The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2017

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Skin Cancer /Melanoma:Surgery

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No Disclosures

Presentation

- Be aware of the increasing Incidence of Melanoma
- Understand the changes in the Staging System
- Understand the Evaluation and importance of Prognostic Factors
- Be familiar with Treatment Management-
- Margins How Wide-Is their a consensus?
- Value of Sentinel Node-When,How and Why
- Management of the Neck
- Be aware of the Role of Adjunctive Treatments
- Radiation and Systemic therapy

Rising Incidence and Mortality of Melanoma in the US

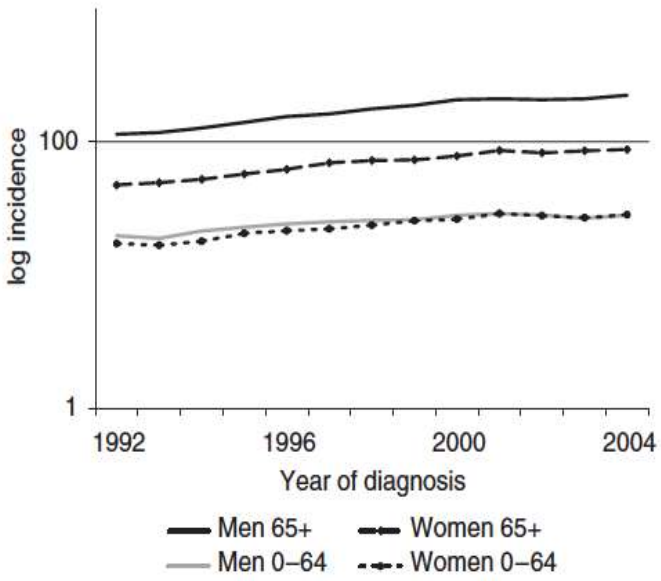


Figure 1. Age adjusted incidence of malignant melanoma per 100,000 according to age and sex 1992–2004. Note: Y axis is logarithmic scale.

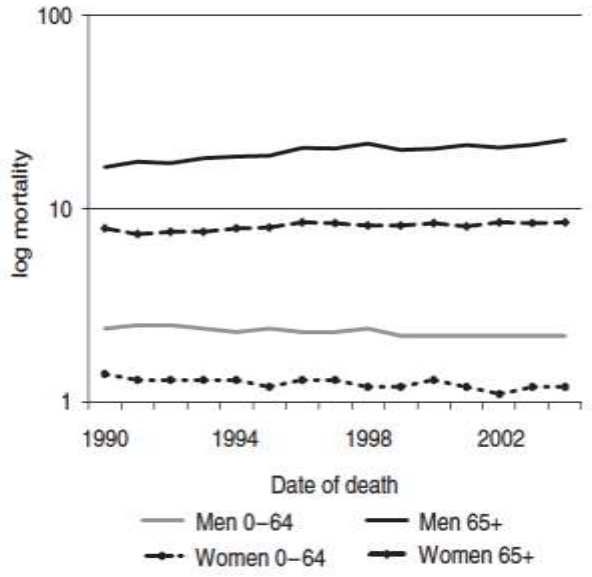
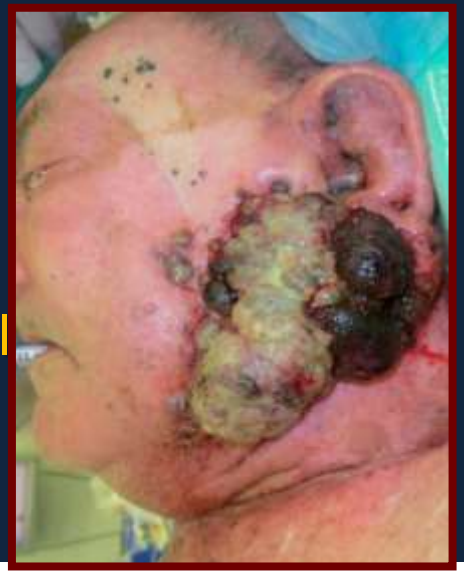


Figure 2. Age adjusted mortality rates from melanoma per 100,000 according to age and sex 1990–2004.

Linos, P et al 2009 J I Derm

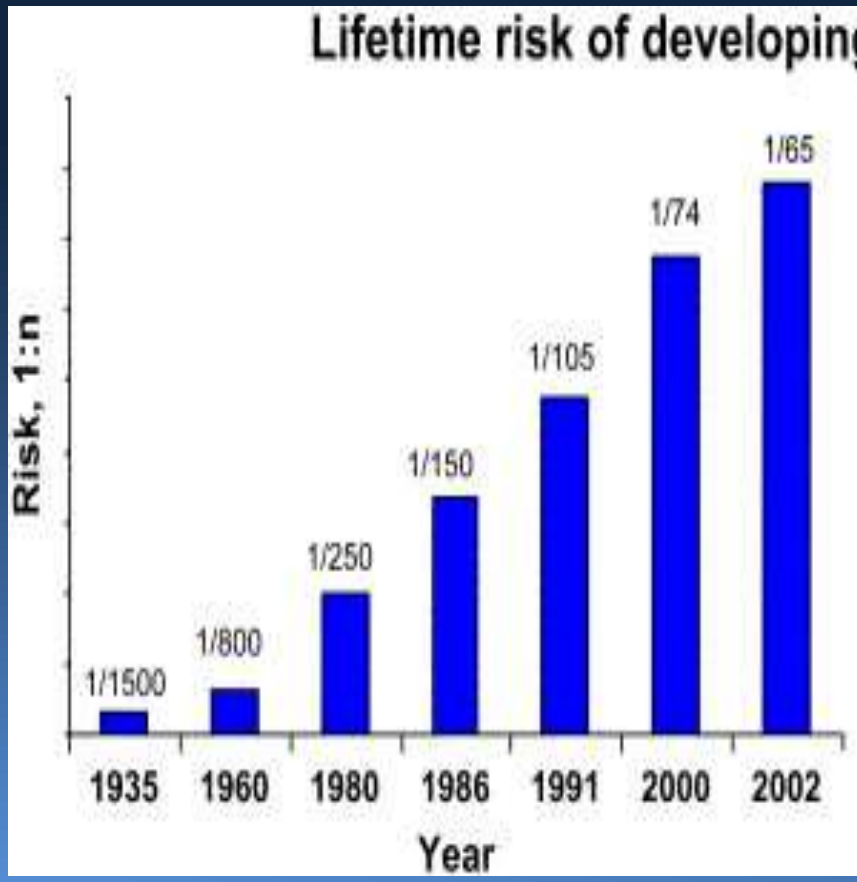
Increasing Incidence

- 2009: 68,000/year
- 2014: 76,100/year
  - lifetime risk of melanoma approximatel
  - 2.0% (1 in 50) for Caucasians



Males				Females		
Prostate	241,740	29%		Breast	226,870	29%
Lung & bronchus	116,470	14%		Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%		Colon & rectum	70,040	9%
Urinary bladder	55,600	7%		Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%		Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%		Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%		Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%		Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%		Ovary	22,280	3%
Pancreas	22,090	3%		Pancreas	21,830	3%
All Sites	**848,170**	**100%**		**All Sites**	**790,740**	**100%**

The Melanoma Epidemic



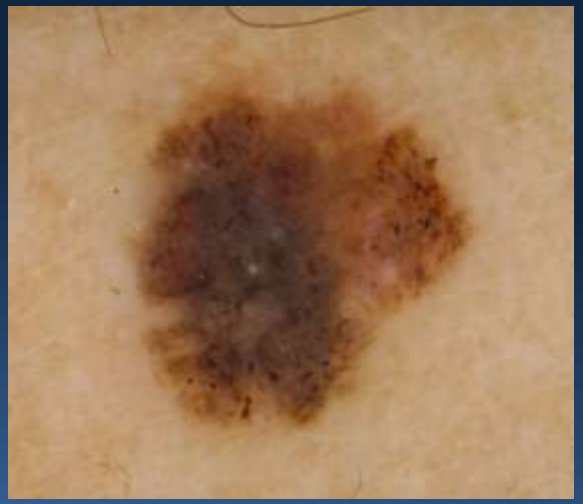
■ US population risk

Country	Lifetime risk, 2002
UK	1:147 (M), 1:117 (F)
USA	1:65
Australia	1:25 (M) 1:34 (F)

2017

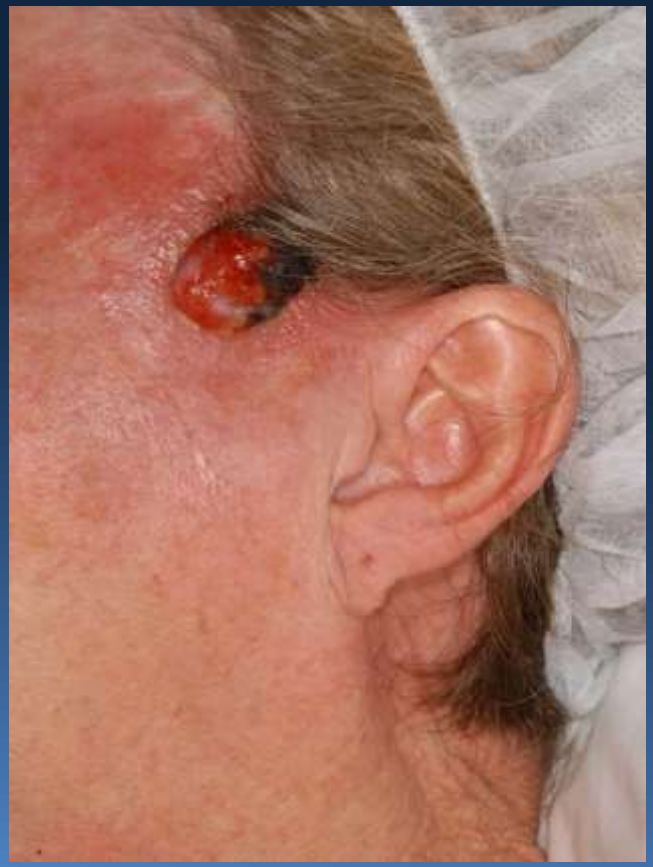
Case Scenario 1 in 2017

- M55
- SSM, 1.8mm
- Not ulcerated
- Clark IV
- Mitotic Rate $1/mm^2$



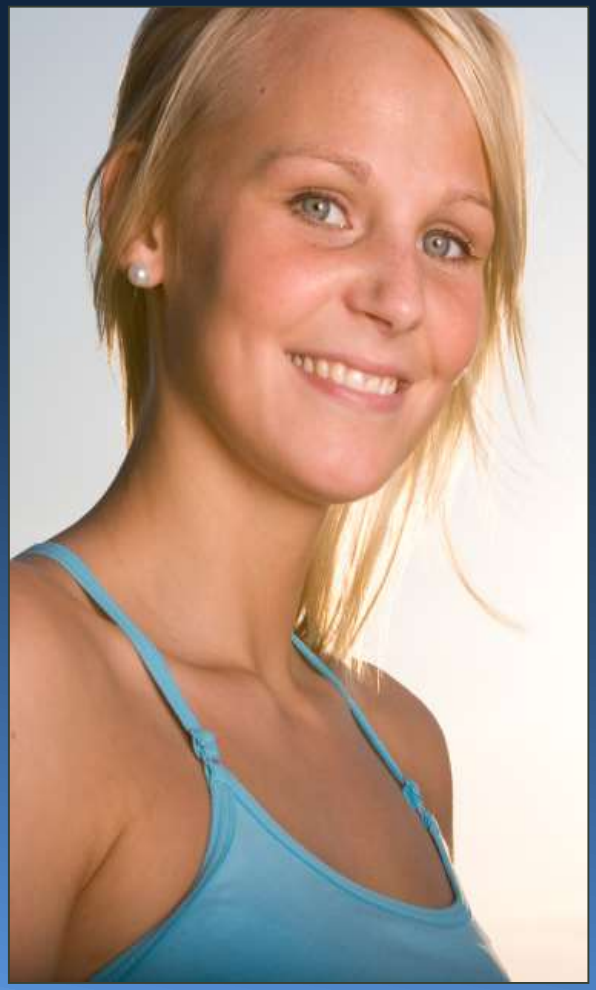
Case Scenario 2 in 2017

- F72
- NM, 7.5mm
- Ulcerated
- Clark V
- Mitotic Rate $7/mm^2$



Case Scenario 3 in 2017

- F17
- SSM, 0.75mm
- Not ulcerated
- Clark III
- Mitotic Rate $1/mm^2$



Introduction

- 15-20% of melanomas present in head and neck
  - 6-10% are mucosal melanomas
- Behaviour is more aggressive than at other sites
- Risk factors:
  - UV light exposure
  - childhood sunburns
  - fair skin
  - Immunosuppression
  - large congenital nevi
  - sporadic or inherited dysplastic nevi
  - genetic disposition
  - previous melanomas

