



Mr Richard Martin

General Surgeon

Melanoma Unit Team

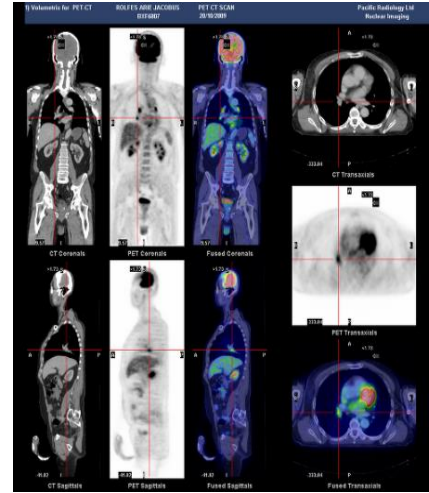
Waitemata District Health Board

Auckland

Friday, June 9, 2017

14:45 - 15:00 Surgery in the Era of Immune and Targeted Therapy

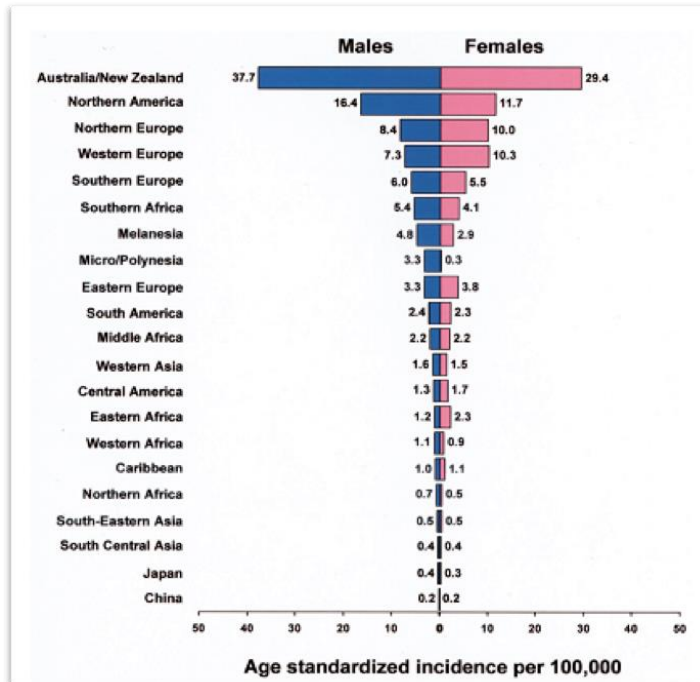
Surgery in the era of immune and targeted therapy



Mr Richard Martin

*Cutaneous Surgical Oncologist
Auckland*

World Melanoma Rates



Melanoma in NZ

- 2325 new cases of Melanoma in 2012 (2346 MIS)
- Most common cancer in
 - Males, age 25-40 yo
 - Females, age 15-24 yo
- Mortality (2013)
 - **Male 232***
 - Female 124

NZ Cancer Registry Data



Overall Survival Metastatic Melanoma

1-year OS Phase III Studies

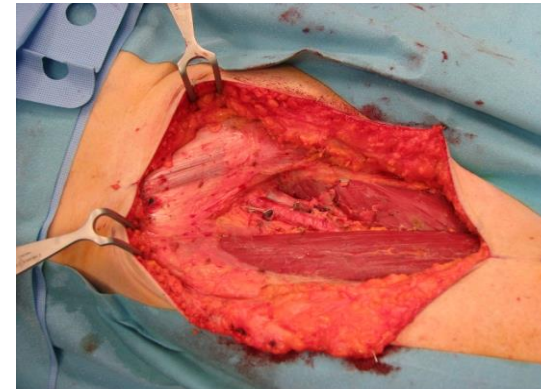
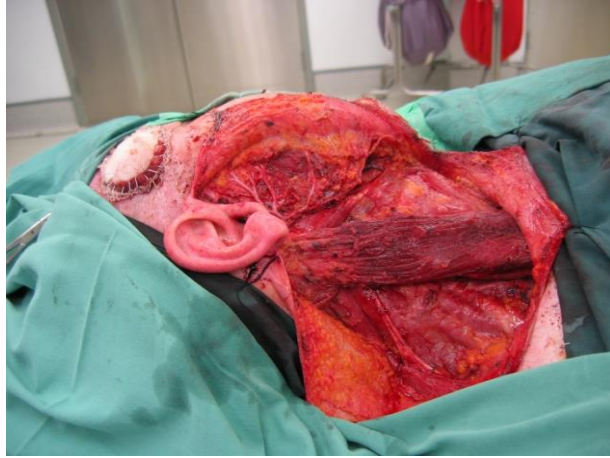


PRESENTED AT **ASCO ANNUAL MEETING '16**

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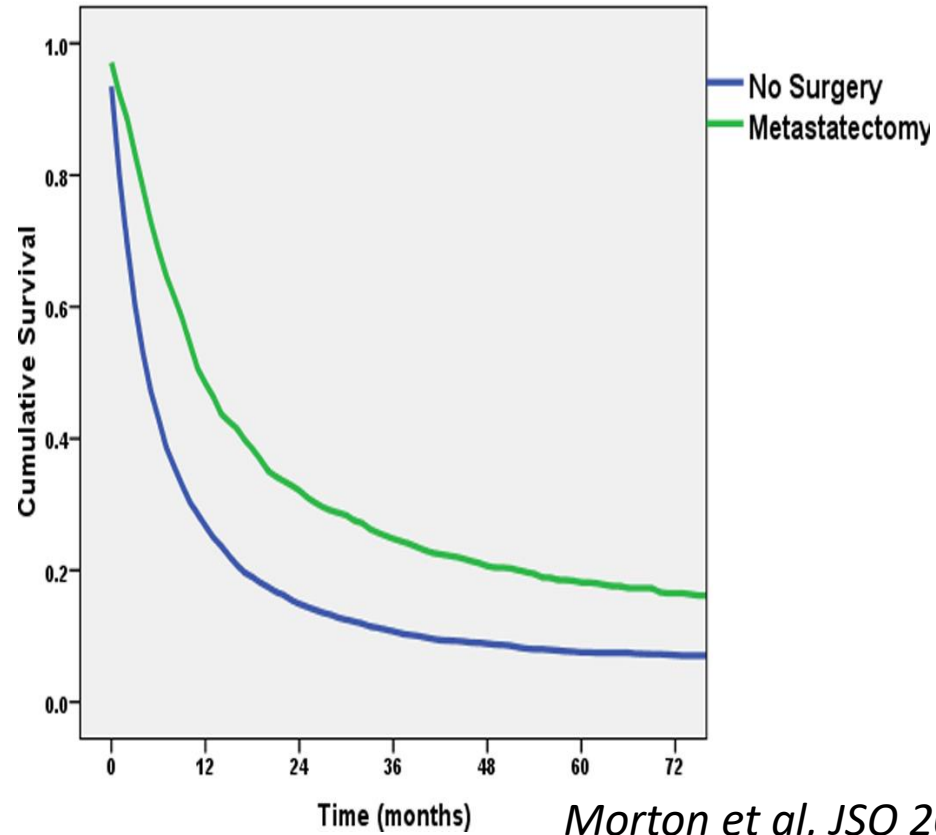
^a BRAF wt only. ^b Pooled pembrolizumab Q2W and Q3W 10mg/kg. ^c Pooled Dab + Tram data; Cobi=cobimetinib, Dab=dabrafenib; Ipi=ipilimumab; Nivo=nivolumab; Pembro=pembrolizumab; Tram=trametinib; Vem=vemurafenib.
Presented by Georgina V. Long

Is surgery still required ???



