

UC San Diego Health

Clinical Case Conference

Melanoma



Epidemiology

- ~60,000 cases and 8,000 deaths per year in US
- Caucasian:African American = 10:1
- 15% arise from existing nevi
- 91% are cutaneous
- 15% are LN+ at presentation
- 5% are M1 at diagnosis
- Types: superficial spreading, desmoplastic, nodular, lentigo maligna, acral lentiginous
- Daily sunscreen reduces incidence (HR = .50) Green AC, J Clin

Oncol. 2011 Jan 20;29(3):257-63.

AJCC Staging 7th ed. 2010

Primary tumor (T)	
TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed primary)
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	≤1.0 mm
	a: without ulceration and mitoses <1/mm ² b: with ulceration or mitoses ≥1/mm ²
T2	1.01-2.0 mm
	a: without ulceration b: with ulceration
T3	2.01-4.0 mm
	a: without ulceration b: with ulceration
T4	>4.0 mm
	a: without ulceration b: with ulceration
Regional lymph nodes (N)	
NX	Patients in whom the regional nodes cannot be assessed (eg, previously removed for another reason)
N0	No regional metastases detected
N1	One lymph node
	a: micrometastases* b: macrometastases•
N2	Two or three lymph nodes
	a: micrometastases* b: macrometastases•
	c: in-transit met(s)/satellite(s) without metastatic lymph nodes
N3	Four or more metastatic lymph nodes, or matted lymph nodes, or in-transit met(s)/satellite(s) with metastatic lymph node(s)
Distant metastasis (M)	
M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph node, normal serum LDH
M1b	Lung metastases, normal LDH
M1c	Metastasis to other visceral metastases with a normal LDH, or any distant metastases and an elevated LDH

Stage	Primary tumor (T)	Regional lymph nodes (N)	Distant metastasis (M)
Clinical staging*			
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1, N2, or N3	M0
Stage IV	Any T	Any N	M1
Pathologic staging*			
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-4a	N1a	M0
	T1-4a	N2a	M0
Stage IIIB	T1-4b	N1a	M0
	T1-4b	N2a	M0
	T1-4a	N1b	M0
	T1-4a	N2b	M0
	T1-4a	N2c	M0
Stage IIIC	T1-4b	N1b	M0
	T1-4b	N2b	M0
	T1-4b	N2c	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Clark Levels

- Level I - Confined to epidermis (in situ); not an invasive lesion
- Level II - Invasion of papillary dermis; invasion past basement membrane
- Level III - Papillary dermis filled by tumor and reticular dermis compressed, but not invaded
- Level IV - Invasion of reticular dermis; subcutaneous tissue not involved
- Level V - Invasion of subcutaneous tissue

Principles of Surgery

- Minimum margins:
 - Tis = 5mm, T1 = 1cm, T2-T4 = 2cm
- Risk of regional recurrence is 30-50% if:
 - ECE, ≥ 4 LN+, >3cm of LN involved,
Cervical LN+, cN+
- Odds of SLN+:
 - T1 = 5%, T2/T3 = 15-20%, T4 = 30-50%

Principles of Surgery

- If SLN+, then 20% likelihood of other regional LN+
- If SLN+, recommend completion dissection. If not, RT recommended

SLNB

- **Multicenter Selective Lymphadenectomy Trial (MSLT-I) (1994-2002)**
- Morton et al., NEJM 2006
- Prospective RCT
- 1,269pts with melanoma undergoing WLE randomized to:
 - SLNB, and if positive -> completion LND
 - Observation, and if clinical LN failure -> LND
- No difference in OS, or DSS
- However, 5yr DSS better for SLN+ patients (72%) vs observed pts who became cLN+ (p = .004)
- 5-yr OS was 90% if SLN- vs. 72% if SLN+
- Conclusion: SLNB is a valuable staging tool
- Open: MSLT-II – randomizes pts with SLNB+ to completion LND vs. obs.

