

Melanoma: old strategies and new ideas

Dr. Andrew McFadden
Surgical Oncology
BCCA

?



SUNSCREEN



Objectives:

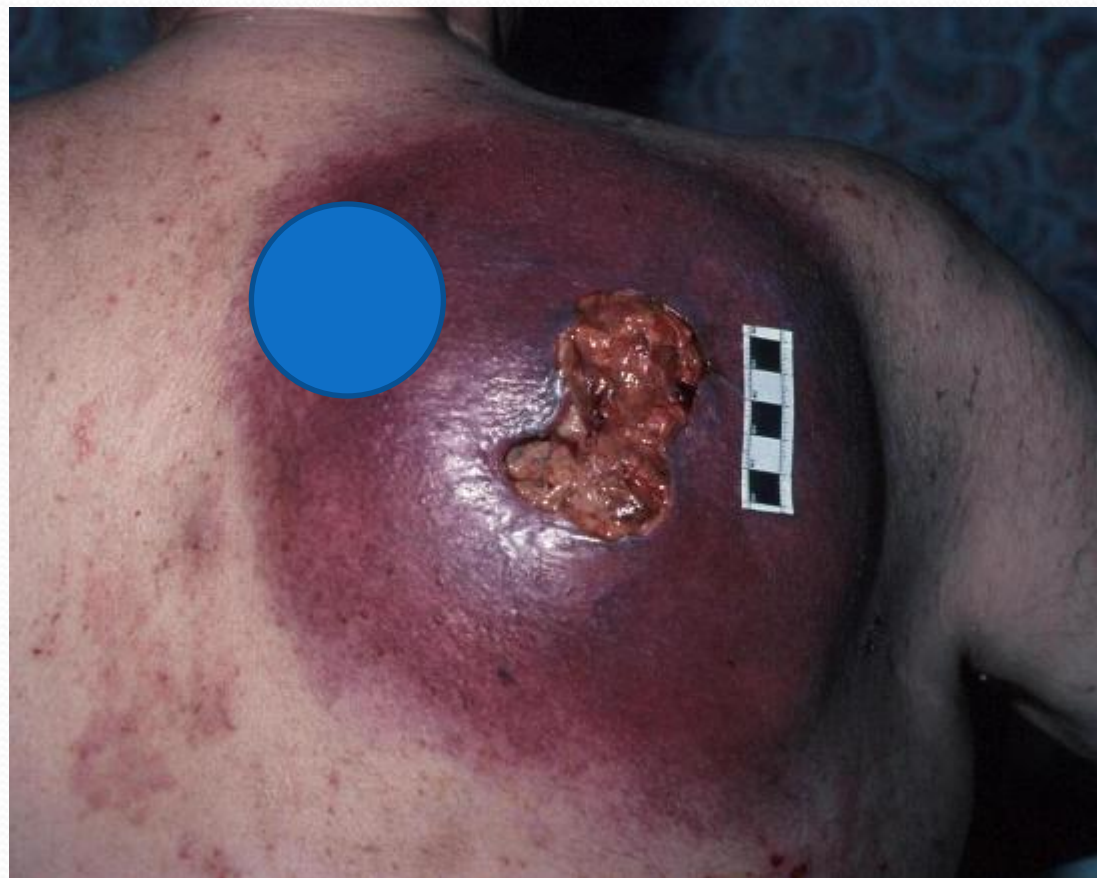


Objectives:

- **Case:**

- 74 year old retired CEO
- melanoma removed 4 years ago on back
- WLE no SNB
- asymptomatic 4cm subcutaneous mass back
- 6cm mass axilla

Objectives:



Objectives

- **Case**
 - FNAB
 - CT scan
 - Bone scan
 - PET/CT
 - Surgery
 - Multidisciplinary conference
 - Radiotherapy

Staging

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Update on the Melanoma Staging System: The Importance of Sentinel Node Staging and Primary Tumor Mitotic Rate