Surgical Metastatectomy

Metastatectomy vs. No Surgery



Morton et al, JSO 2011

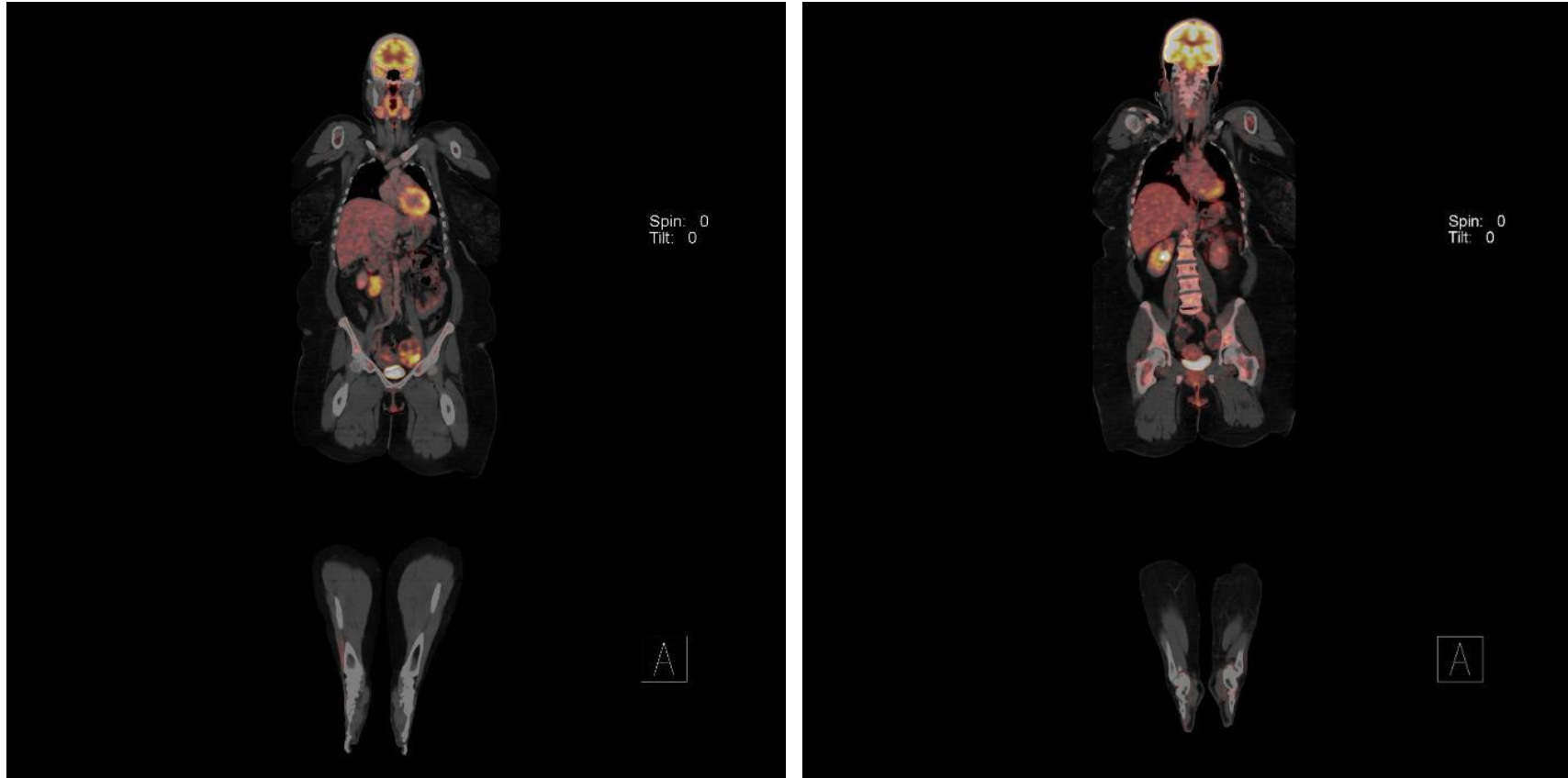


Future of Melanoma Surgical Oncology

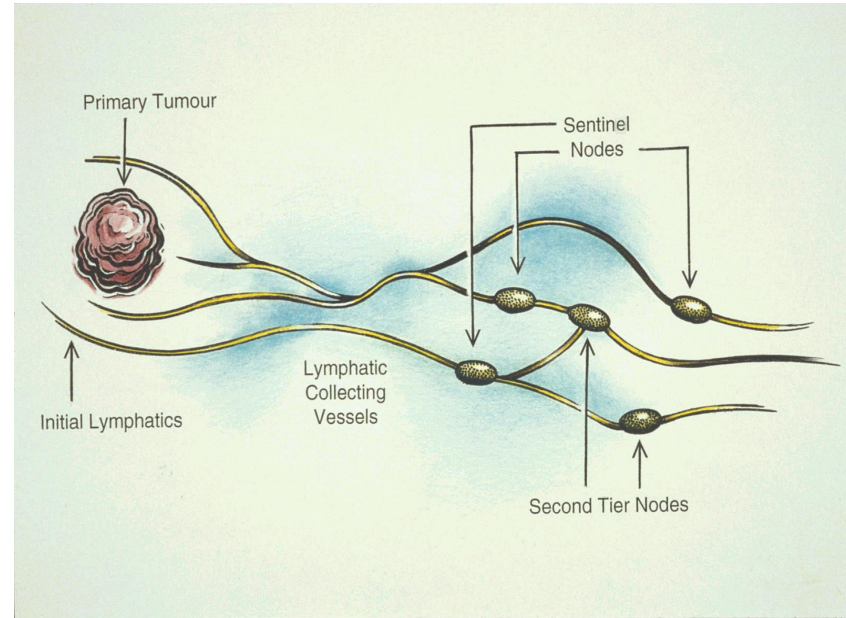
Adjuvant therapy

- DERMA immunotherapy trial (GSK)
 - Negative trial; MAGE-A3 Antigen-Specific Cancer Immunotherapeutic (ASCI) adjuvant vaccine, 2015
- EORTC 18071 (BMS) adjuvant ipilimumab vs placebo
 - 65% vs 54% five-year survival rate
 - 28% reduction of the relative risk of death (hazard ratio 0.72, $p=0.001$)
 - 52 per cent stopped due to adverse events, including five deaths
 - *ESMO 2016*
- COMBI-AD adjuvant BRAF/MEK study (GSK)
 - awaiting results in 2017
- EORTC adjuvant anti-PD-1 study (MK-3475-054 Study, MSD)
 - awaiting results in 2018.