Recommendations

Indications for Radiotherapy

- For the primary site:
 - R2, R1 or close margin
 - Recurrent disease
 - Perineural invasion

- For regional LNs:
 - ECE
 - LN \geq 3cm in size
 - \geq 4 involved LNs
 - Recurrent disease after LND
 - See ANZMTG 01.02/TROG 02.01

Studies

Adjuvant RT to Lymph Nodes

- Ballo et al. – MDACC – IJROBP 2006
- Retrospective
- 466pts with melanoma and +LN, s/p WLE and LND
- High risk features for inclusion:
 - ECE
 - LN \geq 3cm in size
 - \geq 4 involved LNs
 - Recurrent disease after LND
- RT was given as 6Gy x 5, at 2fx per week
- Median f/u 4.2 years

Adjuvant RT to Lymph Nodes

- 5-yr rate of freedom from regional failure in the nodal basin was 89%, which compares favorably to historical controls of an untreated high-risk group (50-70%)
- 5-yr distant-metastasis free survival was only 44%
- 5-yr rates of symptomatic lymphedema were ($p = .0001$):
 - Epitrochlear = 0%, cervical = 1%, axillary = 20%, inguinal = 27%

Dose Per Fraction

- Sause et al. – RTOG 83-05 – IJROBP 1991
- Prospective RCT
- 121 patients with melanoma (gross disease) treated with palliative intent
- Stratified by disease site
- Randomized to
 - 8Gy x 4fx, with 1fx per week
 - 2.5Gy x 20, with 5fx per week
- Electron or MV photons

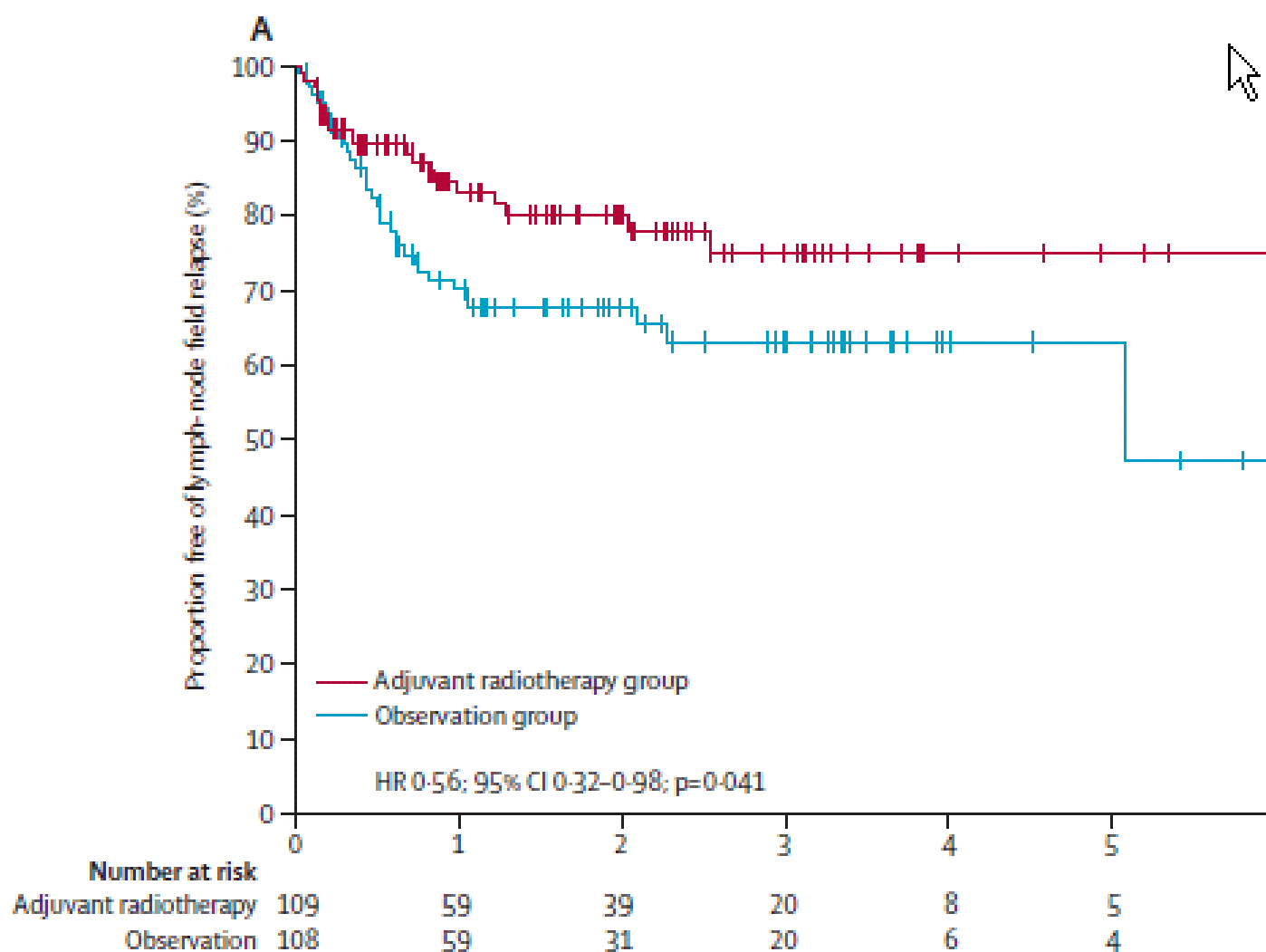
Table 4. Best response by tumor size and treatment arm

