Prevention and Diagnosis of Melanoma

Nancy E. Thomas MD PhD
Chair and Irene and Robert Alan Briggaman Distinguished Professor
Department of Dermatology
University of North Carolina

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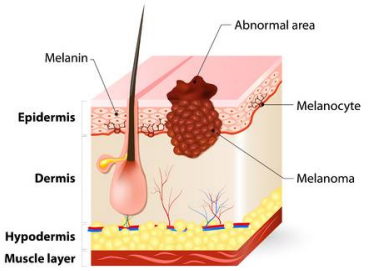
What is Melanoma?

A cancer of the pigment cells (melanocytes).



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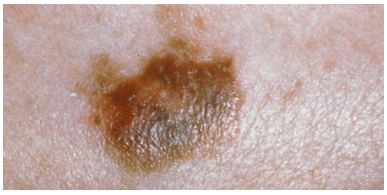
1

Melanoma



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Incidence of Melanoma

- The incidence of melanoma is increasing
- In 2018 in the U.S., an estimated 91,270 new invasive melanomas, and nearly 9,320 deaths due to melanoma
- The 5th & 6th most common cancer among U.S. men and women, respectively
- ~5% of malignant skin tumors, but 60% of skin cancer deaths

American Cancer Society. Cancer Facts and Figures 2018

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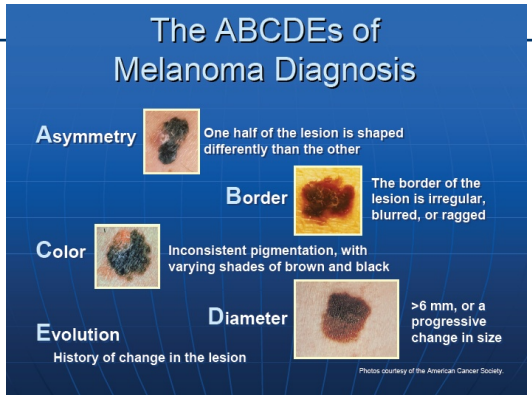
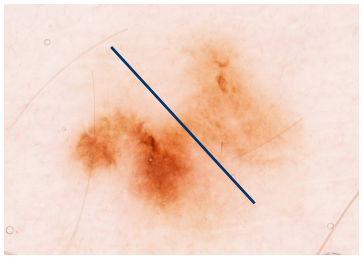


American Cancer Society

4

Asymmetry on the 2 axes



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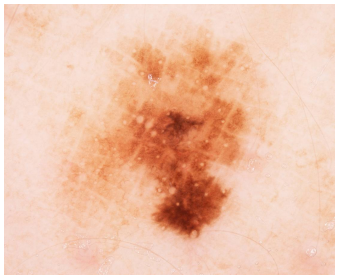
Ragged or Indented Borders



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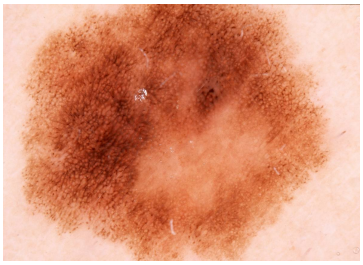
More Than 2 Colors



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Diameter ≥ 6 mm

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Evolution: New Pigmented Lesion

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9

Melanoma

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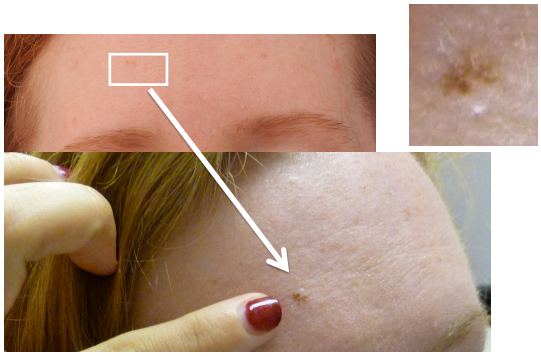
10