Neo-adjuvant treatment-BRAF/MEK inhibitor



Node Based Management in Cutaneous Malignancies



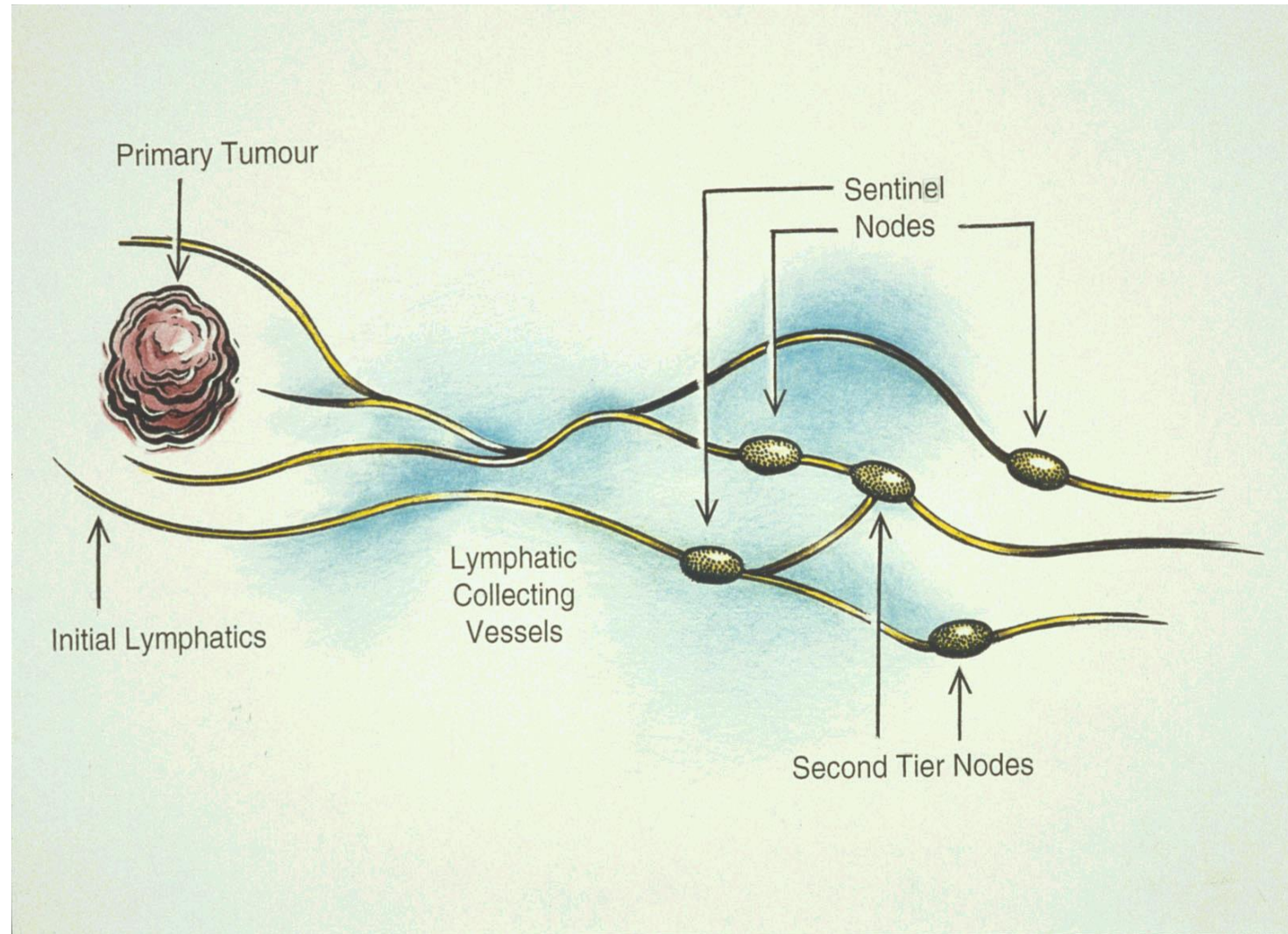
Richard CW Martin

Cutaneous Surgical Oncologist, Head/Neck and General Surgeon, Auckland, NZ

Sentinel node biopsy

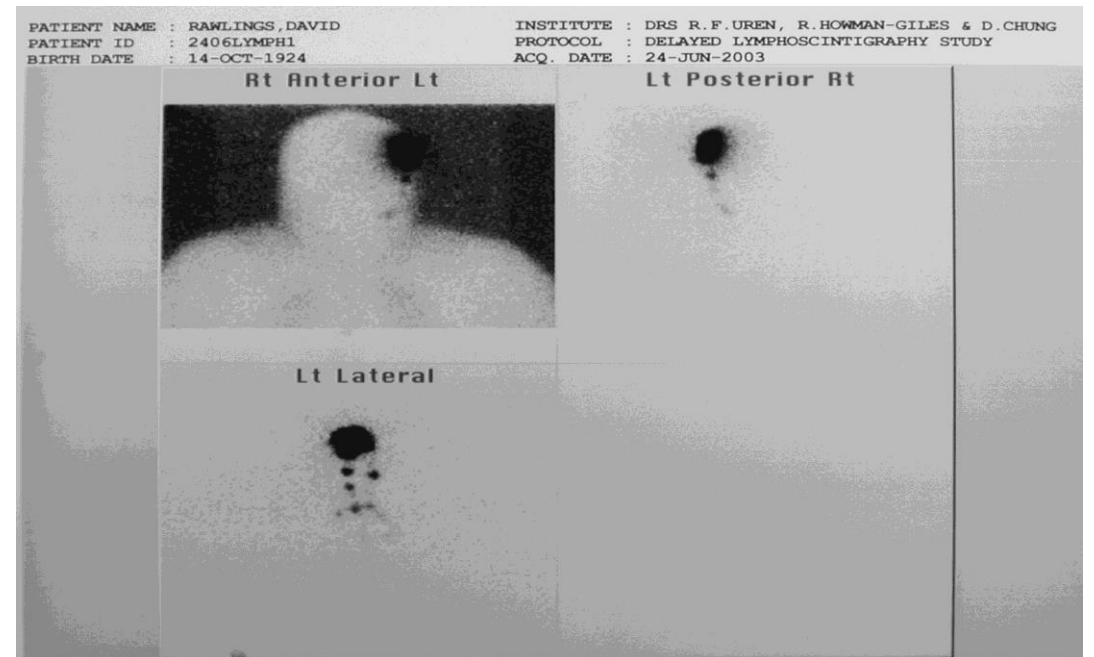
- Melanoma
- High risk cutaneous SCC
- Rare cutaneous malignancies