+	<5 cm		≥5 cm		All sizes		Total
	4 × 8.0 Gy	20 × 2.5 Gy	4 × 8.0 Gy	20 × 2.5 Gy	4 × 8.0 Gy	20 × 2.5 Gy	
Best response							
Complete	33.3%	28.6%	17.1%	19.4%	24.2%	23.4%	23.8%
Partial	18.0%	28.6%	48.6%	38.9%	35.5%	34.4%	34.9%
No change	33.3%	39.3%	34.3%	38.9%	33.9%	39.1%	36.5%
Progression	14.8%	3.6%		2.8%	6.5%	3.1%	4.8%
Total	27	28	35	36	62	64	126
CR + PR rate	0.52	0.57	0.66	0.58	0.60	0.58	

- No difference in response rate between the 2 dose schedule
- Study closed early due to statistical futility
- Grade 3/4 toxicity may have been higher in the 8Gy/fx arm (n=3/3) than the 2.5Gy/fx arm (n=4/0), although no statistical analysis was performed

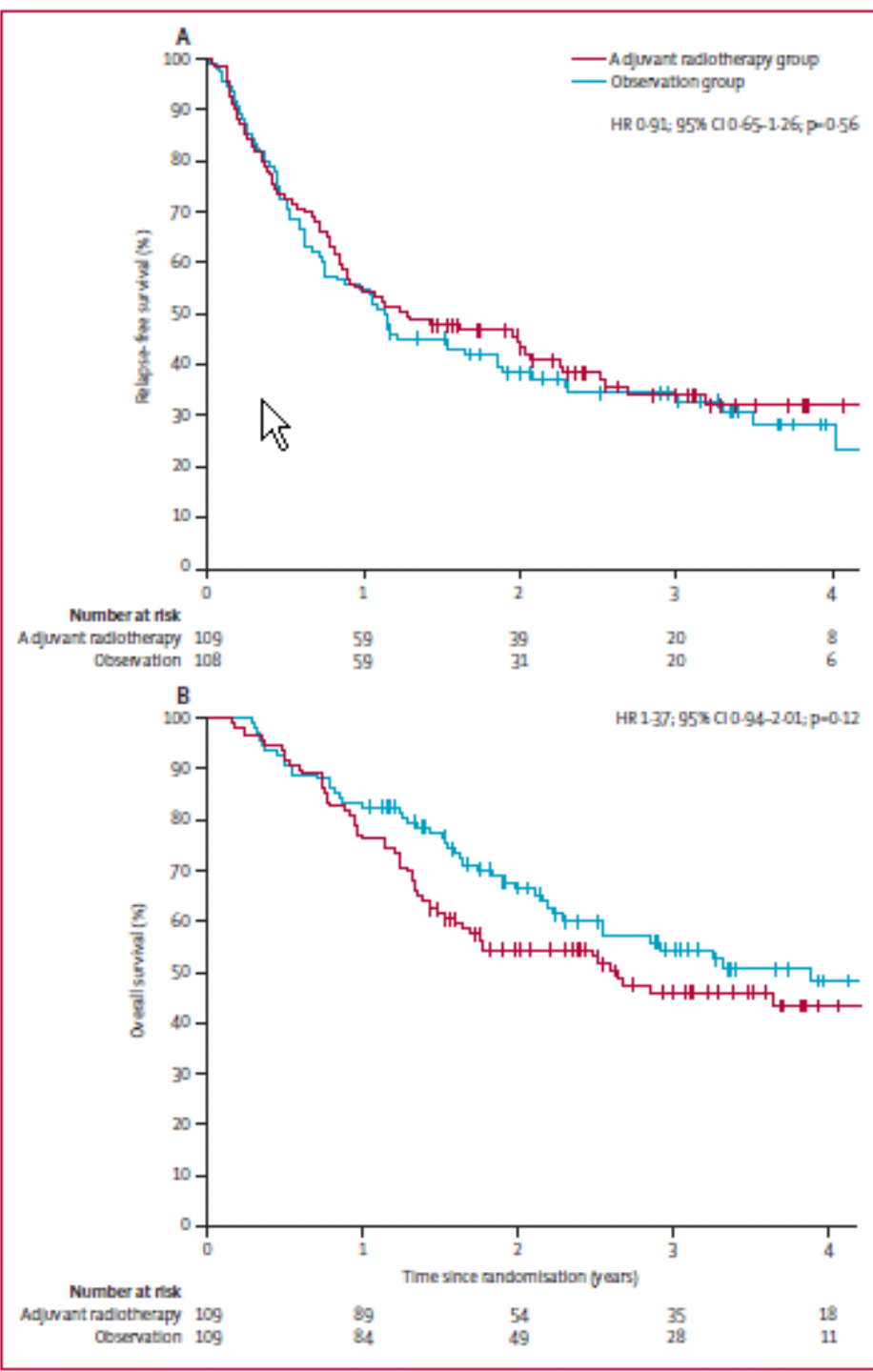
Adjuvant RT to Lymph Nodes

- **ANZMTG 01.02/TROG 02.01**
- Prospective RCT
- Burmeister et al. – Sydney – Lancet Oncology 2012
- RTOG 9302 (similar design) failed to accrue
- 217 pts with melanoma s/p WLE and LND
- Required at least one of the following:
 - ≥ 1 parotid LN
 - ≥ 2 cervical/axillary LNs
 - ≥ 3 inguinal LNs
 - ECE
 - Cervical LN ≥ 3 cm
 - Axillary/inguinal LN ≥ 4 cm
- RT was 2.4Gy x 20fx (as in the phase II TROG 96-06 study)
- Median f/u 40 months



RT improved regional control in intent-to-treat analysis (HR = .56, $p = .041$) and analysis by treatment received (HR = .47, $p = .005$)

RT did not affect
RFS or OS



	Head and neck		Axilla		Ilio-inguinal	
