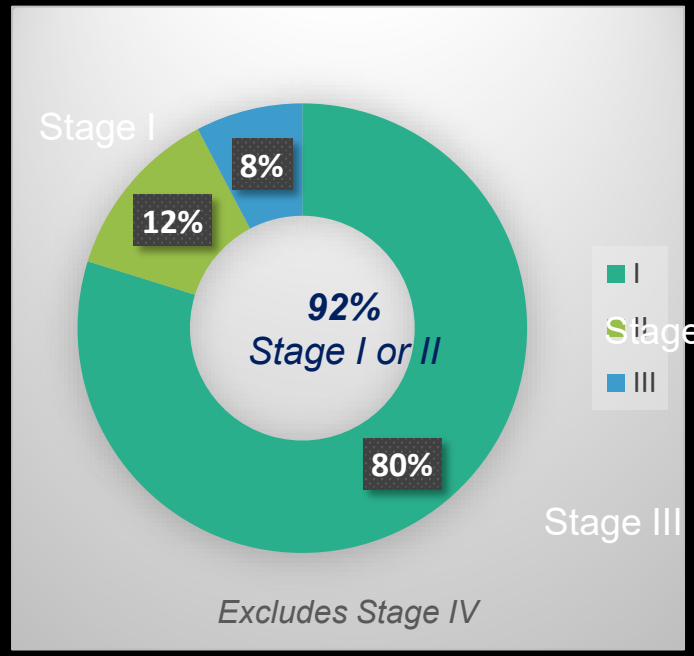
NCCN guidelines recognize that a patient's individual risk of recurrence should drive management decisions and that a patient's individual risk of SLN positivity drives SLN biopsy recommendations

SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy. Source: NCCN Guidelines for Cutaneous Melanoma v2.2022

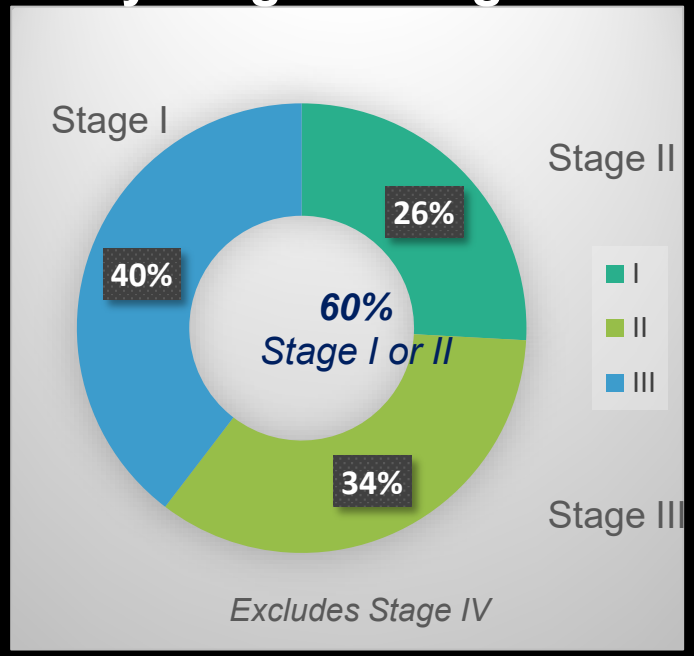
This approach misses patients with aggressive tumor biology

AJCC stage, based mostly on histopathology, is inadequate for predicting clinical outcome