Sentinel Node Theory



Morton et al, Arch Surg 1992

Lymphoscintogram



DFOV 30.6 cm

S

DFOV 30.6 cm

S

R

L

A

P

-18.22

I

HWKCT + IRAC Coronals

A

DFOV 30.6 cm

R

L

-533.49

P

HWKCT + IRAC Transaxials

60.20

I

HWKCT + IRAC Sagittals



RAI

LPS

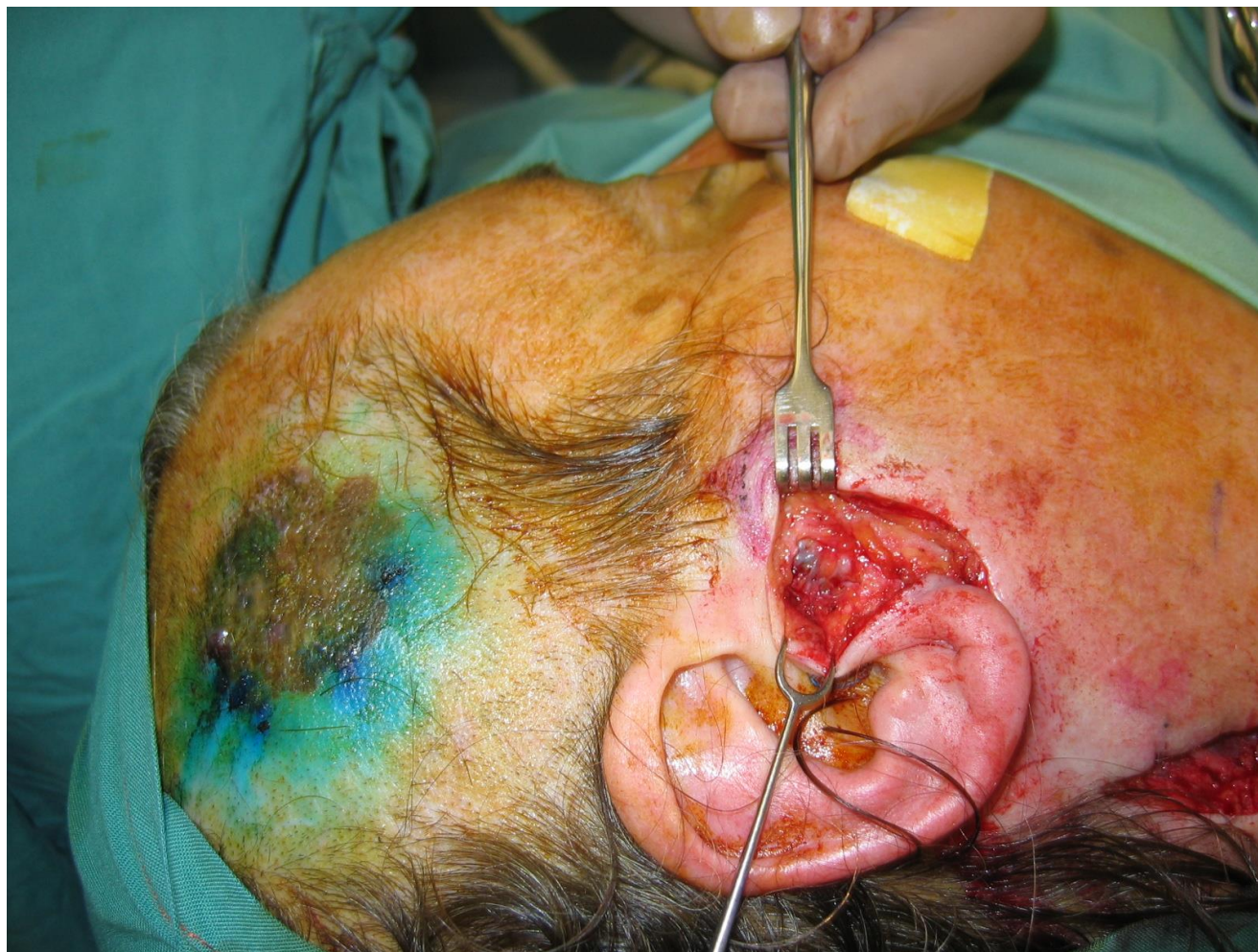
Solid Bone

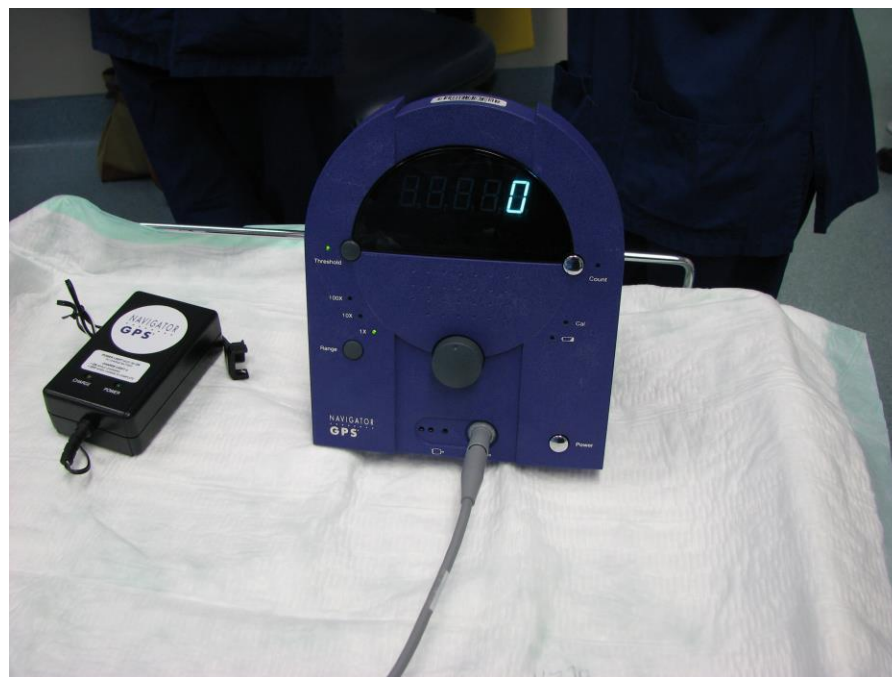
LIP

FUSED

HWKCT + IRAC 3D

1





MSLT-1

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

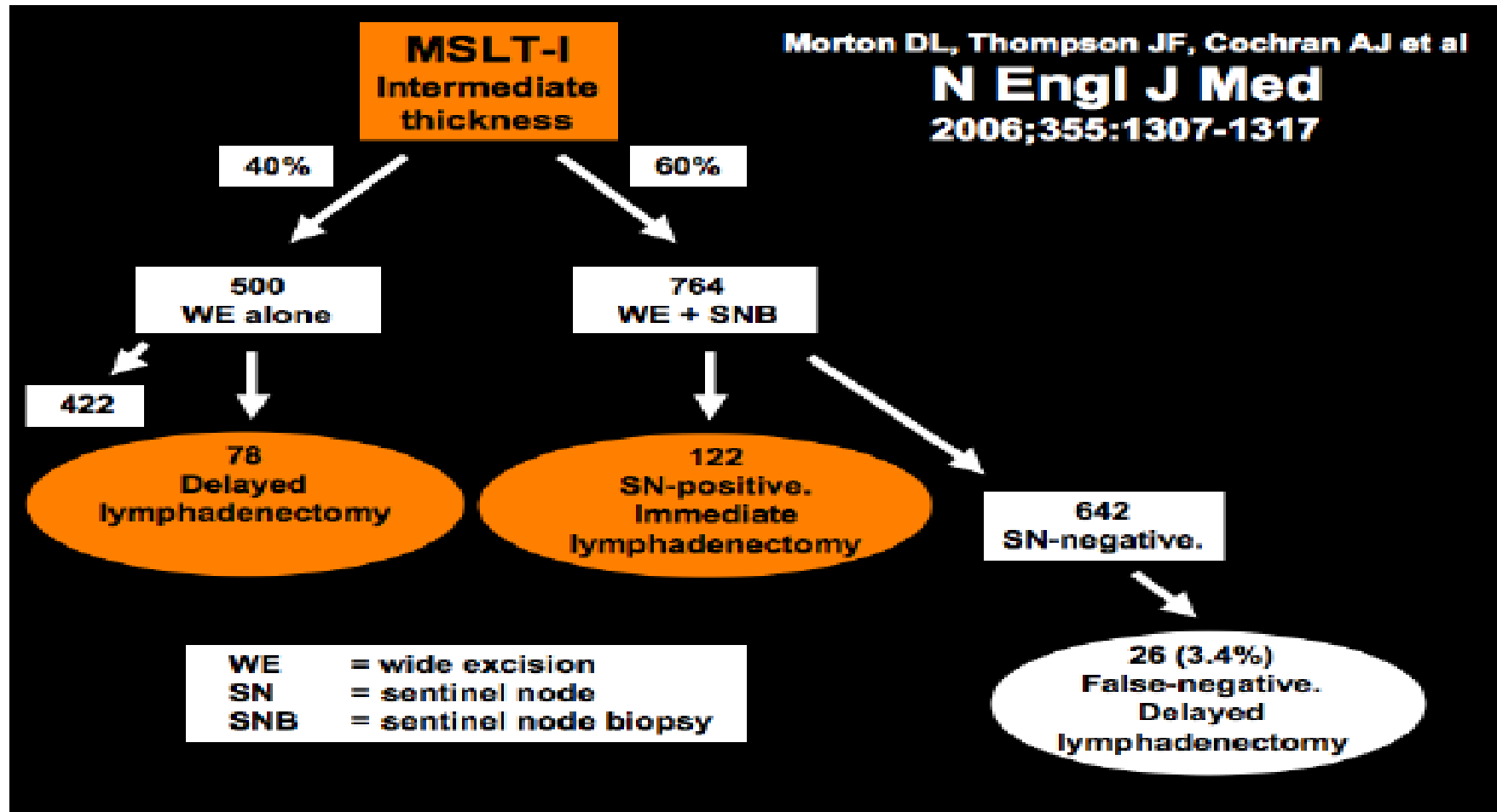
FEBRUARY 13, 2014

VOL. 370 NO. 7

Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma

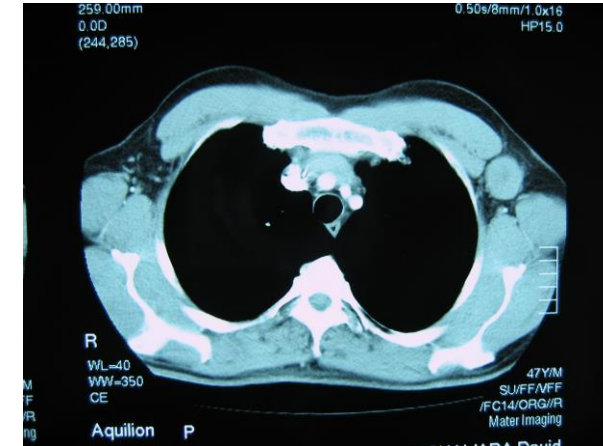
D.L. Morton, J.F. Thompson, A.J. Cochran, N. Mozzillo, O.E. Nieweg, D.F. Roses, H.J. Hoekstra,
C.P. Karakousis, C.A. Puleo, B.J. Coventry, M. Kashani-Sabet, B.M. Smithers, E. Paul, W.G. Kraybill,
J.G. McKinnon, H.-J. Wang, R. Elashoff, and M.B. Faries, for the MSLT Group*

Study Design



MSLT-1 Summary

- 10 year MSS-intermediate thickness group (prognosis) ($p < 0.001$)
 - SN +ve : 62.1%
 - SN -ve : 85.1%
- Regional recurrence ($p < 0.01$)
 - WEX + SNPT + CLND: 4%
 - WEX + CLND: 16%
 - Reduced relative risk of recurrence by 26%
- 10 years MSS in intermediate thickness group ($p < 0.01$)
 - WEX + SNPT + CLND: 62.1% (21.9%)
 - WEX + CLND: 41.5% (19.5%)
 - **Survival benefit of 20.6%**
 - Hazard Ratio 0.56
 - *No difference in all patients**
- No. of +ve Nodes ($p < 0.001$)
 - SNP + lymphadenectomy: 1.6
 - Delayed lymphadenectomy: 3.3