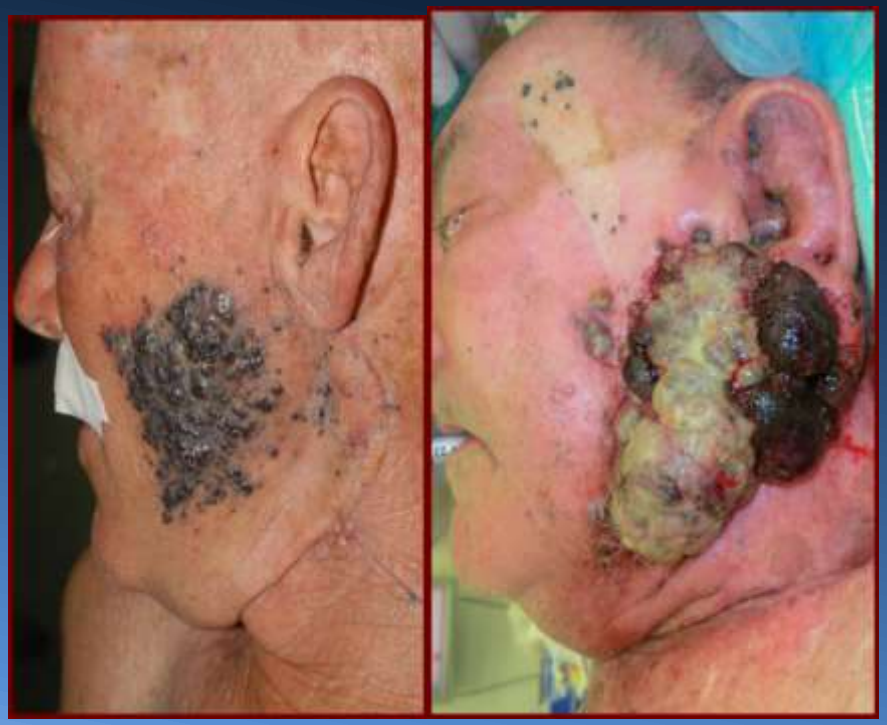
Cutaneous Head & Neck Melanoma

- Associated with Poorer Prognosis
  - ?influence of scalp primaries
- Risk of nodal metastases - thickness
  - <0.75mm Rare
  - 0.75 – 1mm ~5%
  - 1 – 4 mm 8 – 30%
  - >4mm ~40%

Head & Neck Melanoma

- Most succumb from systemic disease despite regional control
  - Relative Absence of effective systemic agents

- Loss of disease control
  - Anatomical
  - Aesthetic
  - Functional



Staging-7th now 8th edition

Staging

TNM staging categories for cutaneous melanoma (seventh edition)

T Classification	Thickness	Ulceration Status
Tis	NA	NA
T1	≤1.00 mm	a: without ulceration and mitosis <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

N Classification	# of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: micrometastasis[a] b: macrometastasis[b]
N2	2–3	a: micrometastasis[a] b: macrometastasis[b] c: in transit met(s)/satellite(s) without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M Classification	**Site**	**Serum LDH**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

AJCC Staging And Survival

Table 3. Survival Rates for Melanoma TNM and Staging Categories

Pathologic Stage	TNM	Thickness (mm)	Ulceration	No. + Nodes	Nodal Size	Distant Metastasis	No. of Patients	Survival ± SE			
								1-Year	2-Year	5-Year	10-Year
IA	T1a	1	No	0	–	–	4,510	99.7 ± 0.1	99.0 ± 0.2	95.3 ± 0.4	87.9 ± 1.0
IB	T1b	1	Yes or level IV, V	0	–	–	1,380	99.8 ± 0.1	98.7 ± 0.3	90.9 ± 1.0	83.1 ± 1.5
	T2a	1.01-2.0	No	0	–	–	3,285	99.5 ± 0.1	97.3 ± 0.3	89.0 ± 0.7	79.2 ± 1.1
IIA	T2b	1.01-2.0	Yes	0	–	–	958	98.2 ± 0.5	92.9 ± 0.9	77.4 ± 1.7	64.4 ± 2.2
	T3a	2.01-4.0	No	0	–	–	1,717	98.7 ± 0.3	94.3 ± 0.6	78.7 ± 1.2	63.8 ± 1.7
IIB	T3b	2.01-4.0	Yes	0	–	–	1,523	95.1 ± 0.6	84.8 ± 1.0	63.0 ± 1.5	50.8 ± 1.7
	T4a	> 4.0	No	0	–	–	563	94.8 ± 1.0	88.6 ± 1.5	67.4 ± 2.4	53.9 ± 3.3
IIC	T4b	> 4.0	Yes	0	–	–	978	89.9 ± 1.0	70.7 ± 1.6	45.1 ± 1.9	32.3 ± 2.1
IIIA	N1a	Any	No	1	Micro	–	252	95.9 ± 1.3	88.0 ± 2.3	69.5 ± 3.7	63.0 ± 4.4
	N2a	Any	No	2-3	Micro	–	130	93.0 ± 2.4	82.7 ± 3.8	63.3 ± 5.6	56.9 ± 6.8
IIIB	N1a	Any	Yes	1	Micro	–	217	93.3 ± 1.8	75.0 ± 3.2	52.8 ± 4.1	37.8 ± 4.8
	N2a	Any	Yes	2-3	Micro	–	111	92.0 ± 2.7	81.0 ± 4.1	49.6 ± 5.7	35.9 ± 7.2
	N1b	Any	No	1	Macro	–	122	88.5 ± 2.9	78.5 ± 3.7	59.0 ± 4.8	47.7 ± 5.8
	N2b	Any	No	2-3	Macro	–	93	76.8 ± 4.4	65.6 ± 5.0	46.3 ± 5.5	39.2 ± 5.8
IIIC	N1b	Any	Yes	1	Macro	–	98	77.9 ± 4.3	54.2 ± 5.2	29.0 ± 5.1	24.4 ± 5.3
	N2b	Any	Yes	2-3	Macro	–	109	74.3 ± 4.3	44.1 ± 4.9	24.0 ± 4.4	15.0 ± 3.9
	N3	Any	Any	4	Micro/macro	–	396	71.0 ± 2.4	49.8 ± 2.7	26.7 ± 2.5	18.4 ± 2.5
IV	M1a	Any	Any	Any	Any	Skin, SQ	179	59.3 ± 3.7	36.7 ± 3.6	18.8 ± 3.0	15.7 ± 2.9
	M1b	Any	Any	Any	Any	Lung	186	57.0 ± 3.7	23.1 ± 3.2	6.7 ± 2.0	2.5 ± 1.5
	M1c	Any	Any	Any	Any	Other Visceral	793	40.6 ± 1.8	23.6 ± 1.5	9.5 ± 1.1	6.0 ± 0.9
Total							17,600				

AJCC 7th edition Staging Changes - Reasons

- Importance of Breslow thickness (Clark's level only has a role in tumours < 1mm deep)
- Importance of *ulceration and mitotic rate*
- Importance of in-transit and satellite lesions
- Based on a belief that micrometastatic disease better than clinically enlarged nodes
- Number of nodes *not size* important

AJCC 8th edition Staging Changes - Reasons

Cutaneous Melanoma

- pT1a and pT1b categories introduced
  - pT1a ≤ 0.8mm
  - pT1b > 0.8mm -1mm

- M category
  - M1a Skin, subcutaneous tissue or non regional lymph nodes
  - M1b Lung
  - M1c Other non-central nervous system sites
  - M1d Central nervous system
- M Category modified by elevated or non-elevated LDH
- Stage Revised

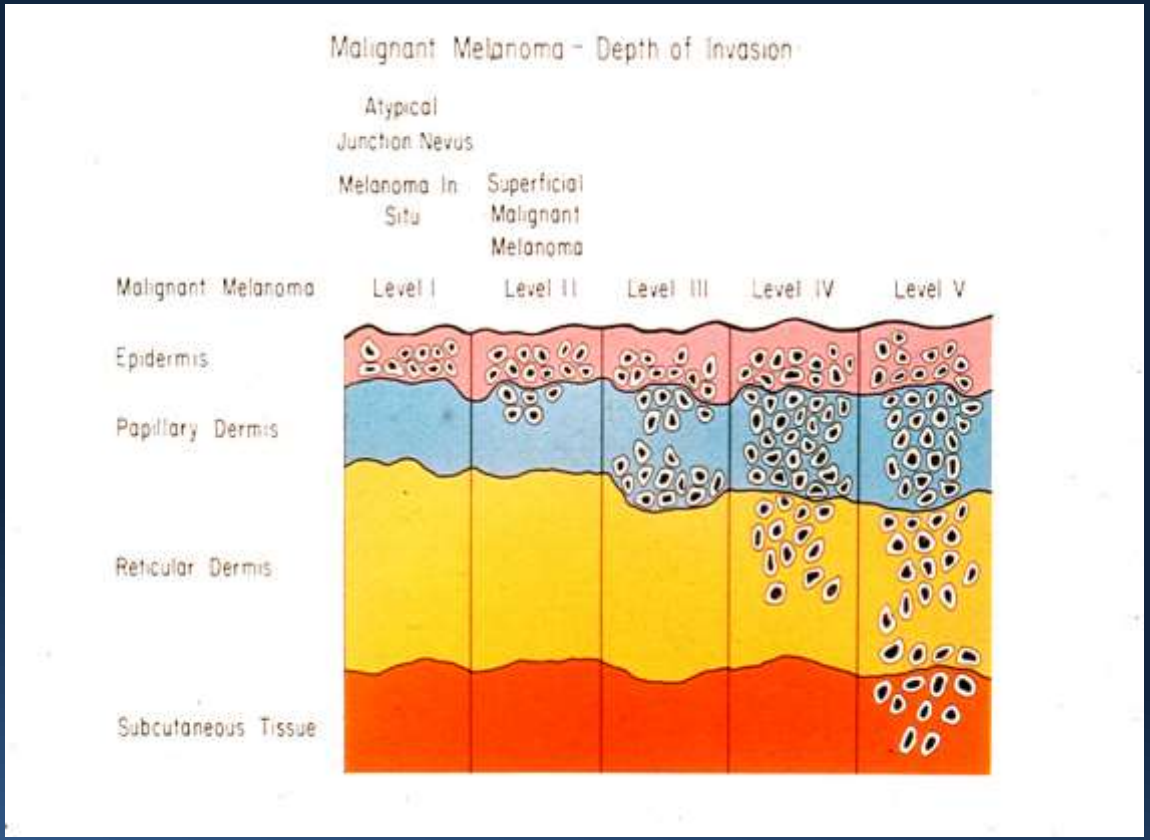
Workup prior to definitive treatment?