Stage at Diagnosis



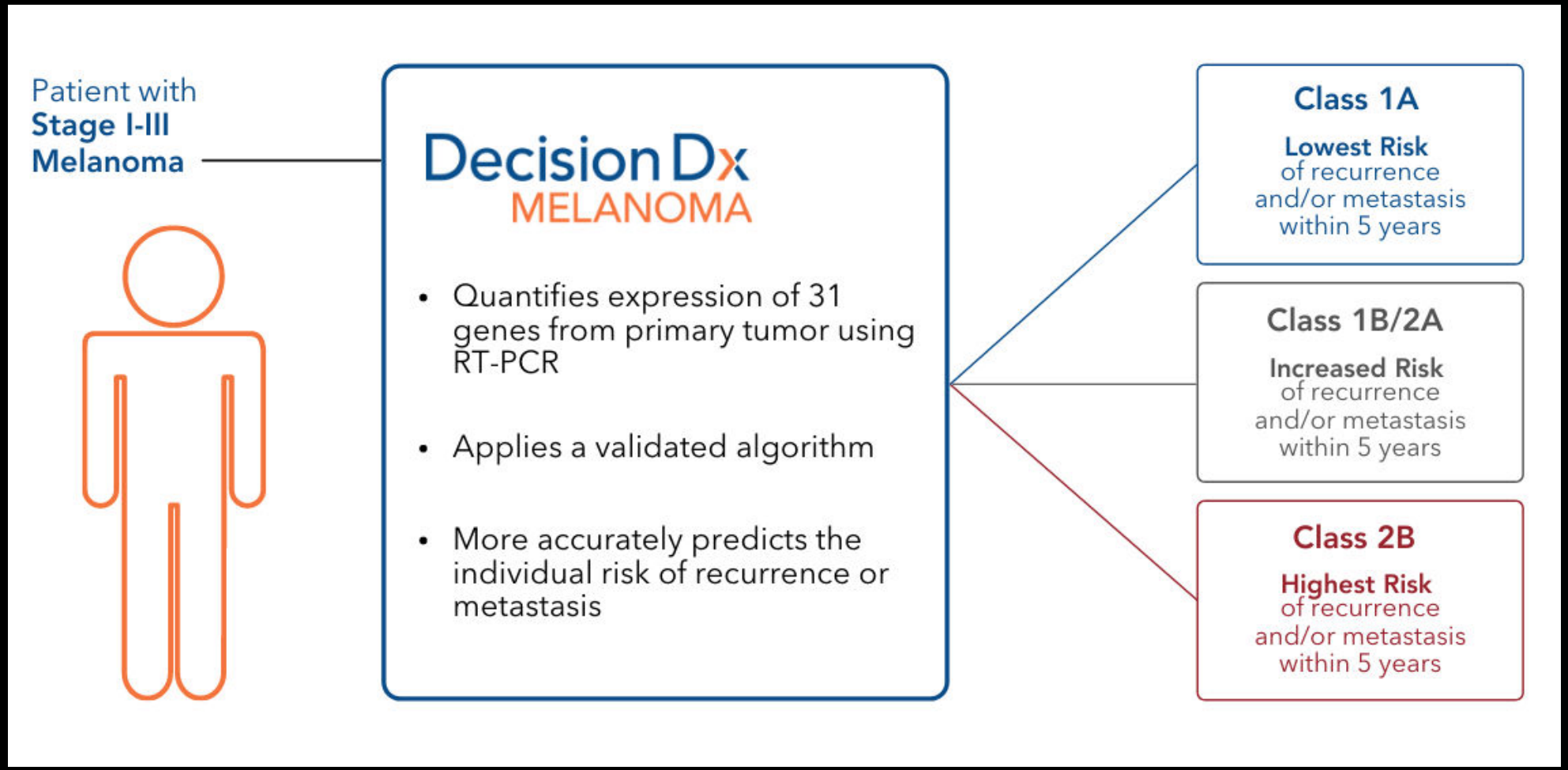
Melanoma Deaths by Stage at Diagnosis



- Many high-risk tumors are being **misidentified** as low-risk at time of diagnosis
- **Prognostic accuracy** may be improved to inform patient management decisions
- Patients **twice as likely to survive** if they had asymptomatic detected recurrence than symptomatic recurrence