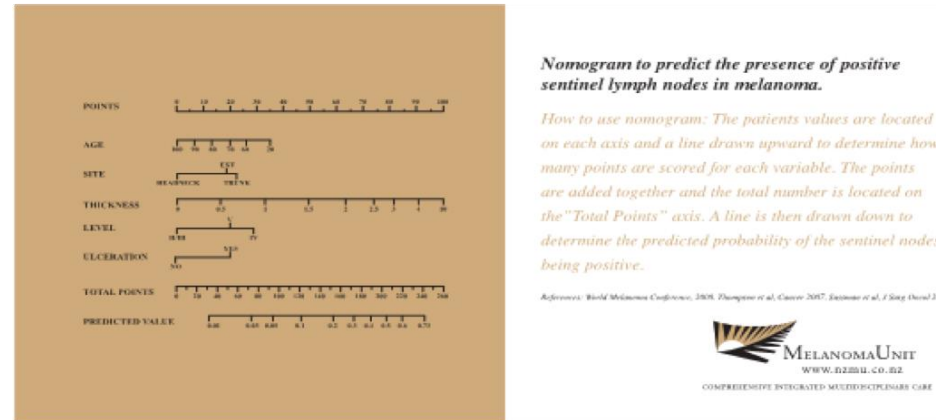
Complications of SNB

- MSLT-1
 - Total: 14.6%
 - Lymphoedema
 - 3.1% (cf 1.1% WEX only)
 - Seroma/haematoma
 - 5.5%
 - Infection
 - 4.6%
 - Other
 - 1.2%
 - Allergy to Patent Blue
Bye
 - 0.4%



Indications for SNB in Melanoma

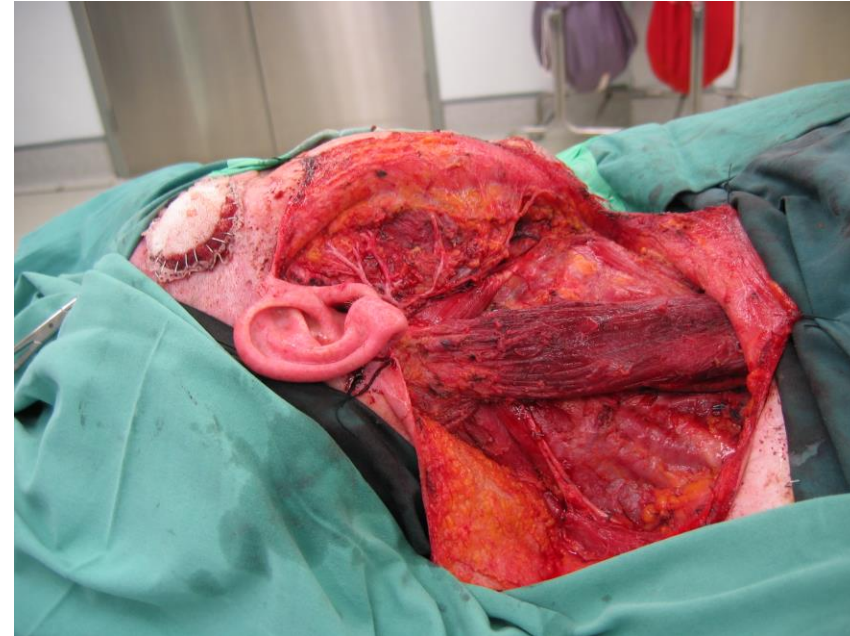
- > 1mm Breslow thickness
- 0.75mm to 0.99mm
 - Clark IV or V
 - Ulceration
 - High Mitotic count (>1)
 - >50% regression
 - < 35yo
- <0.75mm
 - 2.3% +ve nodes



SN+ve rate approx 10x Breslow depth

Sentinel Node Positive, Current Standard of Care

- PET-CT staging
 - For Macro metastases only
- Completion lymph node dissection**
- 3 monthly follow up





The NEW ENGLAND
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ESTABLISHED IN 1812