Evolution: Changing Pigmented Lesion



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11

Melanoma

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12

Types of Melanoma

- Superficial Spreading
- Nodular
- Lentigo Maligna
- Acral Lentiginous

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13

Superficial Spreading Melanoma

- Most common subtype
- Location – any anatomic site

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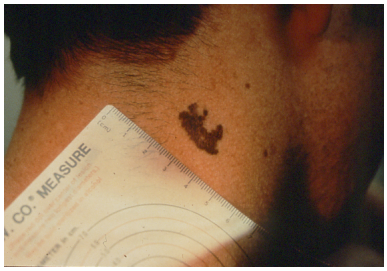
14

Superficial Spreading Melanoma



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15

Nodular Melanoma

Less common (about 10%)
Location – any anatomic site

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Nodular Melanoma

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17

Lentigo Maligna

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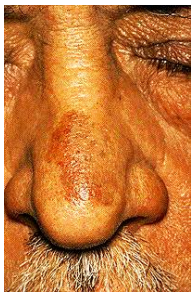
Less common (10-15%)
Sun exposed site such as head or neck



18

Lentigo Maligna

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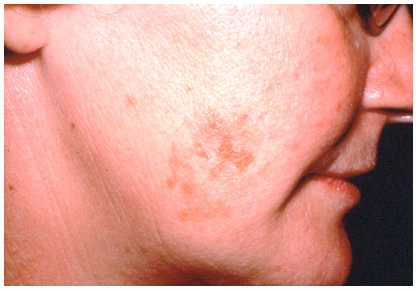

19

Lentigo Maligna

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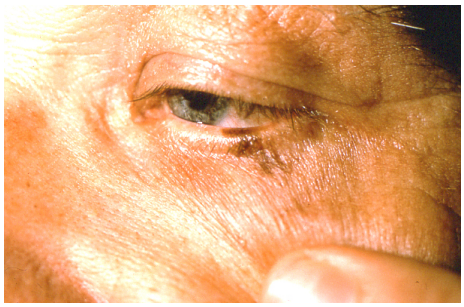


20

Lentigo Maligna Melanoma

21

Acral Lentiginous Melanoma

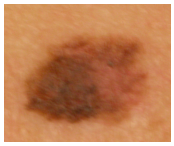
Least common (5%)

Location palms, soles

22

POLL

Which is more likely to be a melanoma based on the ABCDE criteria for melanoma?

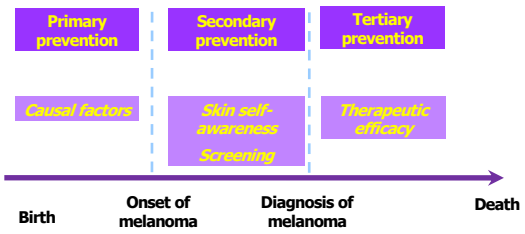
A. 

OR

B. 

23

Towards the control of melanoma



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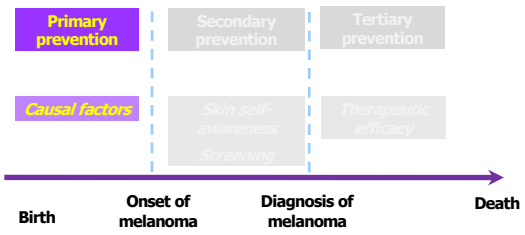
24