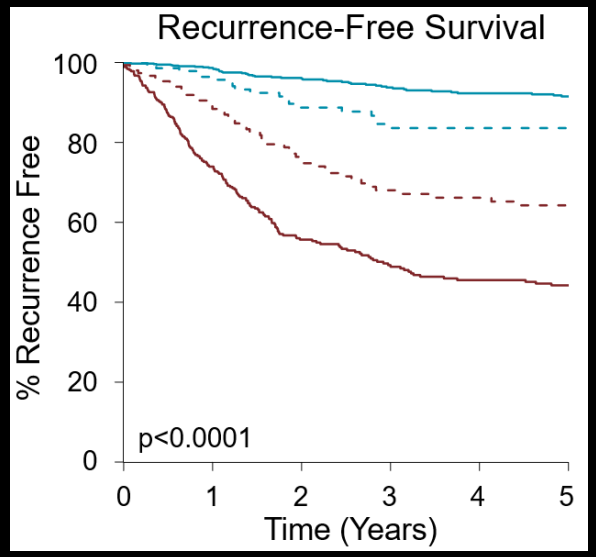
1. AJCCv7 *J Clin Oncol* 2009. 2. SEER data release 2017. 3. Whiteman D et al. *J Invest Derm* 2015. 4. Shaikh W et al. *J Natl Cancer Inst* 2016.

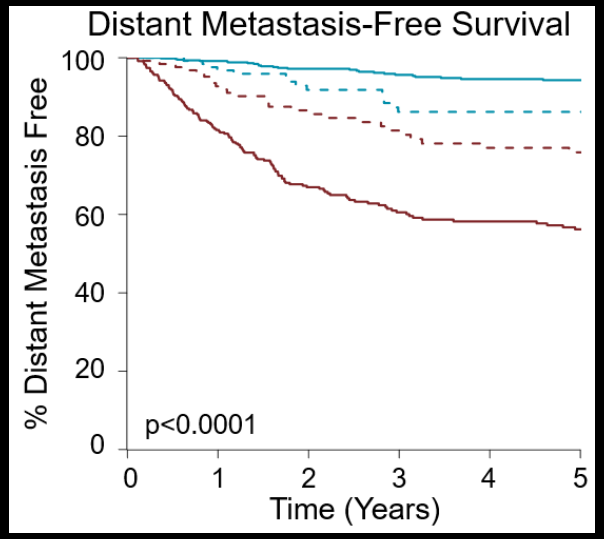
DecisionDx-Melanoma was developed to assess risk of recurrence independent from traditional clinicopathologic factors using tumor biology



Gerami et al. *Clin Cancer Res* 2015; Gerami et al. *JAAD* 2015; Zager et al. *BMC Cancer* 2018; Gastman et al. *JAAD* 2019
*Percent of clinical reports May 2013- Dec 2020 (n=63,765)

Consistent and *independent* prognostic value of DecisionDx-Melanoma across studies





GEP Result	5-year RFS	Recurrence Event Rate	5-year DMFS	Dist Met Event Rate
———		6.7%		5.5%
- - - -		14.2%		12.2%
·····		35.8%		24.1%
———		50.1%		38.8%

Multivariate Hazard Ratios (HR) for Class 2B[a]

Publication	HR
RFS	
Greenhaw et al[b]	7.96
Hsueh et al[b]	5.60
Gastman et al	2.66
Novel Cohort	2.75
Overall[c]	**2.90**
DMFS	
Hsueh et al[b]	5.79
Gastman et al	2.79
Novel Cohort	2.41
Overall[c]	**2.75**