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The 7th Edition of the AJCC Staging Manual includes a detailed summary of melanoma staging and prognosis. The revisions are summarized in this article, along with details on two key aspects of melanoma staging: the incorporation of mitotic rate of the primary melanoma and the key role of the sentinel lymph node biopsy (SLNB) in determining accurate staging for clinically occult nodal metastases. Primary tumor mitotic rate was introduced as a major criterion for melanoma staging and prognosis that replaces the Clark's level of invasion, and is now proven to be an important independent adverse predictor of survival. Analysis of the AJCC melanoma staging database demonstrated a significant inverse correlation between primary tumor mitotic rate (histologically defined as mitoses/mm²) and survival. The use of SLNB reliably identifies melanoma patients with nodal micrometastases, enabling clinicians to identify patients with occult nodal metastases that would otherwise take months or years to become clinically palpable. The number of nodal metastases was the most significant independent predictor of survival among all patients with stage III disease, including among patients with nodal micrometastases, and continues to be a primary criterion for defining Stage III melanoma. A clinical scoring system model and multivariate predictive tool under the auspices of the AJCC has led to a first-generation web-based predictive tool (www.melanomaprognosis.org).

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KEY WORDS: melanoma; staging; mitotic rate; sentinel lymph node

Staging

TABLE I. TNM Criteria for Cutaneous Melanoma (2010).

Melanoma TNM Classification		
T classification	Thickness (mm)	Ulceration status/mitoses
T1	≤1.0	a: Without ulceration and mitoses <1/mm ² b: With ulceration or mitoses ≥1/mm ²
T2	1.01–2.0	a: Without ulceration b: With ulceration
T3	2.01–4.0	a: Without ulceration b: With ulceration
T4	>4.0	a: Without ulceration b: With ulceration

Staging

Melanoma TNM Classification

N classification	No. of metastatic nodes	Nodal metastatic mass
N1	1 node	a: Micrometastasis ^a b: Macrometastasis ^b
N2	2-3 nodes	a: Micrometastasis ^a b: Macrometastasis ^b c: In transit met(s)/satellite(s) <i>without</i> metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) <i>with</i> metastatic node(s)	