Towards the control of melanoma



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Risk Factors

High levels of ambient sunlight are associated with high rates of melanoma

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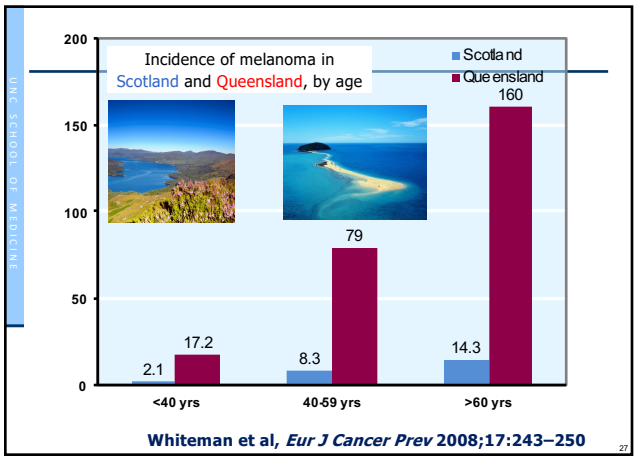
26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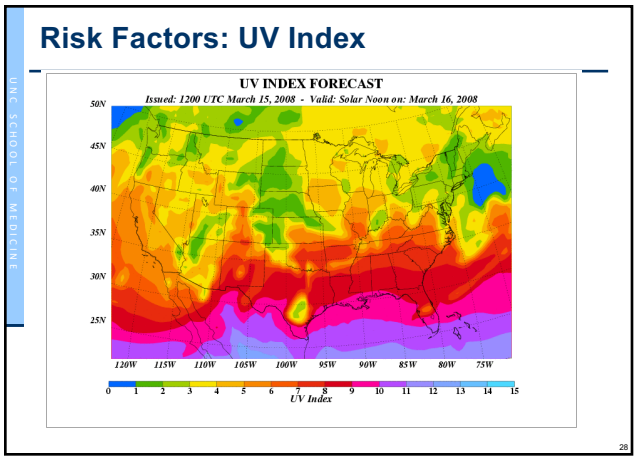
Incidence of melanoma in Scotland and Queensland, by age
Scotland
Queensland
200
150
100
50
0
2.1
17.2
8.3
79
14.3
160
<40 yrs
40-59 yrs
>60 yrs
Whiteman et al, Eur J Cancer Prev 2008;17:243–250
27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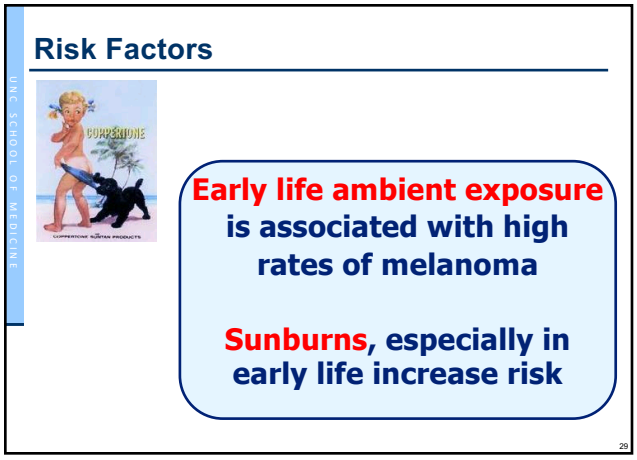
Risk Factors: UV Index
UV INDEX FORECAST
Issued: 1200 UTC March 15, 2008 - Valid: Solar Noon on: March 16, 2008
50N
45N
40N
35N
30N
25N
120W 115W 110W 105W 100W 95W 90W 85W 80W 75W
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
UV Index
28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Risk Factors
COPPERTONE
Early life ambient exposure is associated with high rates of melanoma
Sunburns, especially in early life increase risk
29

Risk Factors

Sun behavior associated with increased risk of of melanoma

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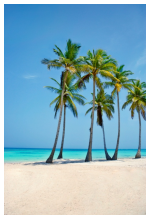
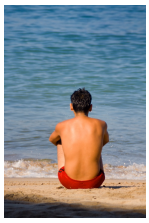
30

Behaviors Associated with Melanoma



Holidays in sunnier climates

Beach activities



Sunburns

Kricker et al. Cancer Causes Control, 2006

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31

UV Listed as a Carcinogen by IARC

International Agency for Research on Cancer (IARC) is a section of the United Nations World Health Organization (WHO) responsible for classifying agents depending on their carcinogenic (cancer causing) potential.

In 2009, the IARC categorized ultraviolet-emitting tanning devices in the highest risk class for cancer, "Group 1: the agent (mixture) is definitely carcinogenic to humans", along with asbestos and tobacco smoking.