Investigations for Melanoma

- Primary
  - Routine investigations are not required for asymptomatic patients
- Locoregional
  - +ve SNB – routine investigations are not indicated in the absence of systemic symptoms
  - Macroscopic nodes – CT +/- PET for symptoms, or in cases where change of management may result
  - FNA to confirm stage III disease
- Systemic
  - CT, MRI, PET, serum LDH for symptoms suggestive of systemic disease
  - Further investigations as indicated by treatment

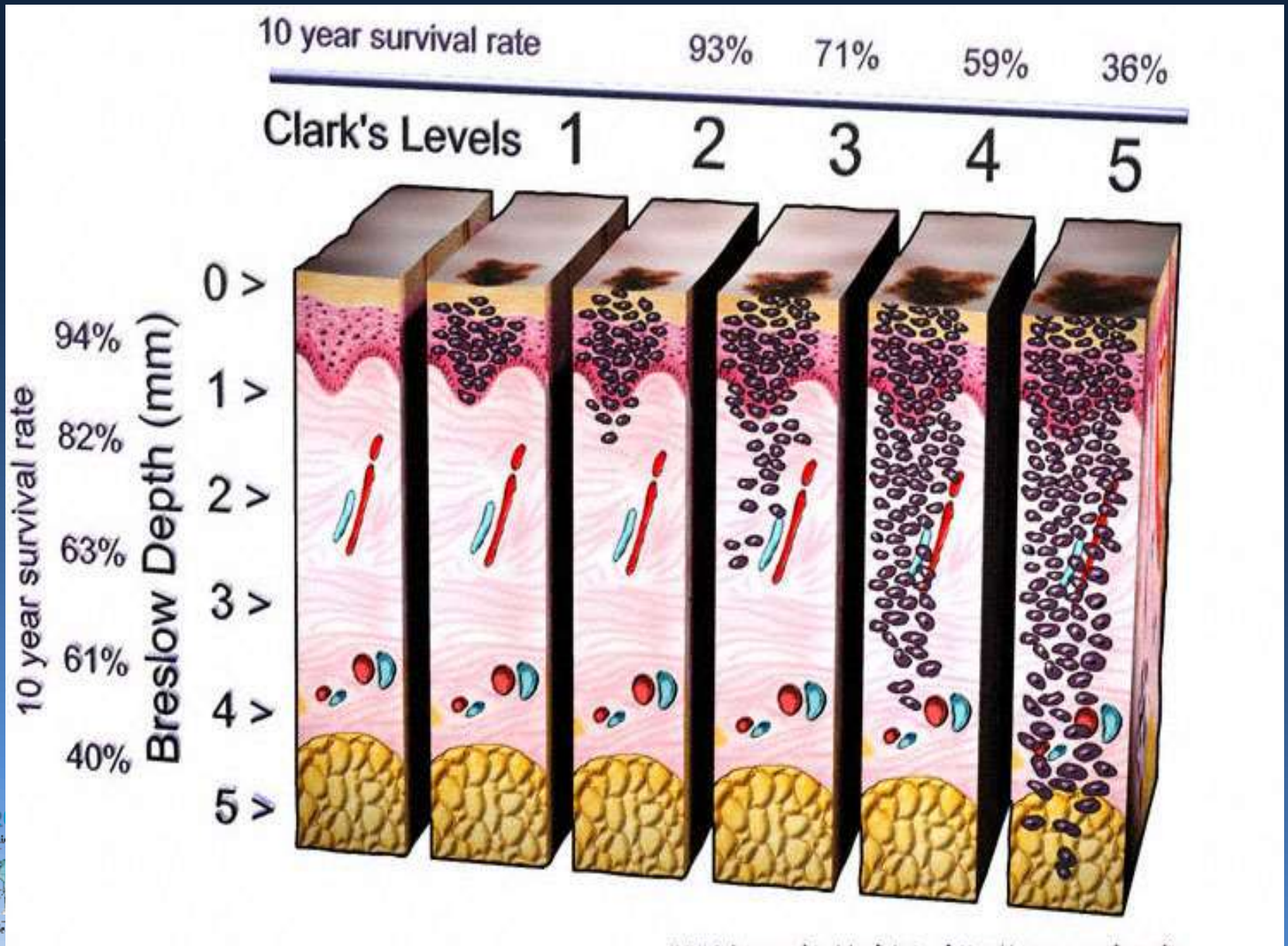
Diagnosis

- ABCD(E)'s Of Melanoma:
  - Asymmetry, border, colour variegation, diameter >6mm, evolution
  - Bleeding, ulceration, tingling
- Full-thickness, excisional biopsy of suspicious lesions
- Tumour markers: HMB-45, S-100



Level	Anatomical Invasion
Level 1	Melanoma confined to the epidermis (melanoma in situ)
Level 2	Invasion into the papillary dermis
Level 3	Invasion to the junction of the papillary and reticular dermis
Level 4	Invasion into the reticular dermis
Level 5	Invasion into the subcutaneous fat

10 Year survival Rates



Prognostic Factors

- Clinical prognostic Factors
  - Older age
  - Male
  - Head and neck site
- Histologic prognostic factors
  - Nodal metastases
  - Tumor thickness/depth
  - Ulceration
  - Vascular invasion
  - Microsatellite lesions

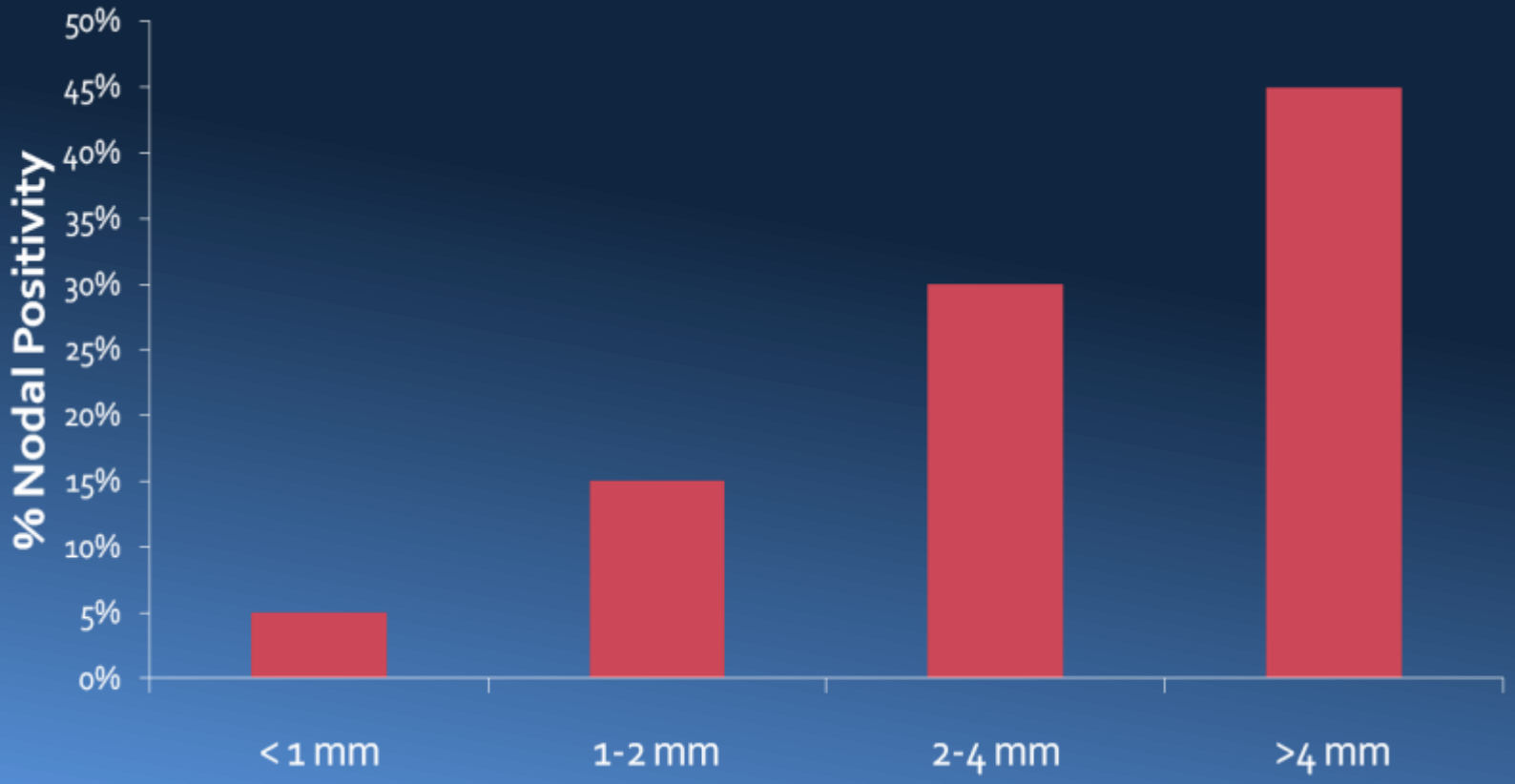
Prognostic Factors:
Nodal metastases

- Single most powerful predictor of recurrence and survival
- Occurs in 15-20% of patients
- Decreases survival by 40%-50% independent of other prognostic factors

- Increases with increasing tumor thickness

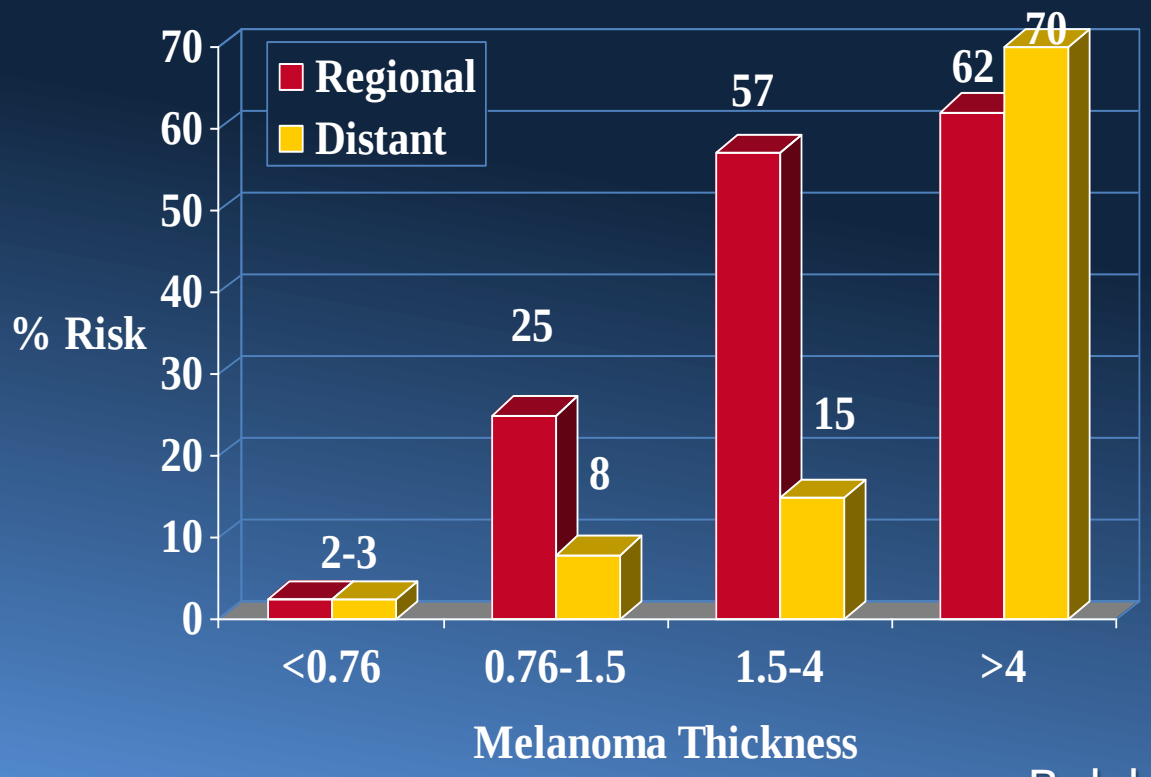
Thin (T1)	< 1.0mm	~ 2-5% risk
Intermediate (T2)	1.01-2.0 mm	~ 15%-25%
Intermediate (T3)	2.01-4.0 mm	~ 30%
Thick (T4)	> 4.0 mm	~ 45%

