CROSS TUMOUR SITES AND MDT ISSUES FOR MELANOMA

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First issue is complexity of staging

Sub-stage		AJCC 10 year survival (Balch et al., 2001)	SEER 10 year survival in % (Gimotty et al., 2005a)
IA	≤1	87.9 +/- 1.0	97.4
IB	≤1 with ulceration or dermal mitoses	83.1 +/- 1.5	90.2
	1.01-2.0 no ulceration	79.2 +/-1.1	84.1
IIA	1.01-2.0 with ulceration	64.4 +/- 2.2	65.2
	2.01-4.0 no ulceration	63.8 +/- 1.7	67.3
IIB	2.01-4.0 with ulceration	50.8 +/- 1.7	62.1
	>4 no ulceration	53.9 +/- 3.3	56.3
IIC	>4 with ulceration	32.3 +/- 2.1	47.5
IIIA	1 node	62.0 +/-4.4	
	2-3 nodes	56.9 +/- 6.8	
IIIB	Micromets and ulcerated primary	37.8 +/- 4.8	
	1 node	35.9 +/- 7.2	49.7
	2-3 nodes	47.7 +/- 5.8	43.6
	Satellites no nodes	39.2 +/- 5.8	59.2
IIIC	1 node and ulcerated primary	24.4 +/- 5.3	36.6
	2-3 nodes and ulcerated primary	15.0 +/- 3.9	32.9
	≥4 nodes	18.4 +/- 2.5	22.4
IV	Overall		14.1
	Skin and SC	15.7 +/- 2.9	
	Lung	2.5 +/- 1.5	
	Other visceral	6.0 +/- 0.9	

New AJCC LDH blood

M Classification		
M1	Distant skin, subcutaneous or lymph node mets	Normal LDH
M2	Lung mets	Normal LDH
M3	All other visceral or any distant mets	Normal LDH Elevated LDH

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AJCC Staging requirements

- Pathology report primary
  - Breslow thickness
  - Tumour ulceration
  - Mitotic rate per mm2
  - Presence of micro satellites
- Sentinel node status (usually p
  primary)
- Presence or otherwise of palpal
  - Pathology report thereof
- Stage IV
  - Imaging
  - LDH

Primary path report

AJCC staging by the MDT

- After WLE and SNB if to be done
- At progression so that survival can be computed for each stage and compared

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AJCC staging based mainly on histology: **but other factors also impact on survival**

Leeds Cohort Study: Determinants of relapse free and overall survival in 822 patients recruited at least 2 years (median 4.7 years)

Parameter	HR (95% CI) for RFS	HR (95% CI) for OS
Age: per year	1.01 (0.99, 1.02)	1.04 (1.02, 1.06)
Gender: male vs female	1.66 (1.10, 2.49)	1.01 (0.68, 1.56)
Site: head and neck vs trunk	0.69 (0.39, 1.24)	0.59 (0.34, 1.05)
Site: limbs vs trunk	0.77 (0.49, 1.22)	0.61 (0.38, 0.98)
Site: others vs trunk	0.87 (0.44, 1.73)	0.46 (0.22, 0.97)
Breslow thickness: per mm	1.32 (1.23, 1.41)	1.28 (1.21, 1.35)

Variation in outcome related to the biology of the tumour: biomarkers, *BRAF*, *NRAS* etc

- The somatic changes that are emerging will lead to targeted therapy
- But they will also contribute to differences in outcome with the identification of better prognostic biomarkers as well as predictive biomarkers
- We now have the tools to produce genomic profiles from even very old, small, formalin fixed primary melanomas
- Biomarker status will therefore shortly be an essential component of staging for melanoma

Data collection for skin cancers

- Problems
  - Sheer number of cases
  - Treatment by multiple MDTs
    - Head and neck team
    - Gynae team
    - Urology
    - Haematology

Cross team working

- Melanomas in rare sites eg gynae, penile, ENT should be reviewed by the melanoma SSMDT meeting even if the primary management is carried out by another team
  - Clinical trials
  - Evolving knowledge of biological origin of melanoma and its implications for treatment
- Data collection contentious
  - AJCC melanoma staging is applicable to melanomas vulva and penis
  - No AJCC staging system developed for rare mucosal site melanomas
  - My view is that we should none-the-less collect the melanoma data set for all melanomas irrespective of site where the specialist SSMDT melanoma pathologist is happy to do so

a-MSH

c-kit

EGFR

c-kit mutations in melanomas in sun protected sites

PTEN

PIP2

PI3K

BRAF

BRAF (50%) mutated in intermittently sun exposed sites and SSM

NRAS mutations (20 to 30%) more common in chronically sun exposed sites and nodular melanoma

MEK1/2

ERK1/2

C-Fos

MITF

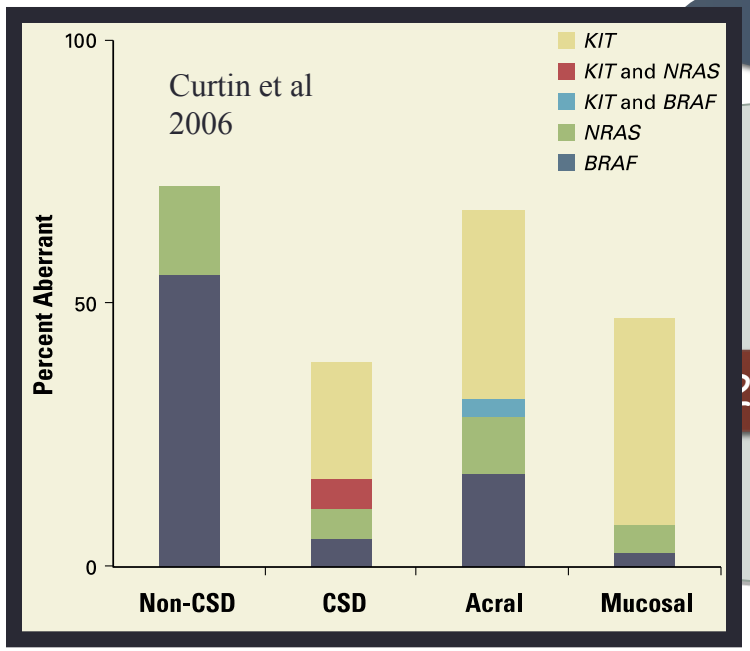
C-Jun

NFkb

Proliferation

Proinflammatory cytokines eg IL 6

APOPTOSIS



Moxley et al 2011

- The 2002 modified AJCC staging criteria were predictive of overall survival (p=0.006) in patients with malignant melanoma of the vulva.
- In the largest multi-site series of vulvar melanoma, the AJCC-2002 staging system for cutaneous malignant melanoma appears to be applicable to primary vulvar melanoma.

Van Geel et al 2007

- Penile melanoma
- Presence of ulceration, tumor depth of 3.5 mm or more, and tumor diameter greater than 15 mm had a significantly adverse effect on prognosis.

- My view is therefore that both site specific and melanoma data sets should be collected for rare site melanomas