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32

Artificial Tanning

IARC:

- The risk of melanoma goes up when you use a tanning bed at any age
- If you start using tanning beds before age 30, your risk of developing melanoma jumps by 75 percent

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33

Phenotypic Risk Factors

- Increased nevi
- Fair skin
- Red hair
- Blue Eyes
- Freckles
- Increased tendency to burn
- Decreased ability to tan

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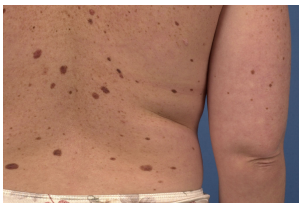
34

Multiple Nevi Strongest Risk Factor



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35

Risk Factors: Genetics

- Family history
- Rare genetic mutations (e.g. in p16)
- Common gene polymorphisms
  - Red hair gene (*MC1R*)
  - Other pigmentation genes (*OCA2, HERC2*)
  - Nevus related genes (e.g. *IRF4*, *PLAQ26*)
  - Cell cycle genes e.g. (*CCND1*)
  - DNA repair genes

36

POLL

Which is not a risk factor for melanoma

A. Many freckles
B. A family history of melanoma
C. Brown eyes
D. Many moles
E. A history of sunburns

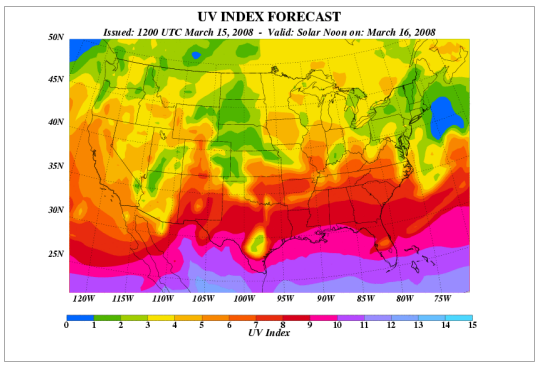
37

Prevention

- Monitor and limit sun exposure especially during peak daylight hours ~10 a.m. to 3 p.m.
- Protect yourself on cloudy days, too
- Seek shade
- Wear protective clothing and sunglasses
- Liberally apply broad spectrum sunscreen, at least 15 SPF, to exposed skin

38

Can Check the UV Index online



39

Prevention: Seek the Shade



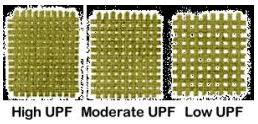


40

Clothing and sunglasses

41

Prevention: Wear UV-protective clothing.



Tighter weave
increased protection

UPF = ULTRAVIOLET PROTECTION FACTORY → **UPF 50**

42

Sunscreen Regulation Since 2011

- Sunscreen labels must include warnings about skin cancer
- Sunscreen labels cannot have misleading statements like '~~**Water-proof**~~" or "~~**Sunblock**~~"
- FDA established water resistance testing and labelling guidelines
- New broad-spectrum testing standards
- 2014 Sunscreen Innovation Act created an improved FDA process for reviewing and approving new ingredients

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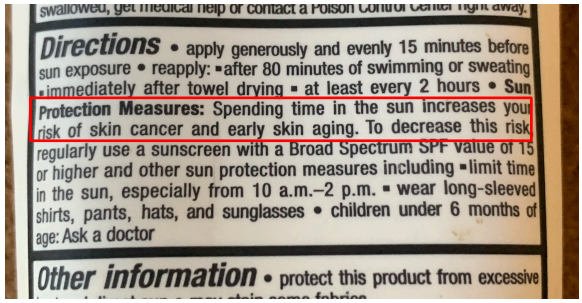
Sunscreen: Warnings about Skin Cancer


swallowed, get medical help or contact a Poison Control Center right away.

Directions • apply generously and evenly 15 minutes before sun exposure • reapply: ▪ after 80 minutes of swimming or sweating ▪ immediately after towel drying ▪ at least every 2 hours • **Sun Protection Measures:** Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk regularly use a sunscreen with a Broad Spectrum SPF value of 15 or higher and other sun protection measures including ▪ limit time in the sun, especially from 10 a.m.–2 p.m. ▪ wear long-sleeved shirts, pants, hats, and sunglasses • children under 6 months of age: Ask a doctor

Other information • protect this product from excessive

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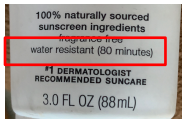
Sunscreen: Water Resistant

- No sunscreen lasts indefinitely when you're swimming or sweating so FDA bans the use of "waterproof" or "sweatproof" on product labels.
- "Water resistant" means the sunscreen is formulated to perform well despite the presence of water or sweat.
- FDA has a specific test and you should find one of two ratings:
  - –Water resistant for 40 minutes
  - –Water resistant for 80 minutes