Risk Of Nodal Metatasis



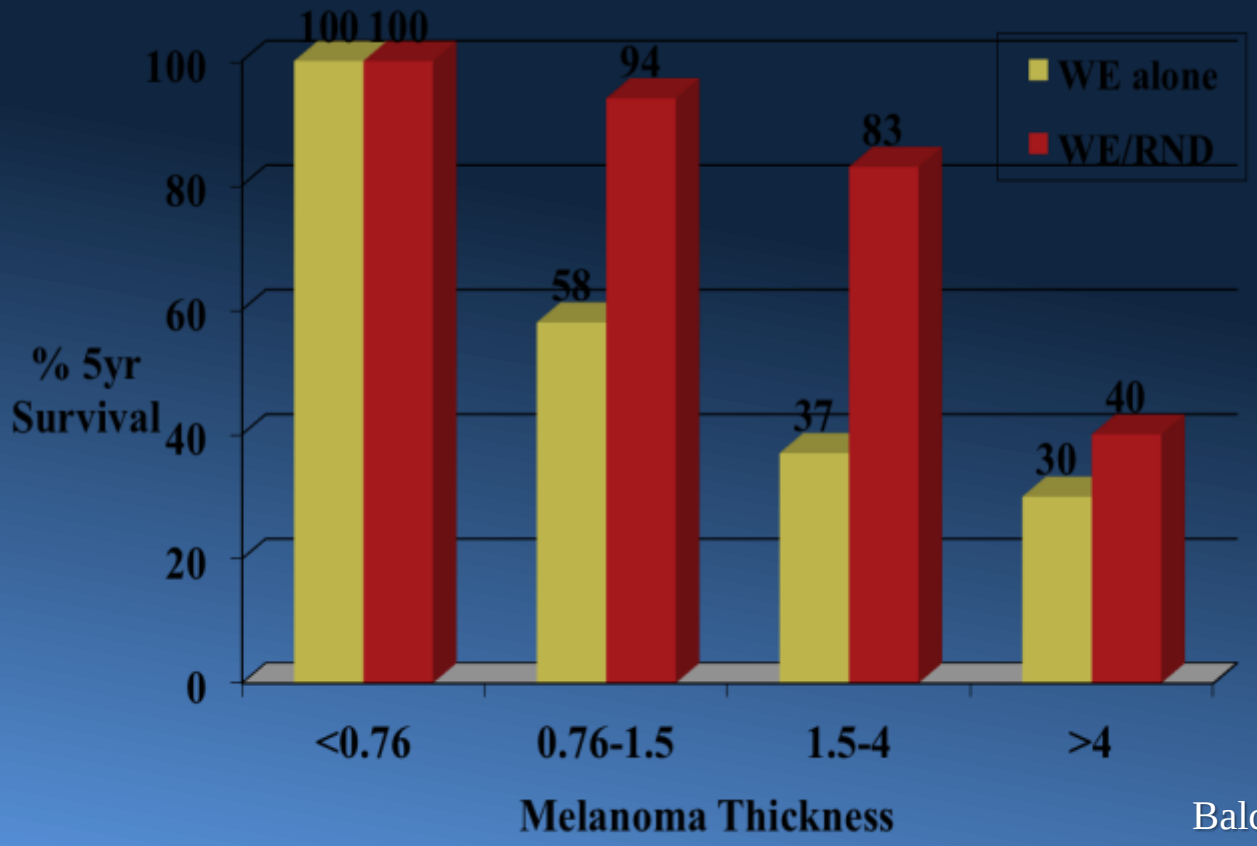
McMasters K, et al. Surgery 2001

Rationale for ELND



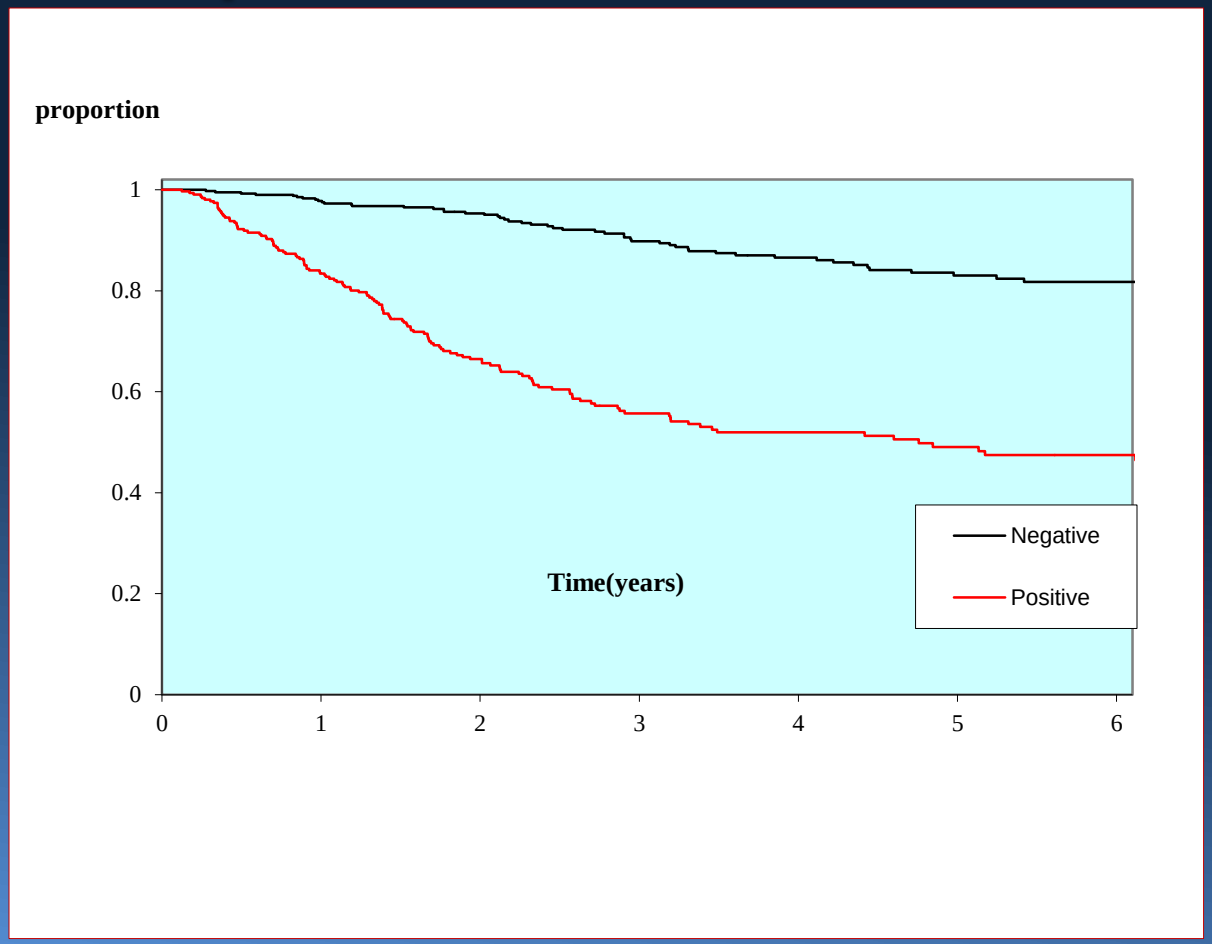
Balch 1980

Rationale for ELND



Balch 1979

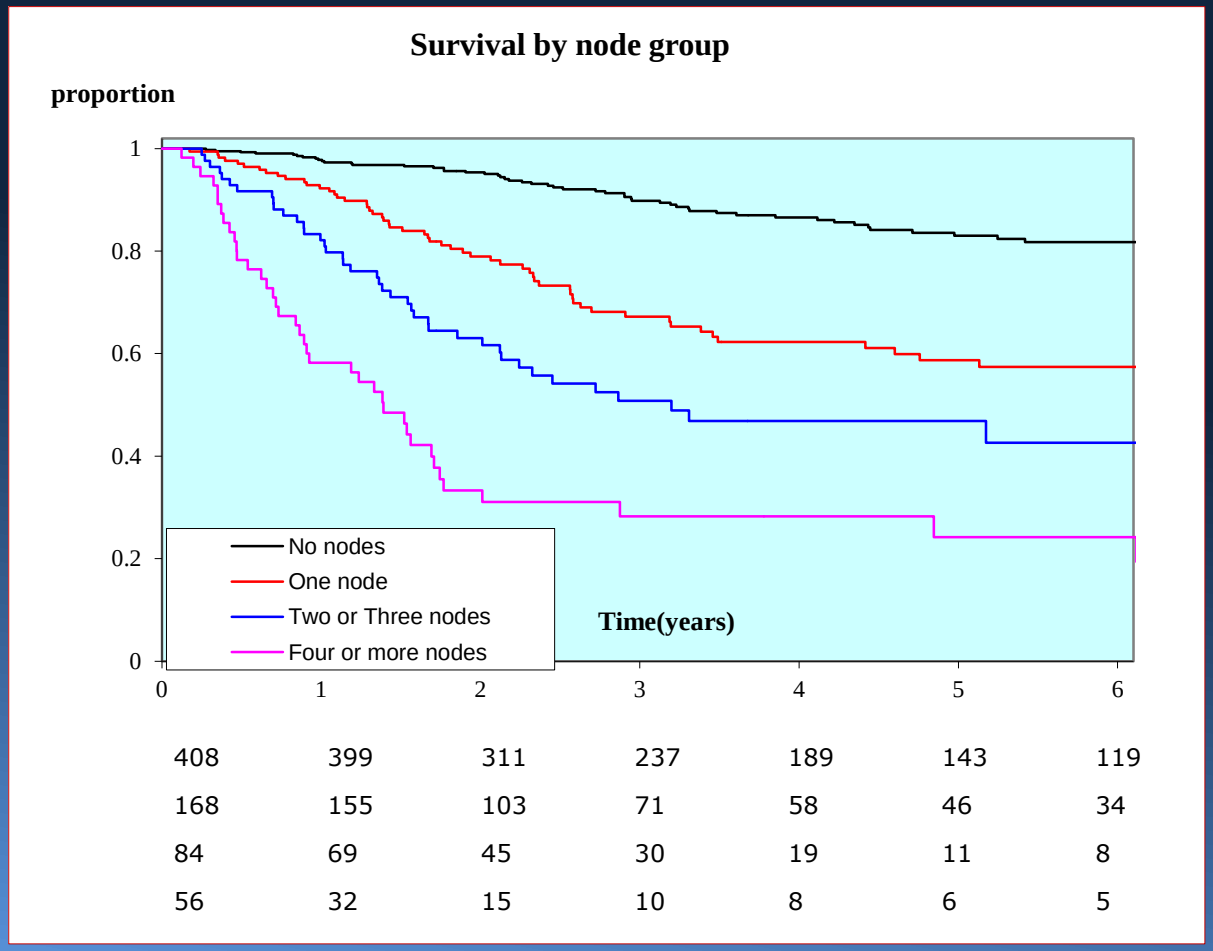
Impact of Nodal Metastases



5 ys 83% vs 49%
P<0.0001

Martin et al

Impact of N Stage



Mortality

- Mortality is typically related to the development of distant metastases

- Goals of management are
  - Locoregional control
  - Prevention of systemic disease
    - Adjuvant immunotherapy &/or chemotherapeutic agents
    - May have significant side effects
    - Expensive

Management

- Wide local excision of primary
- Neck management
  - Watch & wait policy
  - Elective lymph node dissection
  - Sentinel node biopsy & nodal management

Treatment of Primary Melanoma

- Wide local excision

… But How Wide?