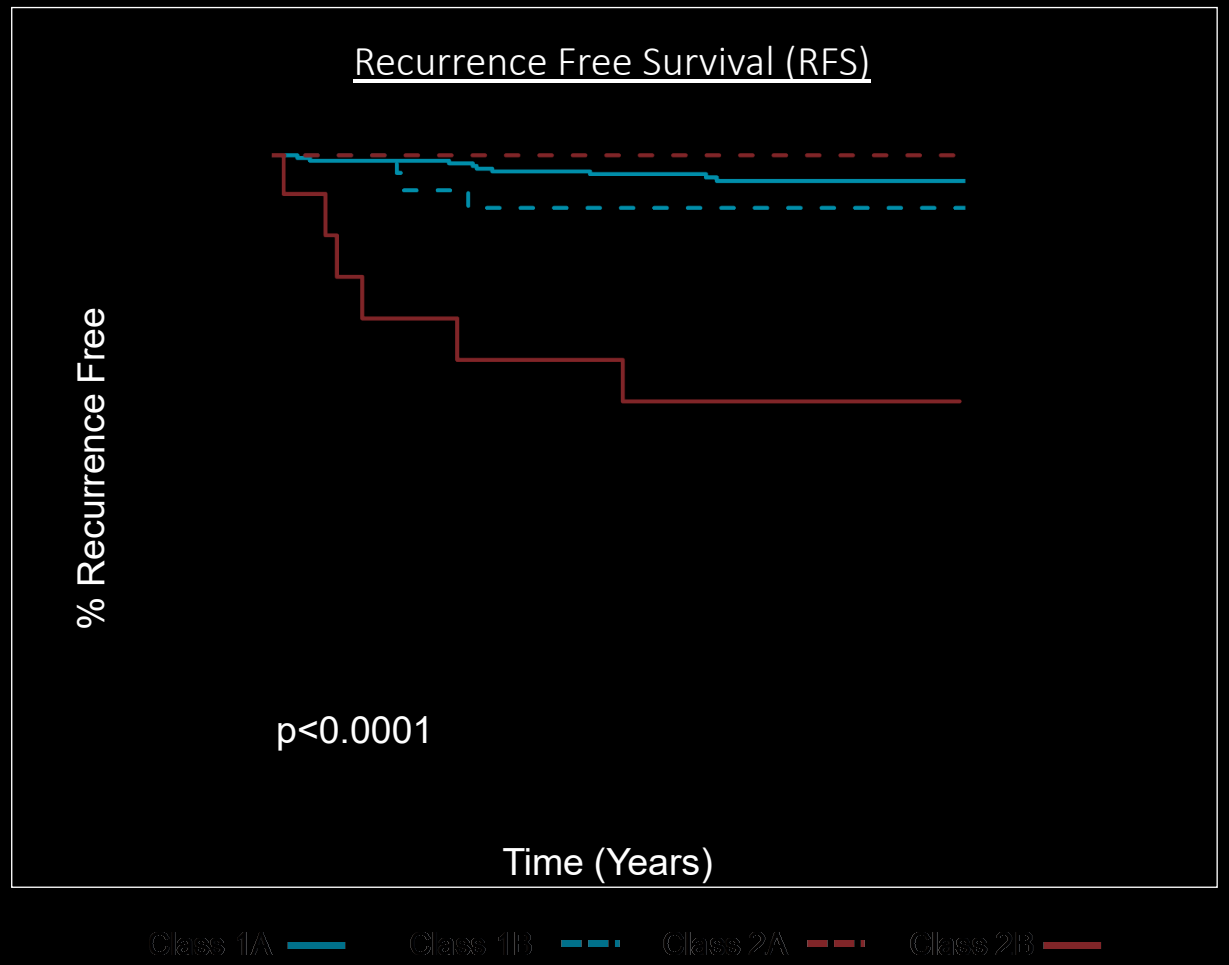
Greenhaw et al. *JAAD* 2020; [a]Multivariate model included all 31-GEP subclasses, age, Breslow thickness, ulceration, and node status; [b]Prospective study; [c]Same hazard ratio with fixed effect and random effects models

Thin Tumors

How does DecisionDx-Melanoma perform in thin tumors?

DecisionDx-Melanoma in thin tumors (< 1.0 mm)

DecisionDx-Melanoma identifies patients at high risk of recurrence and distant metastasis in patients with thin (≤1mm) tumors



GEP Class	5-year RFS	Event Rate (n)
1A (n=217)	97%	4% (9)
1B (n=34)	91%	9% (3)
2A (n=15)	>99%	0% (0)
2B (n=15)	65%	40% (6)

Cox Multivariate Analysis	RFS	
	HR	P-value
Breslow depth	0.6	0.80
Mitotic rate	1.03	0.83
Ulceration	2.26	0.35
Positive node	4.16	0.09
GEP Class 1B	0.52	0.58
GEP Class 2A	0	1.0
GEP Class 2B	9.34	0.004

Melanoma

- Evaluation
- Surgery
- Lymph Node Dissection
- Adjuvant Therapy
- Immunotherapy

Yagerman S and Goldberg DJ
J Dugs and Dematol 2020