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45

Sunscreen: SPF

- SPF 15 blocks 93% of UVB rays
- SPF 30 blocks 97% of UVB rays
- SPF 50 blocks 98% of UVB rays
- SPF 100 blocks 99% of UVB rays

46

Sunscreen: SPF

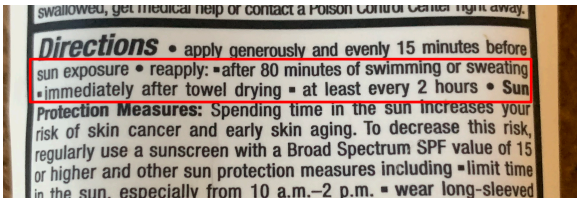
- Apply liberally
- 1 oz covers the body

3 oz so
3 applications

47

Sunscreen: Time between Applications

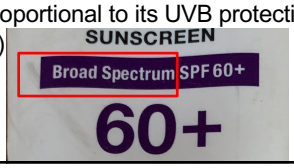
- SPF ratings don't tell you how long you can wait before reapplying.
- FDA recommends that you reapply any sunscreen every two hours, regardless of its SPF rating.



48

Sunscreen Regulation Since 2011

- UVB and UVA can cause sunburn, skin cancer, and premature skin aging.
- Sunscreens labeled broad spectrum to shield skin from both UVB and UVA rays.
- In 2011, FDA required sunscreens advertising "broad spectrum" pass a test
- FDA says a broad spectrum's UVA protection level will be roughly proportional to its UVB protection level (SPF rating)



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Sunscreen: Chemical vs Mineral

- Active ingredients in sunscreens come in two forms, mineral and chemical filters.
- Chemical sunscreens include a combination of two to six of the following active ingredients: oxybenzone, avobenzone, octisalate, octocrylene, homosalate and octinoxate.
- Mineral sunscreens use zinc oxide and/or titanium dioxide.
- A few products combine zinc oxide with chemical filters.

50

Sunscreen Environment Issue

In laboratory experiments, high concentrations oxybenzone caused damage and deformation of coral

Hawaii recently passed a bill, not yet signed into law, to ban sale of oxybenzone-containing sunscreen due to its effects on marine life.

REI vows to ban use of oxybenzone in products sold by fall 2020.

51

POLL

Which is an incorrect statement?

A. Broad spectrum sunscreens protect against UVB and UVA

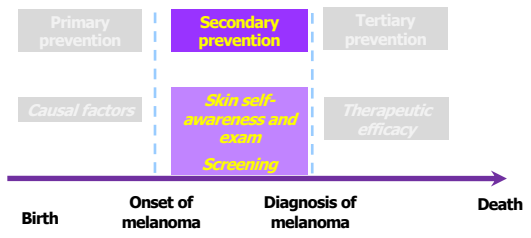
B. A waterproof sunscreen lasts indefinitely when you are swimming

C. SPF 15 sunscreen is the lowest SPF recommended by dermatologists

D. Sunscreen labels must include warnings about skin cancer

52

Towards the control of melanoma



53

Skin Self-Awareness

Self-Screening for melanoma?
Skin Self-Awareness
Skin Self exam

Individuals who are more aware of changes in their skin are more likely know be aware of whether or not a mole or other skin mark has changed over time

Skin Self-Awareness has been show to decrease death from melanoma

Paddock et al. Melanoma Research 2016, 26:401–408

54

Screening for Melanoma

Screening for melanoma?
Who to screen?

Melanoma survivors are screened for second melanomas
No current recommendations for population screening

55

Screening for Melanoma

Population screening for melanoma?
Targeted Screening?

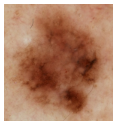
Can we identify and use targeted screening for those at highest risk for melanoma?
- *Increased number of nevi, atypical nevi, fair traits, red hair, increased sun exposure*
- *Genetic?*

56

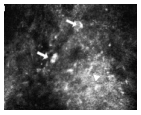
Screening for Melanoma

Baseline pictures

Dermoscopy

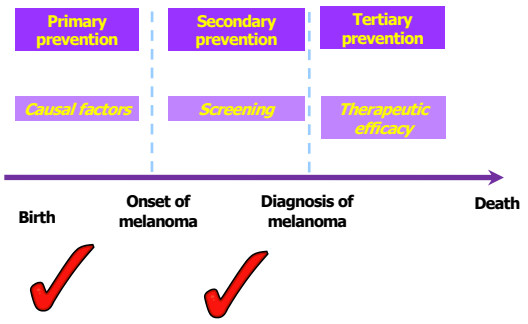


Confocal



57

Towards the control of melanoma



58

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Caring for the Patient with Melanoma or Other Skin cancers. Part 2.