Margins – Randomised trials

- 5cm historical margins

French Co-operative Group, 1985
2cm vs 5cm margin for melanoma ≤ 2mm

NO DIFFERENCE

Khayet et al, Cancer 2003

Margins – Randomised trials

- Intergroup Melanoma Committee
  - Compared 2 v 4 cm margins for MM 1 to 4 mm
  - No significant difference in LR, ITM, survival
  - Fewer SSG, shorter hospital stays
  - Concluded 2 cm safe for intermediate thickness MM

Balch et al, *Ann Surg*, 1993

No evidence to say that a margin > 1cm improves survival

Summary of margins trials

- No overall survival nor local recurrence advantage for margin >2cm
- No overall survival advantage for margin >1cm
- No RCT data for ALM and subungual melanoma
- Optimal margins for T3 primaries not certain

Guidelines for excision margins

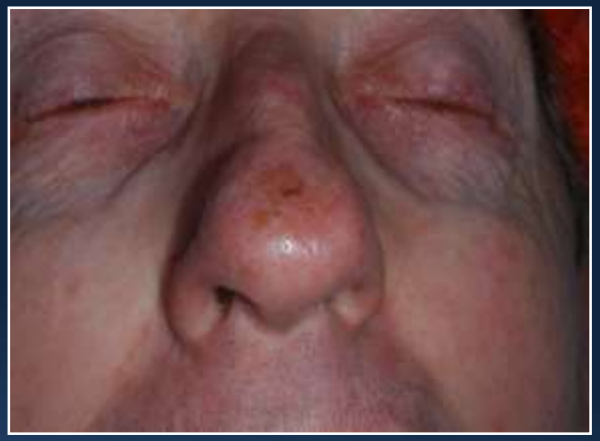
Melanoma	*Margin*
• In-situ	5mm
• 0 to1.0mm	1cm
• 1.0 to 4.0	(minimum 1cm) maximum 2cm
• >4.0	minimum 2cm

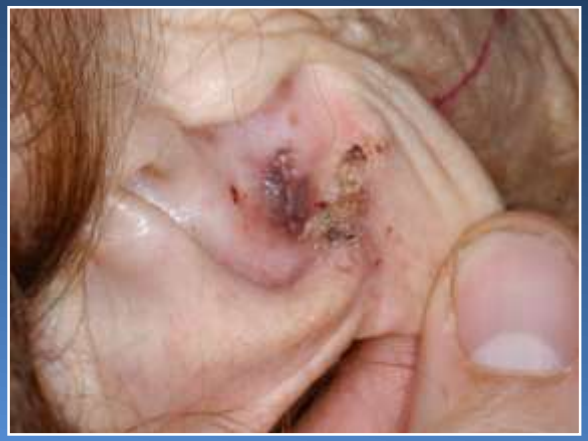
Consider other pathological features

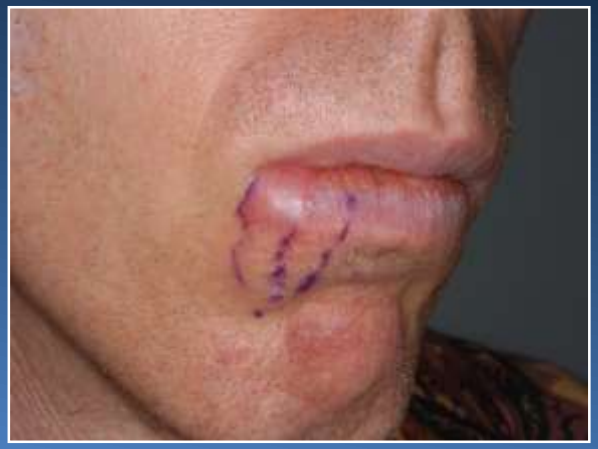
- satellitosis,
- lymphatic invasion,
- desmoplasia,
- neurotropism

2017

Various Melanomas







Excision margins -Head and Neck

T < 1mm
- 1cm margin

T > 1mm
- As wide a margin up to 2cm that can be
- closed without graft / complicated flap or
- significant disfigurement
- If a graft or flap is required for the
- minimum margin – take the recommended
- margin (ie 2cm)

Prognostic Factors

- Tumour thickness
- Ulceration
- Clark level
- Histological type
- Cell type
- Primary site
- Regression
- Mitoses
- Lymphocytic infiltration
- Vertical maturation grade
- Blood vessel invasion
- Lymphatic space invasion

- Ploidy
- S-Phase
- DR-1 Expression
- DNA index
- HSP expression
- HLA-DR staining
- p53 mutations
- CAM expression
- Protease expression
- Migration-associated molecule
- Angiogenesis-related factor
- Oncogene expression
- Oestrogen receptor expression
- Cytokine, growth factor expression

Prognosis of Melanoma Based on Tumor Thickness

	Sample Size	10-year survival
Tumor thickness ≤ 1.00 mm		
Level II	975	94.8
Level III	688	84.7
Level IV	450	88.6
Level V	0	
Tumor thickness 1.01-2.00 mm		
Level II	49	78.5
Level III	425	75.8
Level IV	713	72.4
Level V	12	65.6
Tumor thickness 2.01-4.00 mm		
Level II	18	50.9
Level III	237	53.8
Level IV	562	60.4
Level V	55	37.3
Tumor thickness > 4.00 mm		
Level II	14	
Level III	44	36.5
Level IV	194	38.6
Level V	132	38.8

Modified from: Buzaid, AC, Ross, MI, Balch, CM, et al, J Clin Oncol 1997;15:1039.

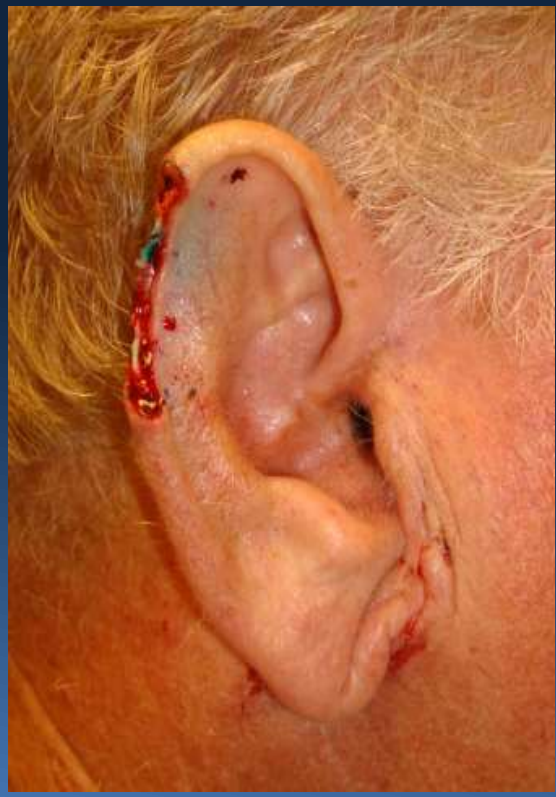
Ten-Year Survival Rates in Patients with Melanoma by Tumor Thickness and Ulceration (n = 4568)

Thickness, mm	Number of patients with		10-year survival rate		
	No Ulceration	Ulceration	No ulceration	Ulceration	P value
0.01 – 1.00	2017 (95.5)	96 (4.5)	92.0	69.1	< 0.0001
1.01 – 2.00	944 (78.8)	255 (21.2)	77.7	62.9	< 0.0001
2.01 – 4.00	500 (57.4)	372 (42.6)	59.5	53.2	0.006
> 4.00	146 (38.1)	238 (61.9)	54.5	35.5	0.0006

Modified from Buzaid, AC, Ross, MI, Balch, CM, et al, J Clin Oncol 1997;15:1039

Management of the Primary

- Wide local excision of Primary
- -Margin analysis of the paraffin block
- -No frozen section
- Delayed Reconstruction
- -Margin Status
- -Management of the Neck
- Neck Management
  - Watch & wait policy
  - Elective lymph node dissection
  - Sentinel node biopsy & nodal management



Superficial lesions (<0.76mm thick)

- Excision:
  - 1 cm margin down to fascia
- N0 neck:
  - SLNB not indicated
  - Elective neck dissection not indicated

Intermediate lesions (0.76-3.99mm thick)

- Excision
  - 1-2 cm margin down to fascia
- N0 neck:
  - SLNB
- N1-N3 neck:
  - neck dissection +/- superficial parotidectomy

+/- chemotherapy

+/- interferon α-2b etc.

Deep lesions (>4.0mm thick)

- Excision -- 2 cm margins down to fascia
- N0 neck:
  - elective neck dissections not indicated
- N1-N3 neck: neck dissection
  - +/- superficial parotidectomy

+/- chemotherapy

+/- interferon α-2b

Summary of Management

MELANOMA	DEPTH	MARGIN
pTis melanoma	in situ	5mm
pT1 melanoma	<1.0 mm	1cm
pT2 melanoma	1.0-2.0 mm	1-2cm
pT3 melanoma	2.0-4.0 mm	1-2cm
pT4 melanoma	>4.0 mm	2cm

Management of The Neck In Melanoma

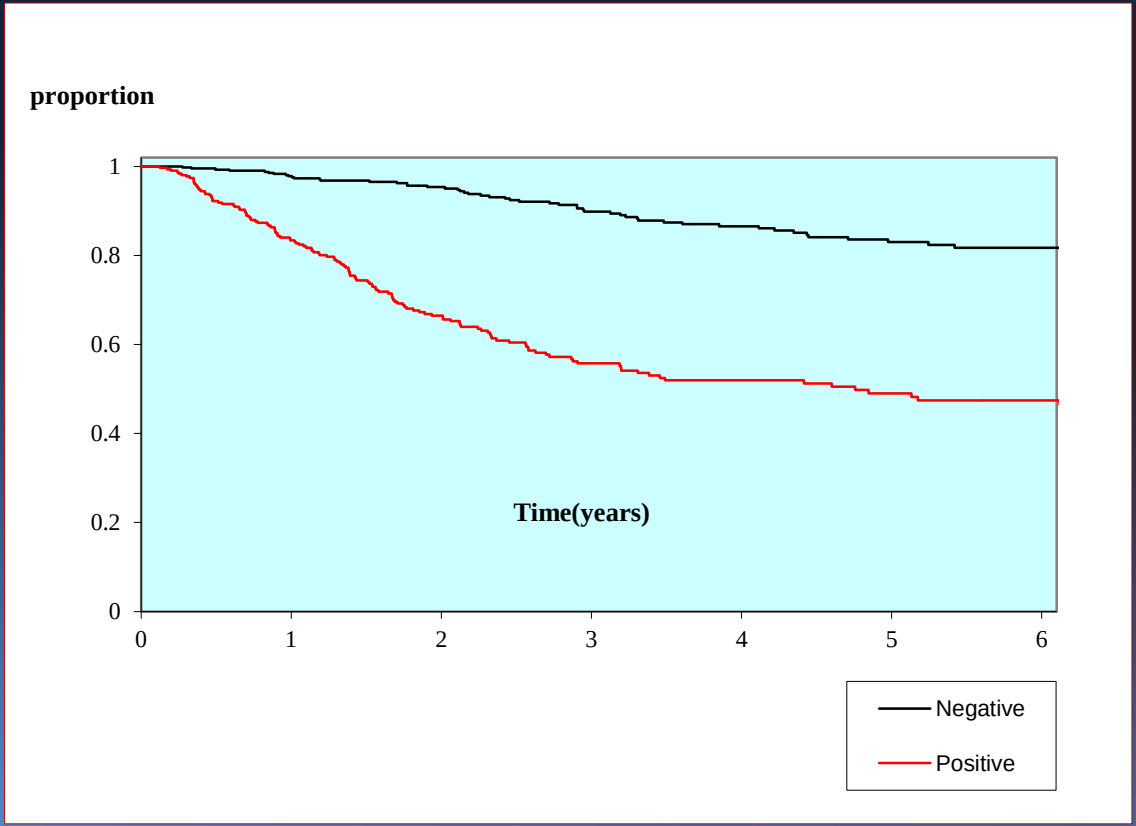
Prognostic Factors

Tumour thickness
Ulceration
Clark level
Histological type
Cell type
Primary site
Regression
Mitoses
Lymphocytic infiltration
Vertical maturation grade
Blood vessel invasion
Lymphatic space invasion