	Adjuvant radiotherapy group	Observation group	Adjuvant radiotherapy group	Observation group	Adjuvant radiotherapy group	Observation group
Related to surgery*						
Seroma	0	0	5	4	4	7
Wound infection	1	0	0	1	2	6
Nerve damage	1	1	0	0	0	0
Wound necrosis	0	0	0	0	0	1
Pain	0	0	0	0	0	1
Related to radiation therapy†						
Dermatitis	3	..	10	..	6	..
Pain	0	..	2	..	0	..

Based on the common toxicity criteria version 2.0.²² *At registration. †2 weeks after radiotherapy.

Table 4: Early adverse events (grade 3 and 4)

RT was generally well-tolerated

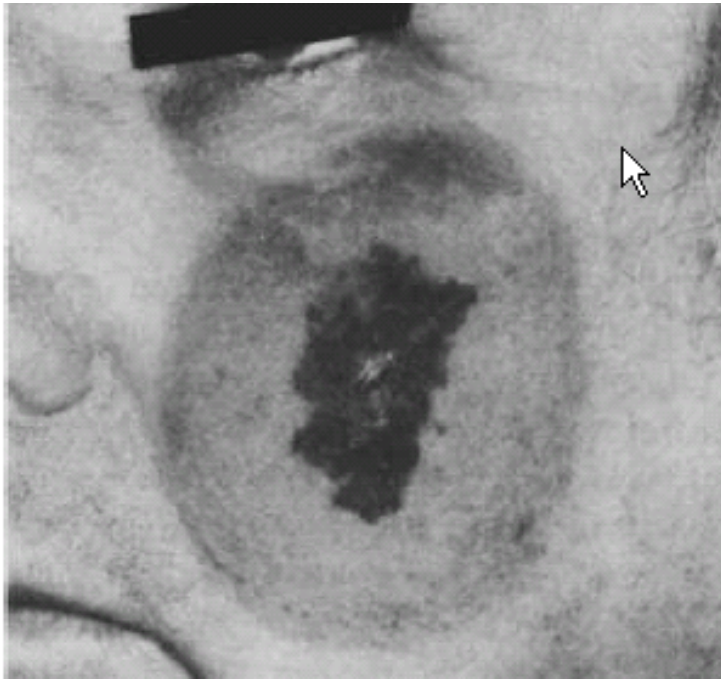
Treatment of the Primary Site

- Harwood et al. – Princess Margaret – Cancer 1981
- Retrospective
- 37 patients with nodular or superficial melanoma of H&N
- Indications:
 - R2 Margin
 - R1 or close margin
 - Recurrent disease
- Local control was 93% for microscopic disease, 67% for gross disease, and 12% for recurrent disease.
- Local control was higher with larger dose per fraction:
 - <4 Gy = 25% vs ≥ 4 Gy = 71%

Desmoplastic Melanoma

- Arora et al. – Univ. of Mich. – Cancer 2005
- Retrospective
- 65 patients with desmoplastic melanoma
- This was believed to be a subtype with high rate of local recurrence and LN involvement
- Treated with WLE alone (no adjuvant RT)
- Neurotropism was seen in 32% overall
- Local recurrence rate was 4% overall, contrary to prior series
- Of these cases of desmoplastic melanoma, LN involvement was seen in 4% of those without neurotropism vs. 28% of those with neurotropism.