Frances Collichio
Clinical Professor, University of North Carolina, Chapel Hill

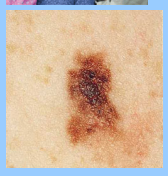
Disclosures:
Amgen
Novartis/GSK
Merck

At the end of this part of the talk you will:

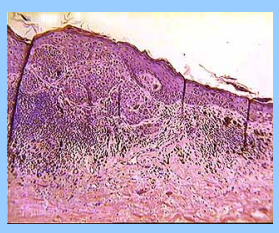
- Understand the principles of immuno-oncology
- Apply these principles to the management of a patient with melanoma in lymph nodes.
- Apply these principles to a patient with advanced disease
- Infer what the side effects of the treatments may be and list them

Our Case

A 49 year old married father of two presents on the urging of his wife due to a mole on his right lower leg that seems to have changed. He is in good health and takes no medication. The mole is shown. The rest of the examination is normal.

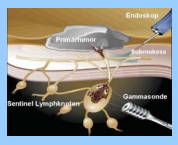


Case 1

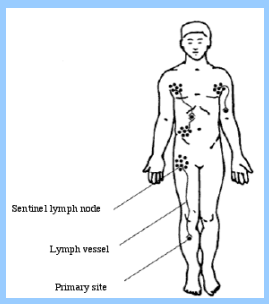


Histologic type:
Superficial spreading melanoma
Breslow depth: 1.8 mm
Ulceration: PRESENT

Sentinel Lymph Node Procedure/Clear the margins

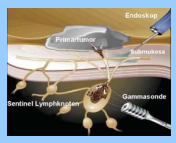


Morton N Engl J Med 355 2008



Case 1

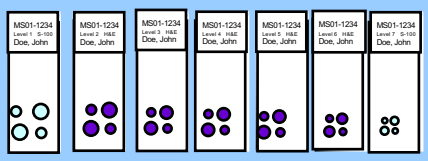
The sentinel lymph node procedure maps to the right groin. There are three sentinel nodes.



Sentinel Lymph Node Evaluation

Lymph node serially sectioned while fresh

Alternate sections paraffin-embedded; remainder snap frozen



Five H&E-stained sections flanked by two S-100 sections

AJCC Staging 1/2018

T

T0: No evidence of primary tumor
Breslow depth
Ulceration
(Mitoses are no longer part of the staging.
T1 category uses 0.8mm as a threshold with T1b of 0.8-1mm w or w/o ulceration

N

N0
N1 one node is involved
N2 two to three
N3 4 or more, or matted nodes, or in transit disease, or satellites (tumor w/in 5cm of the primary).
Clinically occult or clinically detected (instead of microscopic and macroscopic)
"c" categories for microsatellites and in-transit metastases

M

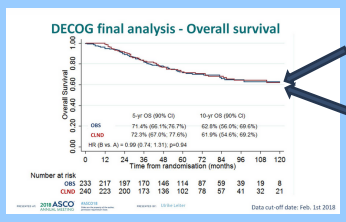
M1a-skin, subcutaneous tissue or distant lymph nodes
M1b-lung
M1c-other site
M1d-CNS

Stage I, II negative nodes
Stage III, positive nodes

T2bN2aM0 Stage IIIb

Case 1

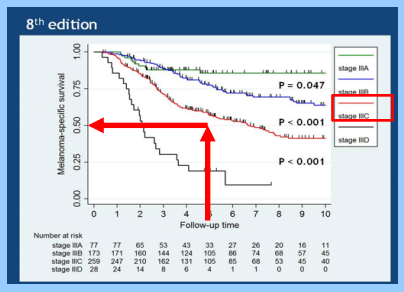
Does the patient need more surgery on his nodes?