Ploidy
S-Phase
DR-1 Expression
DNA index
HSP expression
HLA-DR staining
p53 mutations
CAM expression
Protease expression
Migration-associated molecule
Angiogenesis-related factor
Oncogene expression
Oestrogen receptor expression
Cytokine, growth factor expression

Lymph node status

Impact of nodal metastases 5 Year survival 83% vs 49%

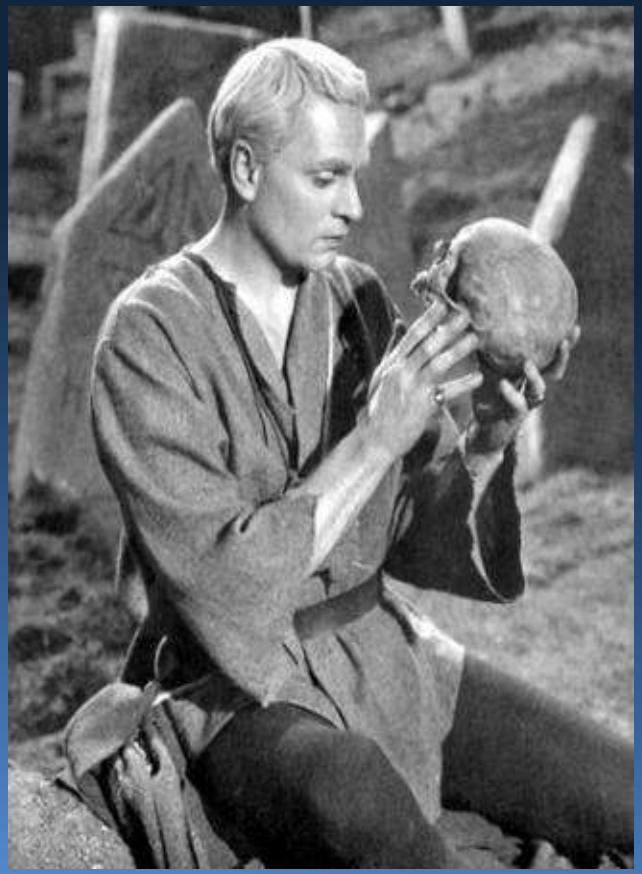


Martin et al

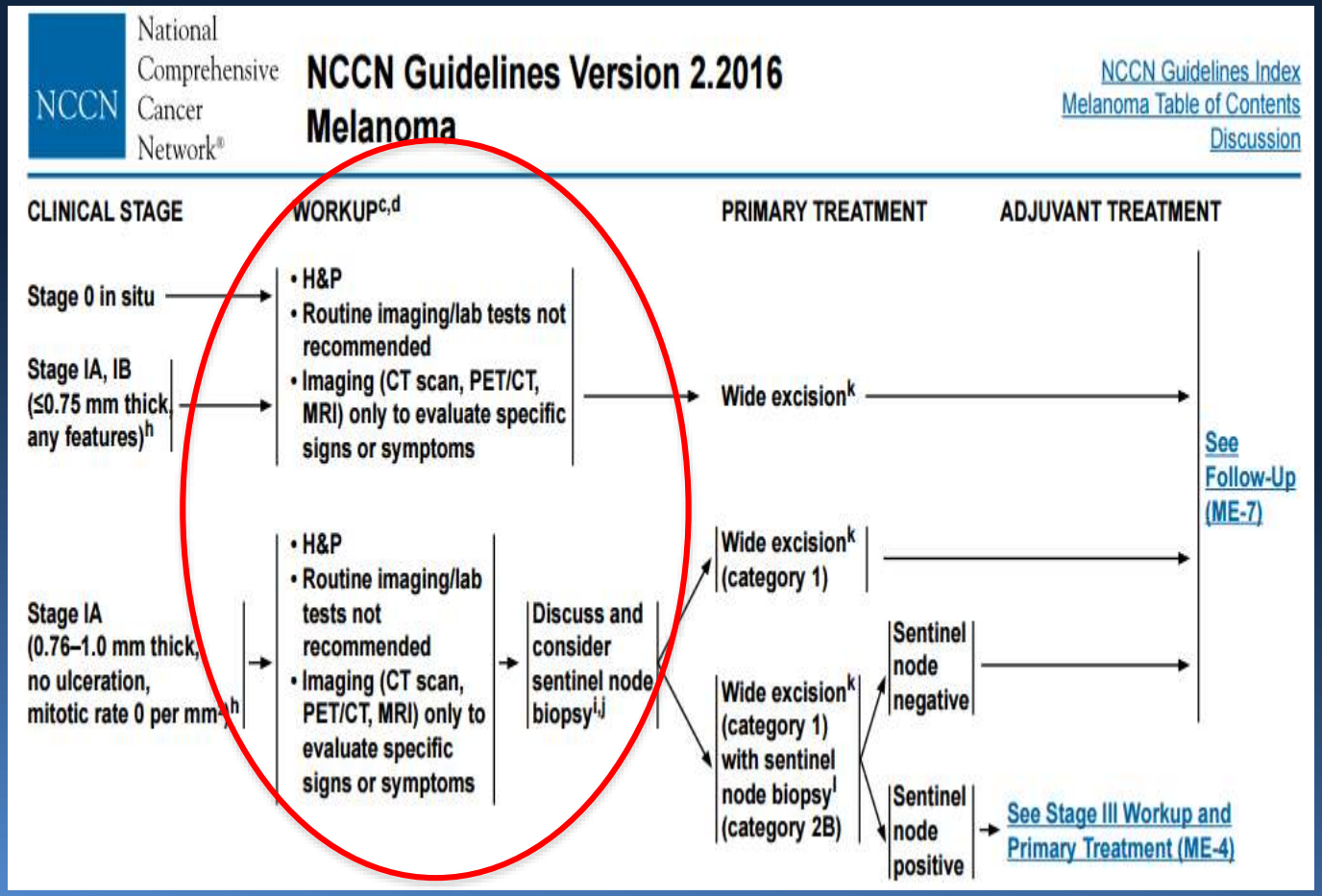
5 ys 83% vs 49%
P<0.0001

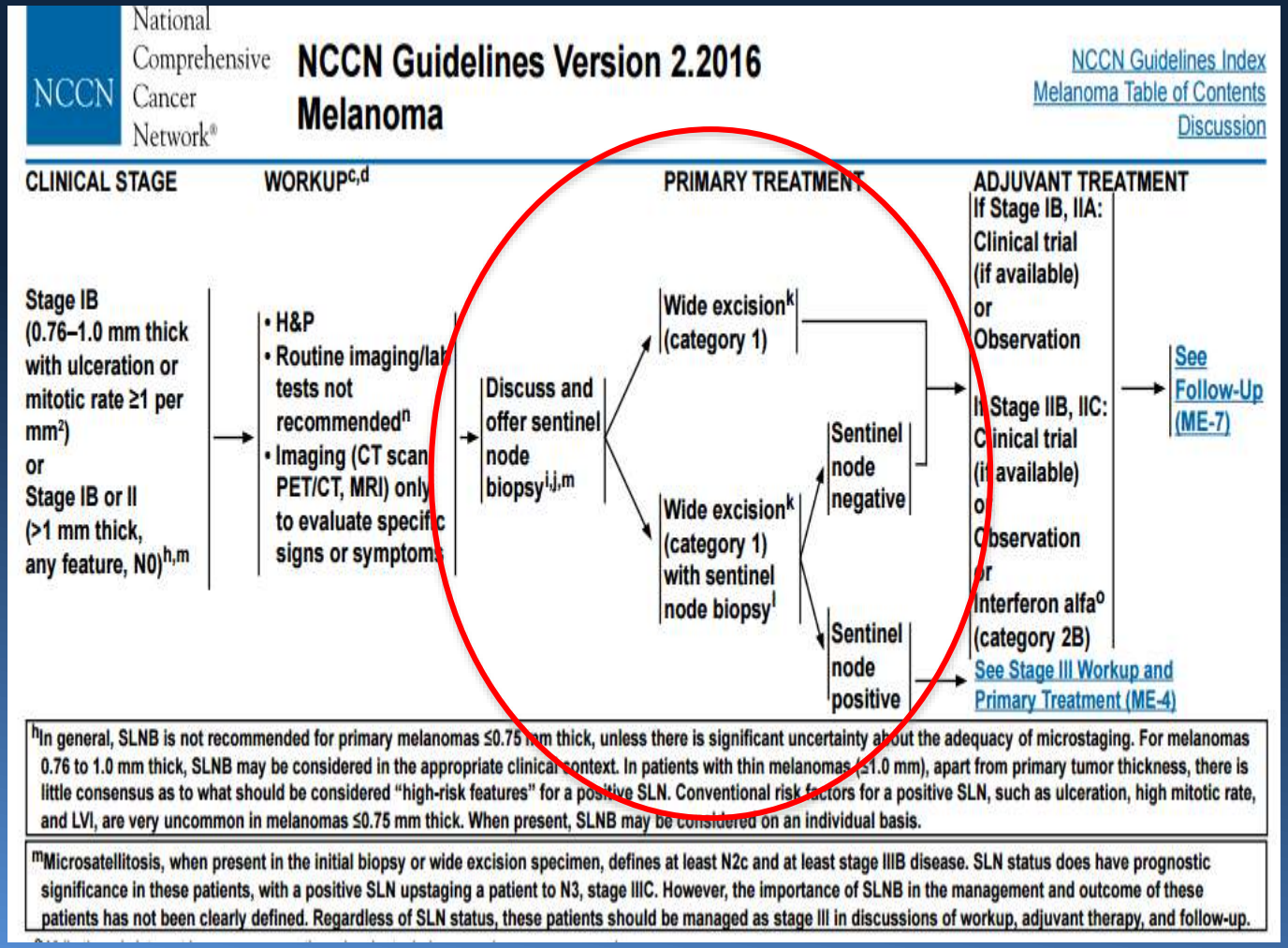
Current Node Management

- SNB offered to
  - 1mm or greater
  - <1mm + ulceration, high MR, (younger age)
- SNB +ve
  - Offered participation in MSLT II, or
  - TLND , extent based on lymphatic mapping
- Clinically N+
  - Confirm diagnosis FNA, systemic staging
  - TLND, selective if appropriate
- pN+
  - Considered for adjuvant XRT
  - Offered adjuvant systemic therapy trials



To $_{sn}$B
or
not to
$_{sn}$B…?





[h]In general, SLNB is not recommended for primary melanomas ≤0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging. For melanomas 0.76 to 1.0 mm thick, SLNB may be considered in the appropriate clinical context. In patients with thin melanomas (≤1.0 mm), apart from primary tumor thickness, there is little consensus as to what should be considered "high-risk features" for a positive SLN. Conventional risk factors for a positive SLN, such as ulceration, high mitotic rate, and LVI, are very uncommon in melanomas ≤0.75 mm thick. When present, SLNB may be considered on an individual basis.