Staging

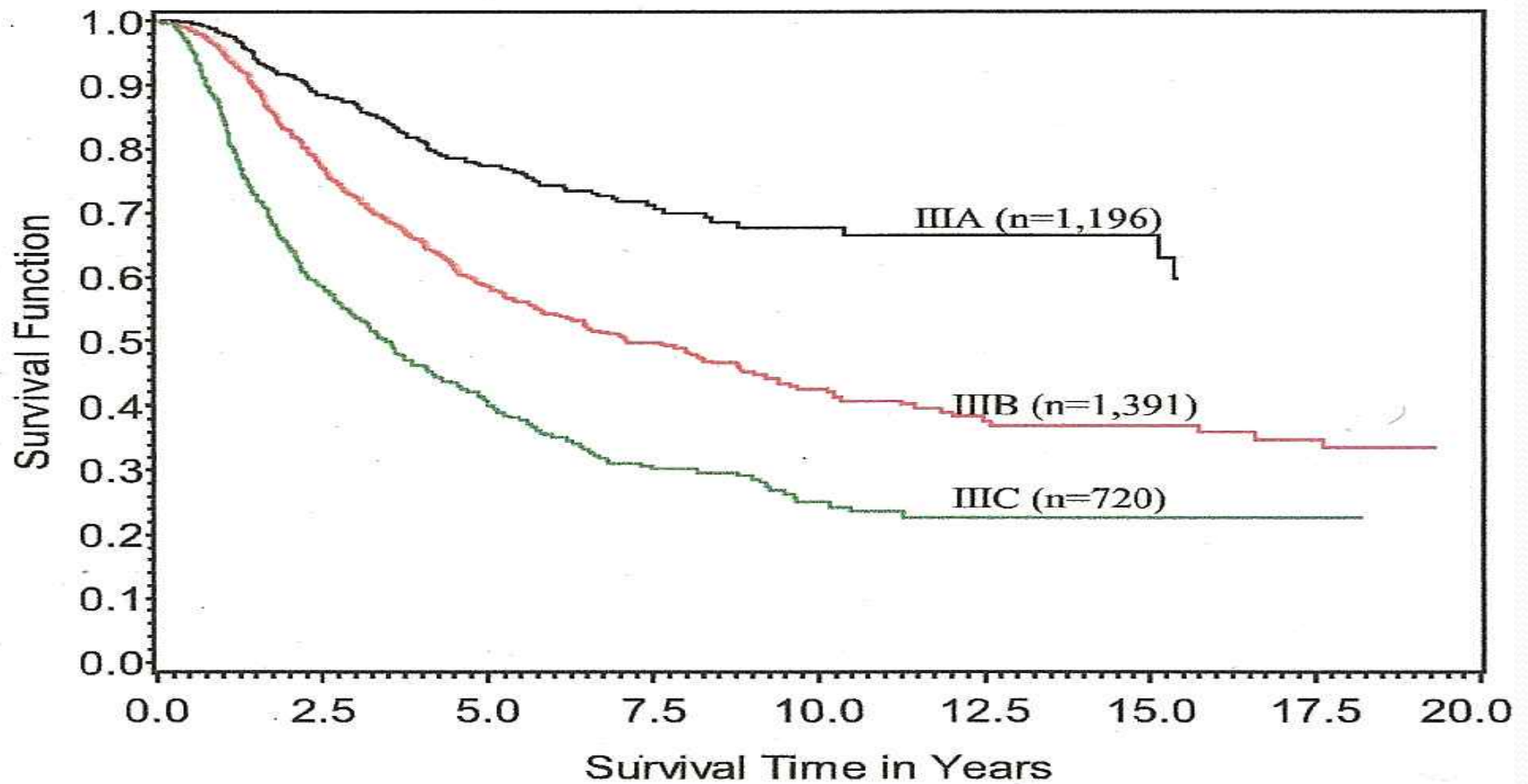
Melanoma TNM Classification

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

Staging

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Balch et al.



1. What if patient had a sentinel node biopsy initially?

Recurrence after formal node dissection:

SNB + 2-10%

Palpable nodes 20-50%

1. What if patient had a sentinel node biopsy initially?

Multicenter Selective Lymphadenectomy Trial (MLST-1)

WLE

+SNB - if positive Node Dissection -72% 5yr survival

Obs – if nodal recurrence Node Dissection – 52% %yr

1. What if patient had a sentinel node biopsy initially?

So

MLST-2

WLE +SNB randomised to Completion node dissection
or Observation

2. What if patient had a deep melanoma originally?

Standard indications for SNB

- $\geq 0.75\text{mm}$ _ thick
- Ulceration
- Mitotic rate ≥ 1 mm²
- Clark level IV
- < 4.0 mm

2. What if patient had a deep melanoma originally?

T₄ primary:

SNB – no ulceration	>90%	5 year survival
SNB -	85%	5year survival
SNB +	47%	5year survival

3. Is there any evidence that surgery for recurrent disease anything more than palliation?

Slingloff

Axillary dissection Stage $\frac{3}{4}$

Asymptomatic 35% 5year survival

Symptomatic 16% 5year survival

4. You referred the patient for radiotherapy?



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CRITICAL REVIEW

THE EVOLVING ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF MALIGNANT MELANOMA

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The incidence of melanoma is rising in the United States, leading to an estimated 68,720 new diagnoses and 8,650 deaths annually. The natural history involves metastases to lymph nodes, lung, liver, brain, and often to other sites. Primary treatment for melanoma is surgical excision of the primary tumor and affected lymph nodes. The role of adjuvant or definitive radiation therapy in the treatment of melanoma remains controversial, because melanoma has traditionally been viewed as a prototypical radioresistant cancer. However, recent studies suggest that under certain clinical circumstances, there may be a significant role for radiation therapy in melanoma treatment. Stereotactic radiosurgery for brain metastases has shown effective local control. High dose per fraction radiation therapy has been associated with a lower rate of locoregional recurrence of sinonasal melanoma. Plaque brachytherapy has evolved into a promising alternative to enucleation at the expense of moderate reduction in visual acuity. Adjuvant radiation therapy following lymphadenectomy in node-positive melanoma prevents local and regional recurrence. The newer clinical data along with emerging radiobiological data indicate that radiotherapy is likely to play a greater role in melanoma management and should be considered as a treatment option. © 2011 Elsevier Inc.