One group: No more surgery

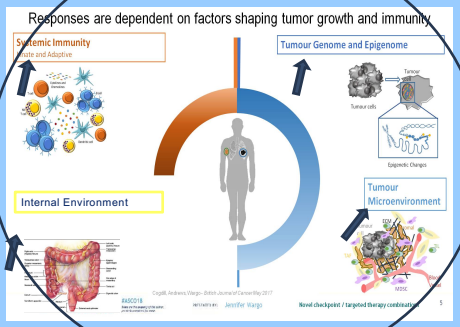
Other group: Remove the rest of the nodes from the nodal basin

Is the patient cured? Can we add to the surgery to increase his chances?



Before we go on…you need some immune-oncology concepts

Immune System Overview



Presented By Jennifer Wargo at 2018 ASCO Annual Meeting

Immunotherapy: How the Immune System Fights Cancer

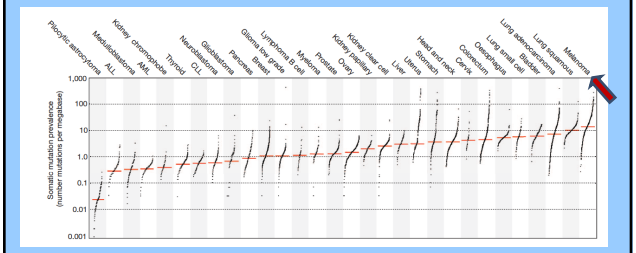
https://www.youtube.com/watch?v=jDdL2bMQXfE

or

unccn.org/video

This video was created by the National Cancer Institute. Permission was obtained to use this video.

Neoantigen Prediction



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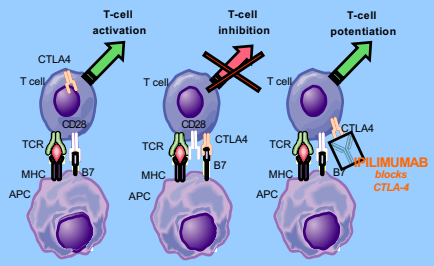
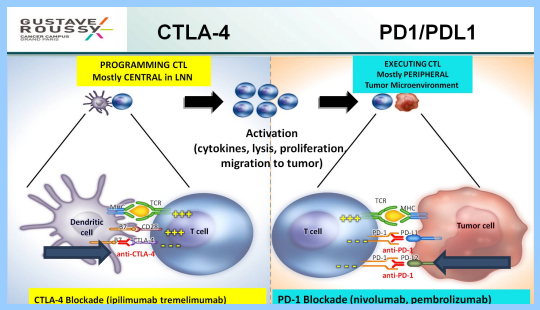
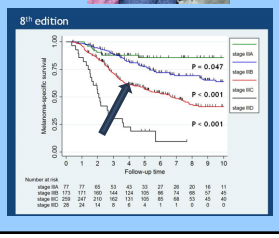
CTLA 4 Ipilimumab---Acts peripherally



Available agents and how they work: Check point inhibitors



Which of the following is the best way to improve this patient's chances?



A. Complete the surgery on the lymph node basin.

B. Give six months of chemotherapy

C. Give a "check point inhibitor"

D. Nothing, his chances are good.

Treatments for Melanoma that has gone to the lymph node after surgery

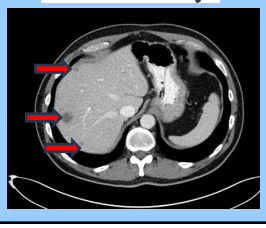
One year of:
Anti CTLA 4: Ipilimumab
Anti PD1: Nivolumab
Anti PD1: Pembrolizumab

The Next Case:

A 33 year old scientist with a history of surgery for stage II melanoma on her leg presents to the doctor because she is tired. She says she has lost 5 pounds without trying.

Our Case 1

Her physical examination is normal. Her laboratory tests are normal including white blood cells, red blood cells, liver function and kidney function.



A biopsy was done of the liver and this was melanoma. A molecular genetic test was done and it showed an abnormal BRAF V600 E gene.