Lentigo Maligna of the face



Emerging Topics: SBRT followed by IL-2

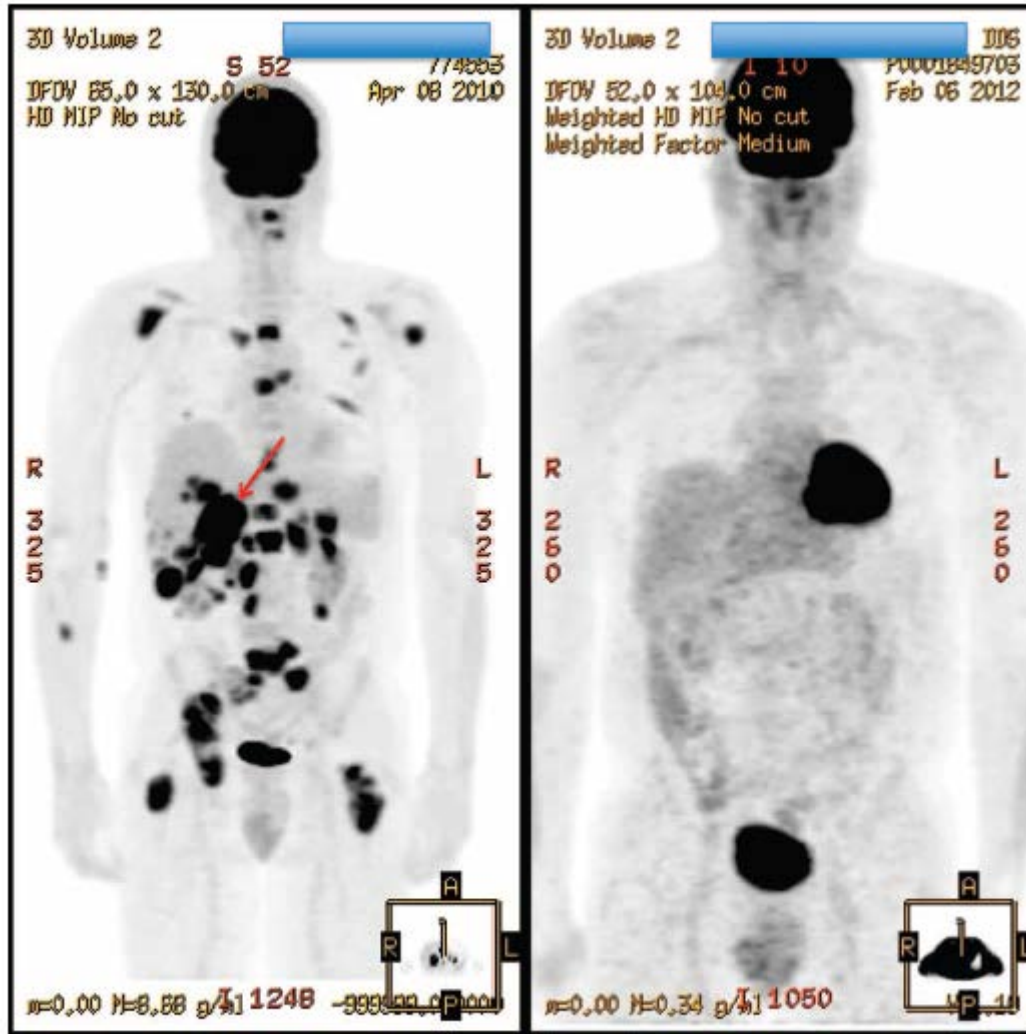


Fig. 2. Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

“Our 71% response rate is statistically significant because its 95% confidence interval does not include the historical response rate of IL-2 monotherapy in melanoma of 16% (2) (P = 0.05 with a power of 80%)”

- Additional References:

- Halperin, Perez & Brady “Principles and practice of Radiation Oncology” 5th ed.
- AJCC cancer staging handbook 7th ed.
- Hansen and Roach III “Handbook of evidence-based Radiation Oncology” 2nd ed.
- http://en.wikibooks.org/wiki/Radiation_Oncology
- Hall and Giaccia “Radiobiology for the radiologist” 6th ed.