Hypofractionation, Brachytherapy, Melanoma cell cycle, Radiosurgery, Biological agents.

4. You referred the patient for radiotherapy?

Burmeister

Patient high risk for recurrence post node dissection:

- > 1 parotid node
- >2 axillary /cervical nodes
- >3 groin nodes
- extra nodal spread
- >3cm node neck/axilla
- >4cm node groin

4. You referred the patient for radiotherapy?

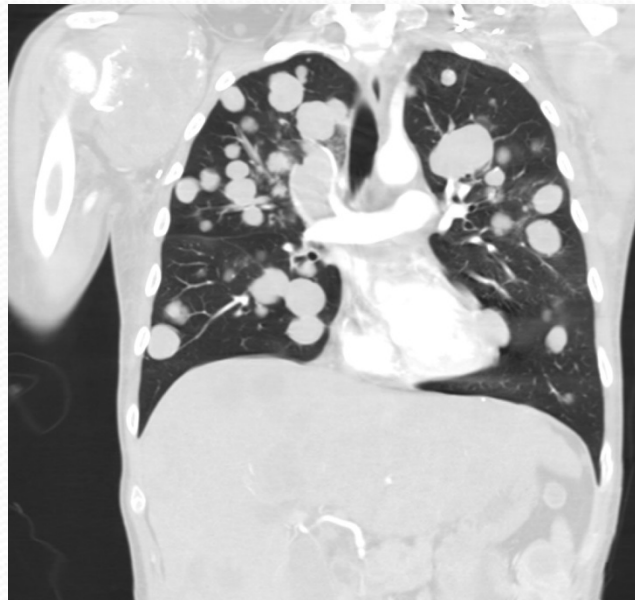
OS the same

Radiated group 16% recurred

Observation 27% recurred

5. What is the point of the CT and PET scans?

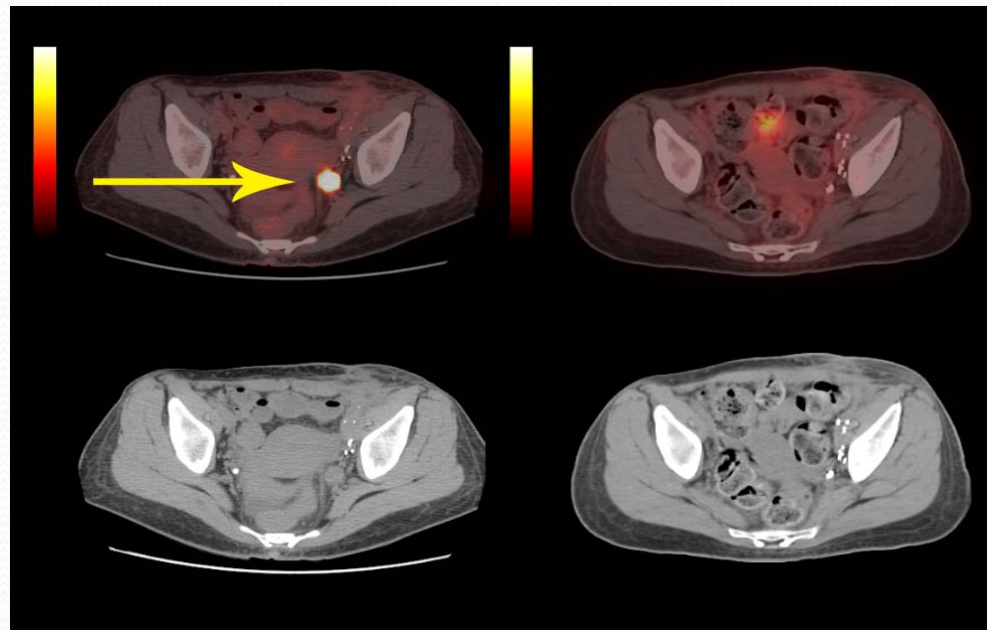
- 50-80% of metastatic melanoma patients present with involvement of 1 organ before developing wide spread mets
- mets in different sites have different prognosis