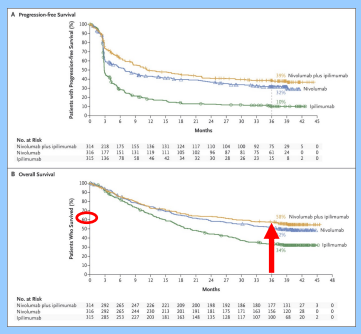
What does all this mean?

What is her stage of cancer?
Can she be cured?
What is the gene test?
How do you know what to treat her with?

What is her stage?

Stage 4
M1a
M1b
M1c
M1d
Prognosis is predicted by the patients overall health and the immune markers.

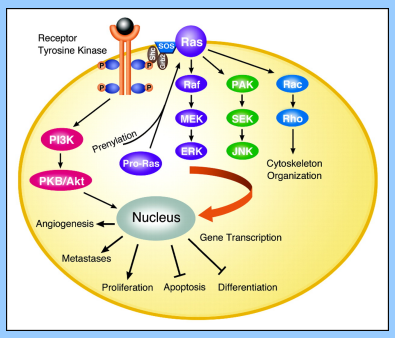
Can she be cured?



Wolchok JD et al. N Engl J Med 2017;377:1345-1356.

The NEW ENGLAND JOURNAL of MEDICINE

Gene pathways in Melanoma



Beeram, M. et al. J Clin Oncol; 23:6771-6790 2005

JOURNAL OF CLINICAL ONCOLOGY

Double block

RAS

BRAF inhibitor

RAF

MEK inhibitor

MEK

ERK

Choice of therapy

Immune therapy
- Generally preferred
- Combination versus single?
- Combination versus sequence?
- New Immune agents
- Biomarkers
- Caution with existing Autoimmune disease!

Target Therapy
- Hit the Target: BRAF V600E, 600K
- Generally works faster than immune therapy
- Difficult to stop

Answers

What is her stage of cancer?: Stage 4, M1c

Can she be cured? : Maybe

What is the gene test?: It is a mutation that occurs from the environment. It is not a hereditary mutation

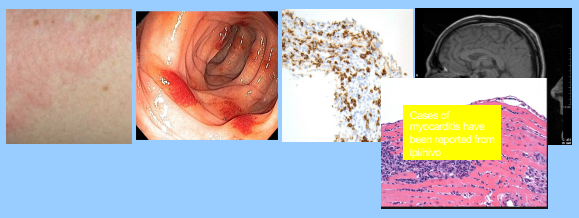
How do you know what to treat her with? This question has taken years of study and we do not have all of the answers but in a young, fit person we start with immune therapy.

Which of the following side effects do you think is common with immune therapy?

A. Hair Loss
B. A decrease in red blood cells
C. Nausea
D. Rash

Toxicities: Side effects of ipilimumab

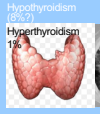
Skin | Colon | Liver | Pituitary



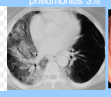
Cases of myocarditis have been reported from ipilimumab

Toxicities: Side effects of PD1 and PDL1 inhibitors

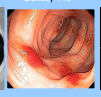
Hypothyroidism (8%?)
Hyperthyroidism 1%



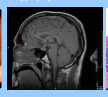
pneumonitis 3%



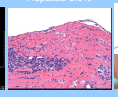
Colitis, 1%



Hypophysitis 0.5%



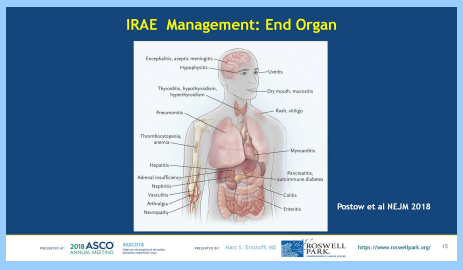
Hepatitis 0.5%



Nephritis 0.5%

Other in less than 1%: dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures, adrenal insufficiency.

Toxicities: any organ



Presented By Marc Ernstoff at 2018 ASCO Annual Meeting

In conclusion:

- We covered the principles of immuno-oncology
- We applied these principles to the management of a patient with melanoma in lymph nodes
- We applied these concepts to a patient with melanoma of advanced stage
- We listed the side effects of the treatment.