[m]Microsatellitosis, when present in the initial biopsy or wide excision specimen, defines at least N2c and at least stage IIIB disease. SLN status does have prognostic significance in these patients, with a positive SLN upstaging a patient to N3, stage IIIC. However, the importance of SLNB in the management and outcome of these patients has not been clearly defined. Regardless of SLN status, these patients should be managed as stage III in discussions of workup, adjuvant therapy, and follow-up.

Neck Management : Watch & wait

- In situ melanoma
- Thin melanoma < 1mm & less than Clark level III and no adverse pathologic features
  - Risk of nodal metastasis <2%
- Thick melanoma > 4mm
  - Some debate as to whether to offer SLNB

Elective Lymph Node Dissection

- No strong evidence in favour of performing ELND in clinically node negative patients with H & N melanoma
- ND unnecessary in > 80% patients
- Clinical prediction of lymphatic dissemination is unreliable
  - Discordancy rate as high as 14%
  - Lymphatic draining patterns vary

Sentinel Lymph Node Biopsy

- Introduced by Cabanas in 1977
- Popularized by Morton 1990
- Staging and therapeutic procedure
  - Increases sensitivity to detect regional metastasis
  - Halts regional progression of disease.
  - Selects patients who might benefit from:
    - Further regional therapy
    - Systemic adjuvant therapy

Role of Sentinel Lymph Node Biopsy

- Popularized by Morton for Melanoma

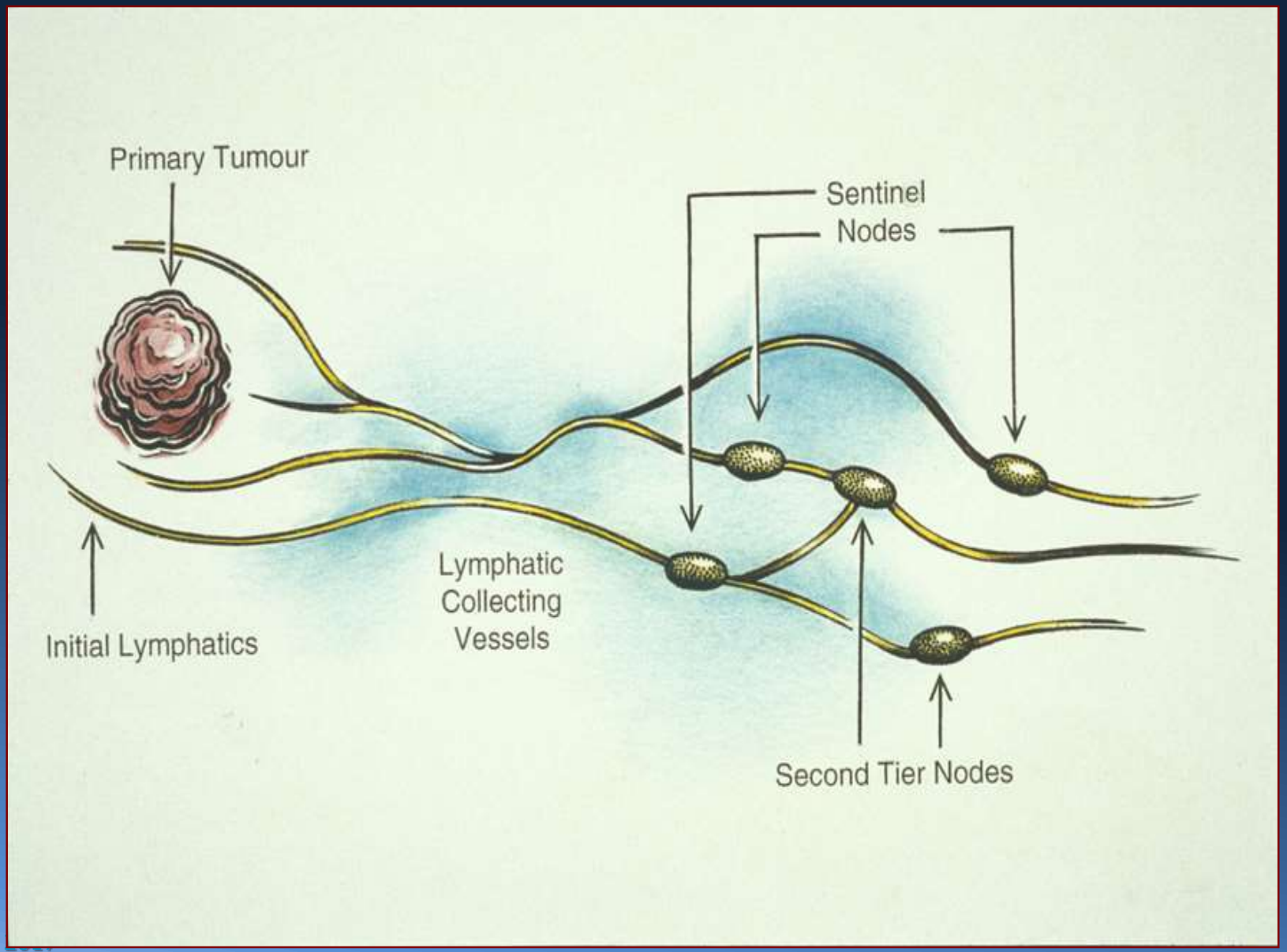
- Rationale
  - Metastases occur through specific lymphatic channels to involve sentinel nodes as first site of spread

  - If the SLN is negative, the assumption is that rest of the regional nodes are very likely to be free of disease as well

"Sentinel Node" - Definition

- "First draining lymph node on the direct drainage pathway from the primary tumor site" Morton

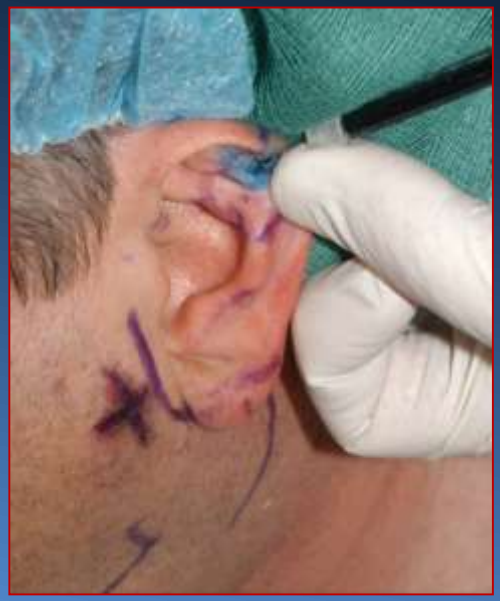
- *"Any* lymph node receiving direct drainage from a primary lesion site" Uren et al

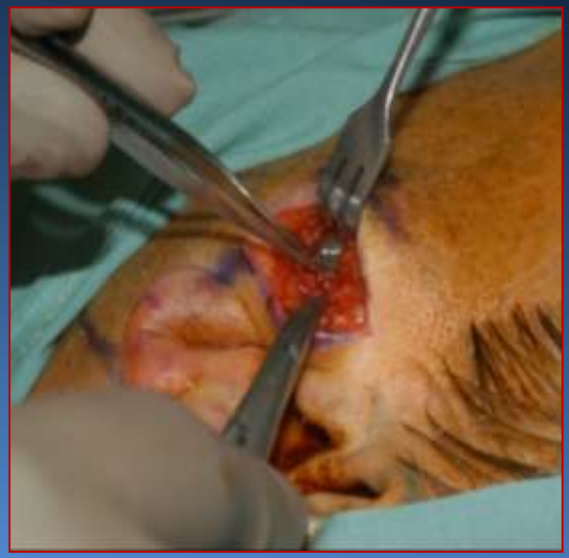

Primary Tumour
Sentinel
Nodes
Lymphatic
Collecting
Vessels
Initial Lymphatics
Second Tier Nodes

Indications

- > 1 mm depth, any Clark level
- < 1mm depth with Clark level IV, V or ulceration
- > 4 mm depth with no adverse risk features
  - Controversial

Sentinel node biopsy





Who should undergo SLN Biopsy? Summary Indications

- 1-4 mm thick

- ? Thin Melanomas
  - Ulcerated
  - Clark level IV or V
  - Mitoses- > 1/mm^2

- ? Thick Melanomas

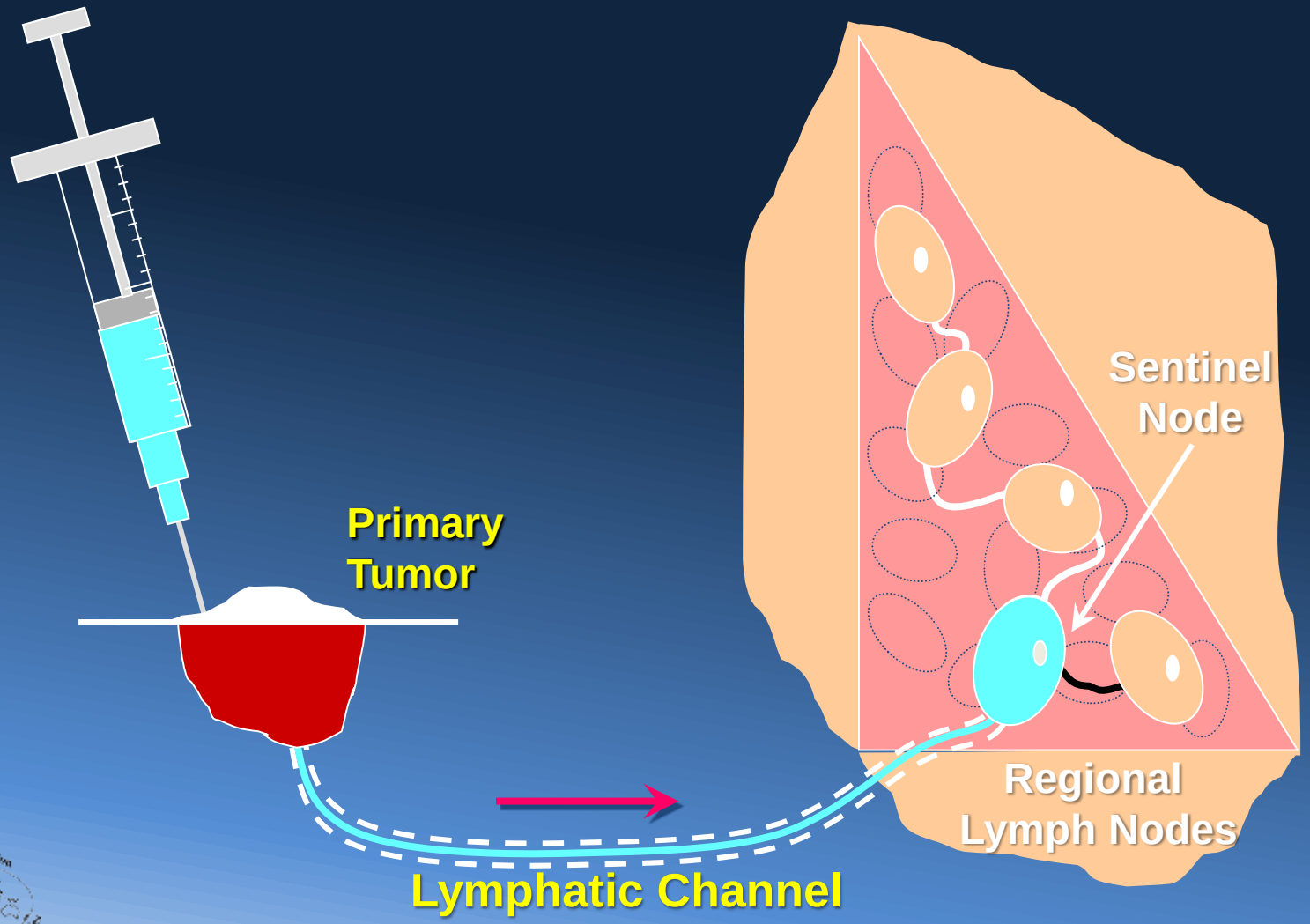
Contraindications

- Clinically or radiographic lymph node metastases
- Tumors > 4 to 5 cm
- Disruption of lymphatic drainage
  - Prior extensive surgery
  - Extensive local flaps
  - Previous radiation to H & N
- Pregnancy and breast-feeding
- Allergy to dye