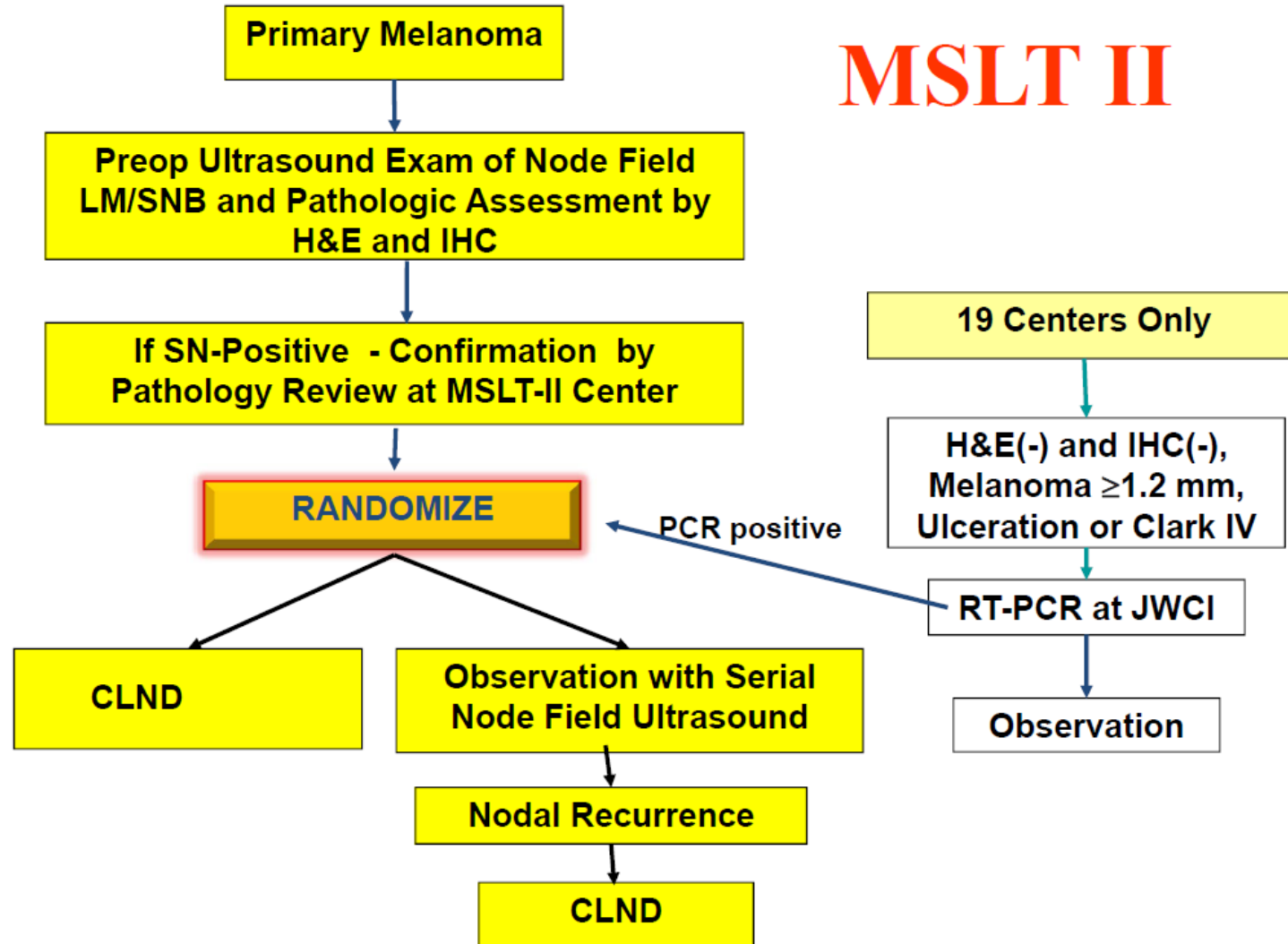
JUNE 8, 2017

VOL. 376 NO. 23

Completion Dissection or Observation for Sentinel-Node
Metastasis in Melanoma

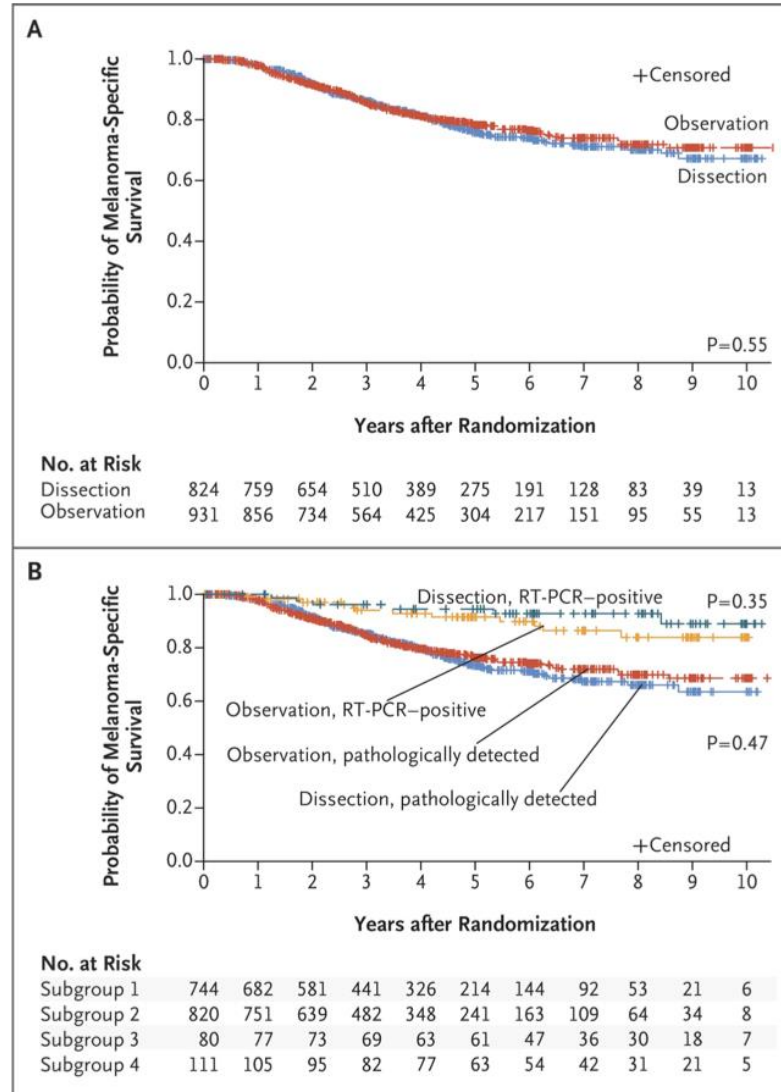
M.B. Faries, J.F. Thompson, A.J. Cochran, R.H. Andtbacka, N. Mozzillo, J.S. Zager, T. Jahkola, T.L. Bowles, A. Testori, P.D. Beitsch, H.J. Hoekstra, M. Moncrieff, C. Ingvar, M.W.J.M. Wouters, M.S. Sabel, E.A. Levine, D. Agnese, M. Henderson, R. Dummer, C.R. Rossi, R.I. Neves, S.D. Trocha, F. Wright, D.R. Byrd, M. Matter, E. Hsueh, A. MacKenzie-Ross, D.B. Johnson, P. Terheyden, A.C. Berger, T.L. Huston, J.D. Wayne, B.M. Smithers, H.B. Neuman, S. Schneebaum, J.E. Gershenwald, C.E. Ariyan, D.C. Desai, L. Jacobs, K.M. McMasters, A. Gesierich, P. Hersey, S.D. Bines, J.M. Kane, R.J. Barth, G. McKinnon, J.M. Farma, E. Schultz, S. Vidal-Sicart, R.A. Hoefler, J.M. Lewis, R. Scheri, M.C. Kelley, O.E. Nieweg, R.D. Noyes, D.S.B. Hoon, H.-J. Wang, D.A. Elashoff, and R.M. Elashoff

MSLT 2 trial design



MSLT 2 Summary

- Immediate completion lymph node dissection showed no survival benefit
 - Even subgroup analysis
 - No. of +ve nodes
 - Nodal tumour burden
- Non SN metastases detected by nodal dissection was only 11.5%
- Lymphoedema rate
 - 24.1% in CLND group
 - 6.3% in observation group



– What does this mean ?

- Only 11.5% of patients who had CLND had other positive nodes
- Just removing a positive SN provide a survival benefit ??
- Stage using SNB but observe or use adjuvant BRAF/MEK or Immunotherapy ?
- Reserve CLND for nodal recurrence after PET staging or treat systemically ?



Sentinel node biopsy in Melanoma Summary

- SNB provides crucial staging information for management planning:
 - Best staging procedure
 - Best prognostic information
 - Decreased regional recurrence rates with CLND
 - **No survival benefit with completion lymph node dissection***
 - New adjuvant treatments will affect survival and nodal status is mandatory prerequisite
 - Patients want to know!

Sentinel node biopsy in high risk cutaneous SCC



Lymph node metastases in Cutaneous SCC

- * Overall metastasis rate:
 - * 4.9%¹
 - * 3.7%²
 - * High risk cSCC over 20%
- * Overall survival: 96.9%
 - * Positive nodes: 46-70%
- * Recurrence rate after node dissection: up to 28%³
- * Distant metastatic disease, survival: 8-14 months³

¹ Brantsch KD et al. *Lancet Oncol.* 2008

² Brougham et al. *J Surg Oncol*; 2012;106:811–815

³ Australia CC. *Clinical Practice Guide: Basal cell carcinoma, squamous cell carcinoma (and related lesions) - a guide to clinical management in Australia.* 2008. November 2008



High risk cSCC

Risk factor	Metastatic likelihood ^{ref 11;13;20}
Size > 2cm	20-30 %
Invasion into subcutaneous fat (Depth $\geq$ 5mm)	16-45%
Poorly Differentiated	12-32%
Desmoplasia	12%
Perineural invasion	40-47%
Lymphovascular invasion	40%
Site: ear or lip	10-30%
Local Recurrence	25-62%
SCC in pre-existing scar	38%
Immunosuppression	13-20 %