5. What is the point of the CT and PET scans

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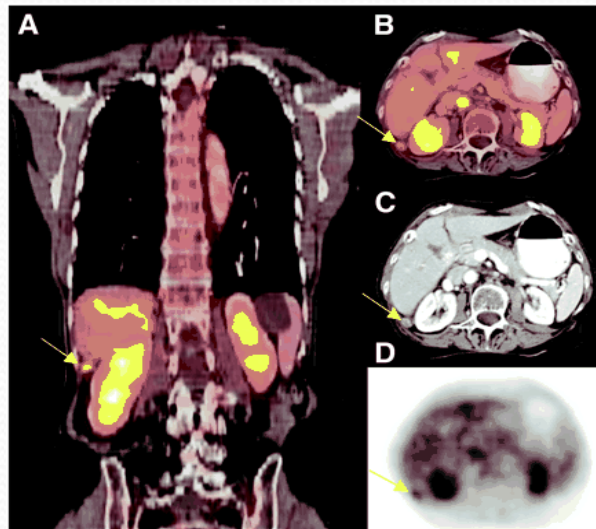


5. What is the point of the CT and PET scans

- What about complete metastectomy in Stage IV disease?

M1a: skin,subcutaneous,nodes

Median survival 15-50months with 11-49% 5 year survival



5. What is the point of the CT and PET scans

- **What about complete metastectomy in Stage IV disease?**

Morton

Complete metastectomy +/- vaccine

Vaccine useless but 40% 5 year survival

SWOG

Complete metastectomy

OS survival 36% 3 years

31% 4 years

5. What is the point of the CT and PET scans

- What about complete metastectomy in Stage IV disease?

M1b:pulmonary

- #mets
- Doubling time
- Staged with PET
- disease free interval
- Extra pulmonary disease
- initial stage (I/II vs. III)

Median survival 11-40 months with 5-31% 5 year survival

5. What is the point of the CT and PET scans

- What about complete metastectomy in Stage IV disease?

M1c: other


GI

Complete resection 15-28 months vs. 5-8 months
90% effective palliation

6. What if patient is unresectable?


**Partial Response To G3139 + DTIC
in Patient With Drug-Resistant
Metastatic Melanoma**

February 10, 1999



Baseline

March 10, 1999



After Treatment

DTIC + G3139 3.1 mg/kg/d

Patient #2.
Jansen et al. *Proc Am Soc Clin Oncol*. 1999;18:531a.

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6. What if patient is unresectable?

- **New Drugs**

1. **Ipilimumab** : IgG Ab that blocks cytotoxic T-lymphocyte associated antigen 4(CTLA-4)

		<u>% alive</u>		
	<u>survival</u>	1	2	3 years
Ipilimumab + DTIC	11.2mths	47	28	20
Placebo +DTIC	9.1mths	36	17	12

6. What if patient is unresectable?

- **New Drugs:**

2. Vemurafenib: BRAF inhibitor selective for V600E mutation

	CR	PR	6 mth survival
Vemurafenib	1%	47.5%	84%
DTIC		5.5%	64%

6. What if patient is unresectable?

BCCA has 1 open BRAF trial

Conclusions:

- 1. Recurrences can be prevented
- 2. Recurrences can be treated with long term control
- 3. Some mets may be resected with long term control
- 4. New drugs with activity against melanoma
- 5. Still unclear if we can cause cures after metastasis
- 6. Multi-disciplinary clinics
- 7. Trials
- 8. Has surgery become specialised?