Rowe et al, J Am Acad Derm 1992

Moore et al, Laryngoscope 2005

Brantsch et al, Lancet Oncol 2008

Results of SNB studies in cutaneous SCC

AUTHOR/YEAR	NO. OF PATIENTS	TUMOUR LOCATION	TECHNIQUE	% NODE POSITIVE
Civantos 2008	10	Face	Scintigraphy	10
Renzi 2007	22	Foot	Scintigraphy + Blue dye	4.5
Renzi 2007	83 (pooled analysis)	Various	Various	17
Ross 2006	85 (systematic review)	Various	Various	21
Nouri 2004	8	Face	Scintigraphy + Blue dye	12
Wagner 2004	11	Face	Scintigraphy + Blue dye	18
Michl 2003	11	Chest, leg	Scintigraphy + Blue dye	18
Reschly 2003	9	Various	Scintigraphy + Blue dye	44
Altinyollar 2002	20	Lower lip	Blue dye	17

Recent reviews:

- **Meta-analysis. Scmitt et al, Nov 2013**
 - SN +ve:12.3%
- **Systematic review. Mostafa et al, Nov 2013**
 - SN +ve:13.5%

7th edition TNM staging for cSCC**

(8th edition released Oct, 2016)

T1	≤ 2cm (< 2 HRF)
T2	> 2cm Any size with >2 HRF
T3	Deep structure invasion (muscle, bone, or cartilage)
T4	Skull base or axial skeleton
N1	Single lymph node ≤ 3cm
N2a	Single ipsilat node, 3-6cm
N2b	Multiple ipsilat nodes, <6cm
N2c	Multiple bilat or contralat nodes ≤ 6cm
N3	Any node > 6cm

- High risk factors (HRF)
 - > 2mm thickness
 - Clark level IV
 - Perineural invasion
 - Location on ear, non-glaborous lip
 - Poor, or un-differentiation

Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck

Sinclair M. Gore, MD, FRCS(Plast),^{1,2*} Douglas Shaw, BSc, MBBS,¹ Richard C. W. Martin, FRACS,^{1,3} Wendy Kelder, MD, PhD,^{1,4} Kathryn Roth, MD,^{1,5} Roger Uren, MD, FRACP,^{6,7} Kan Gao, BEng,¹ Sarah Davies, RN, BSc,¹ Bruce G. Ashford, FRACS,⁸ Quan Ngo, FRACS,⁹ Kerwin Shannon, FRACS,¹ Jonathan R. Clark, MBiostat, FRACS^{1,7,9}

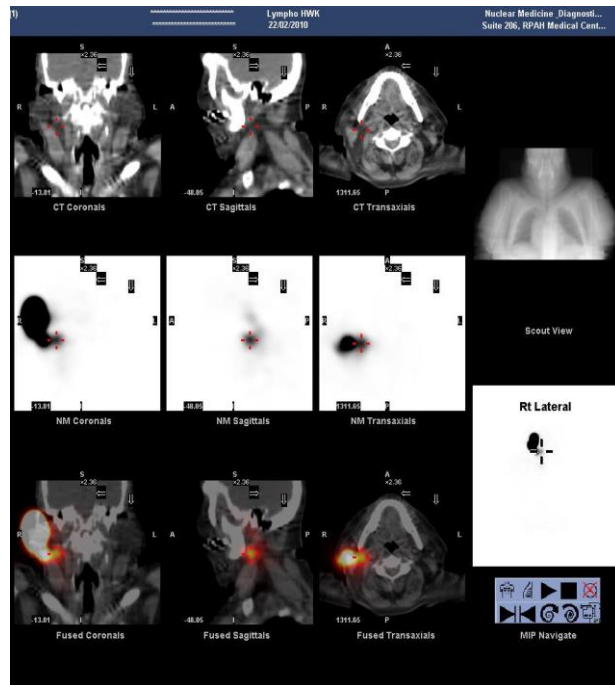
¹Sydney Head and Neck Cancer Institute, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia, ²Blenheim Head and Neck Cancer Centre, Oxford University Hospitals, Oxford, United Kingdom, ³Melanoma Unit, Waitemata Health and Auckland Regional Head and Neck Service, University of Auckland, Auckland, New Zealand, ⁴Department of Surgery, Martini Hospital, Groningen, The Netherlands, ⁵Department of Otolaryngology – Head and Neck Surgery, St. Joseph's Health Care, London, Ontario, Canada, ⁶Nuclear Medicine and Diagnostic Ultrasound, Royal Prince Alfred Hospital Medical Centre, Newtown, New South Wales, Australia, ⁷Sydney Medical School, University of Sydney, New South Wales, Australia, ⁸Wollongong Hospital, Wollongong, New South Wales, Australia, ⁹Liverpool Hospital, Liverpool, New South Wales, Australia.

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Surgery

Pre op Lymphoscintigraphy +/- SPECT / CT imaging



Intra-op blue dye & gamma probe SLNB



Observation of LN basin



SLNB negative



SLNB positive



Appropriate lymphadenectomy +/- RXT

Sentinel node biopsy in Cutaneous SCC summary

- SLNB in high risk cSCC has a 12-14% rate of a positive nodes
- SLNB is effective in identifying patients with occult lymph node disease in high risk cSCC.
- Multivariate analysis showed
 - Greater than 4 primary risk factors was a significant predictor of nodal disease.
 - Perineural invasion
 - Lymphovascular invasion

Gore et al, H&N, 2015

SNB in Rare Cutaneous Malignancies (RCM)

- Rare malignancies were defined by a low prevalence of < 5/100 000 (0.05%)

Epidermal	Rate /10yrs	Dermal	Rate /10 yrs
Pleomorphic carcinoma	5	Epithelioid cell sarcoma	11
Fibro-epithelial tumour of Pinkus	201	Malignant fibrous histiocytoma	113
Pilomatrix carcinoma	53	Dermatofibrosarcoma, NOS	1228
Adenoid cystic carcinoma	179	Liposarcoma, NOS	16
Merkel cell carcinoma	1515	Leiomyosarcoma, NOS	289
Skin Appendage carcinoma	387	Rhabdomyosarcoma, NOS	7
Sweat gland adenocarcinoma	176	Angiosarcoma	108
Apocrine adenocarcinoma	52	Malig. haemangioendothelioma	2
Sebaceous adenocarcinoma	713	Malig. Epithelioid haemangioendothelioma	1
Mucoepidermoid carcinoma	25	Neurofibrosarcoma	2
Mucinous adenocarcinoma	76		
Mixed tumour NOS			

Conclusions

- Sentinel node biopsy in cutaneous malignancies provides:
 - Important staging and prognostic information
 - Vital information for management planning
 - MSLT 2 result is practice changing, but needs thought
 - New adjuvant treatments will affect survival and nodal status is mandatory prerequisite
 - Patients want to know!

Thank you



COMPREHENSIVE INTEGRATED MULTIDISCIPLINARY CARE