SLNB Technique

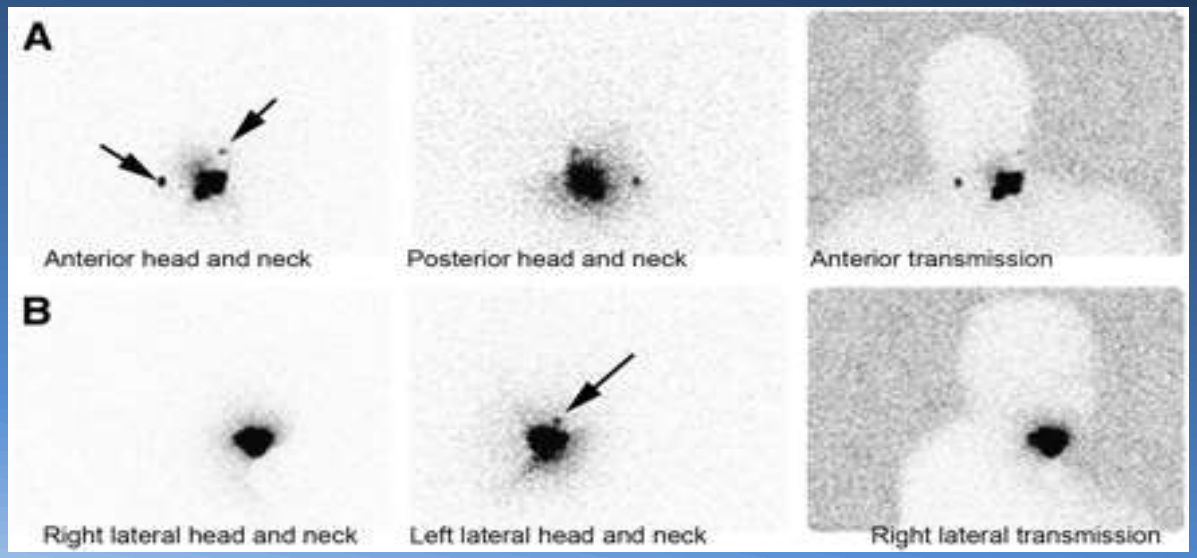
- Morning of Procedure:
  - Injection of primary site with radiolabelled sulfur colloids (technetium-99m)
  - Planar Lymphoscintigraphy (15 min – 1 hour)
- Inject tumour with blue dye (15 min)
- Wide Local Excision of Primary Site
- Use lymphoscintigraphy imaging, Gamma Probe and visualized blue dye to identify sentinel node

Sentinel Node Technique

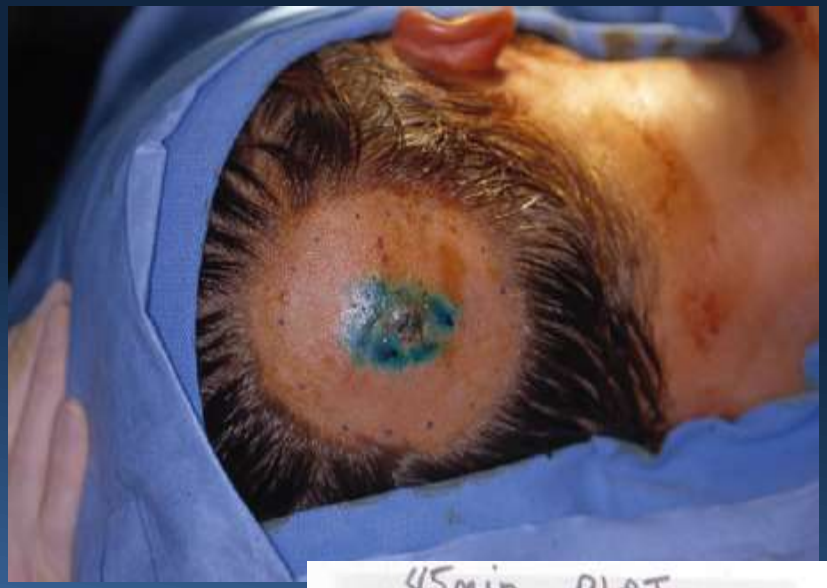


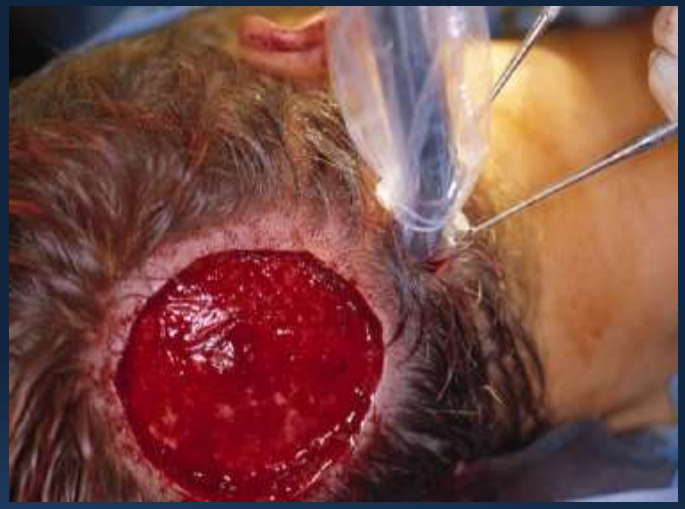
Pre-operative Details

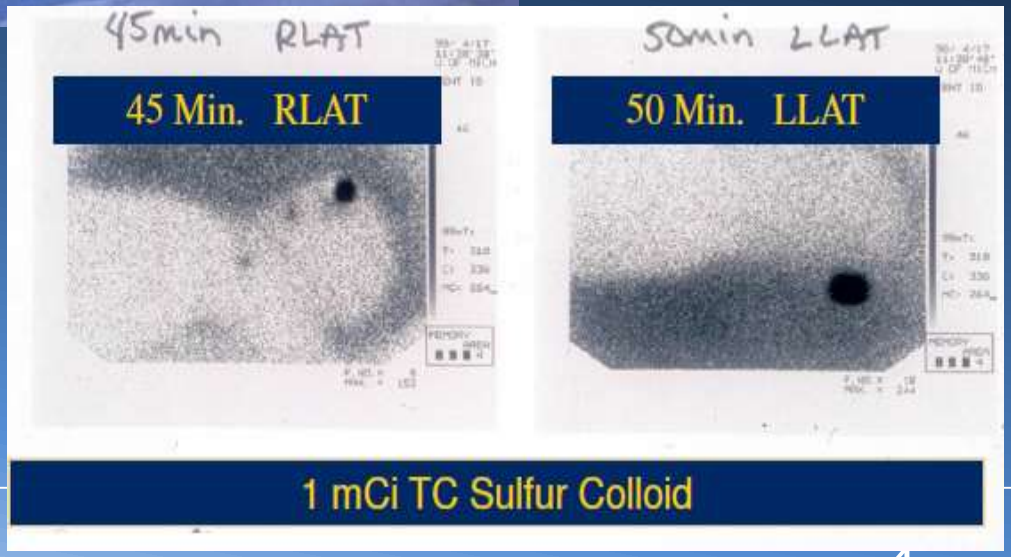
- Dynamic Lymphatic mapping is performed
- Multiple peripheral intradermal injections of Tc-99 Sulfur Colloid 40mBq within 12 hrs of surgery
  - Choice of radiocolloid
- Uptake sites labeled on skin surface



SLNB Technique



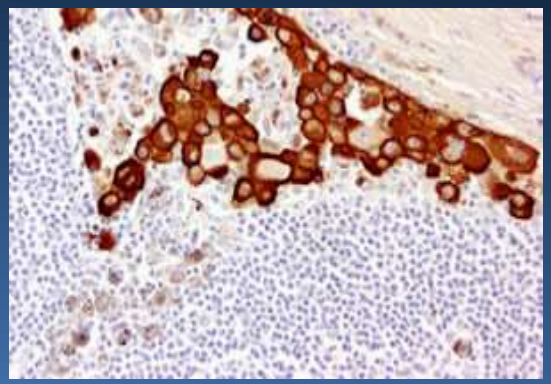




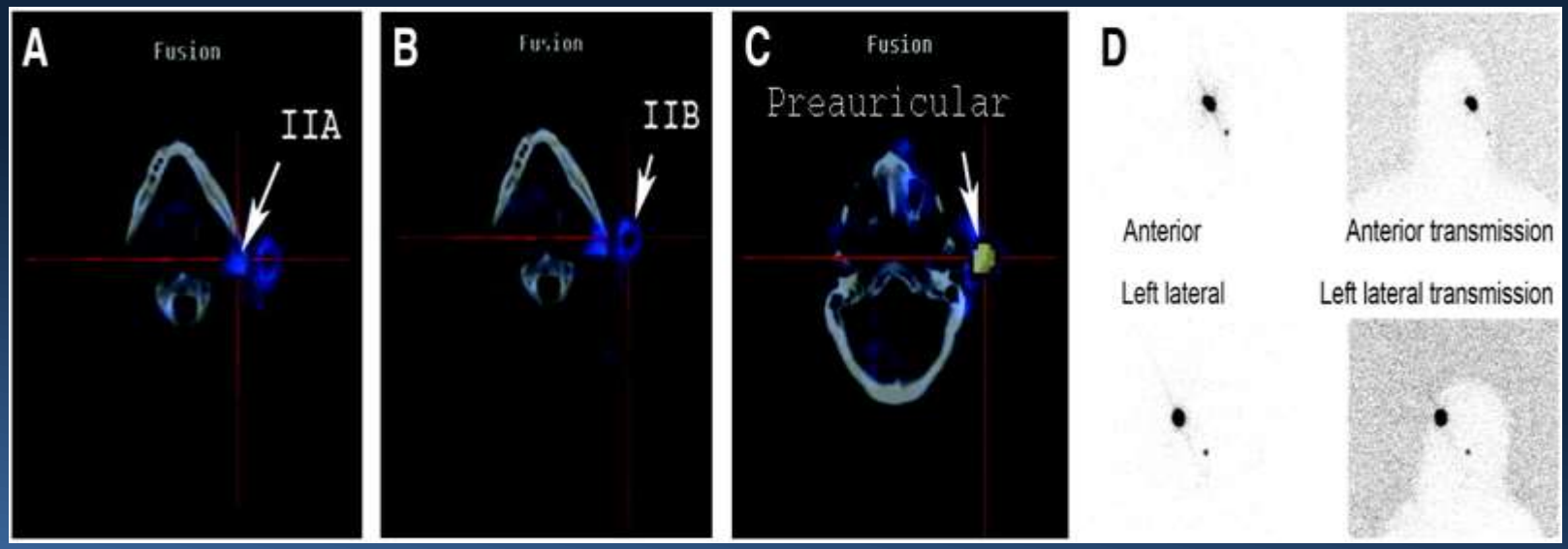
SLNB Technique

- SLN serially section by pathology
  - As oppose to a single cut through the node

- Immunohistochemistry
  - S-100
  - Melan-A
  - HMB-45



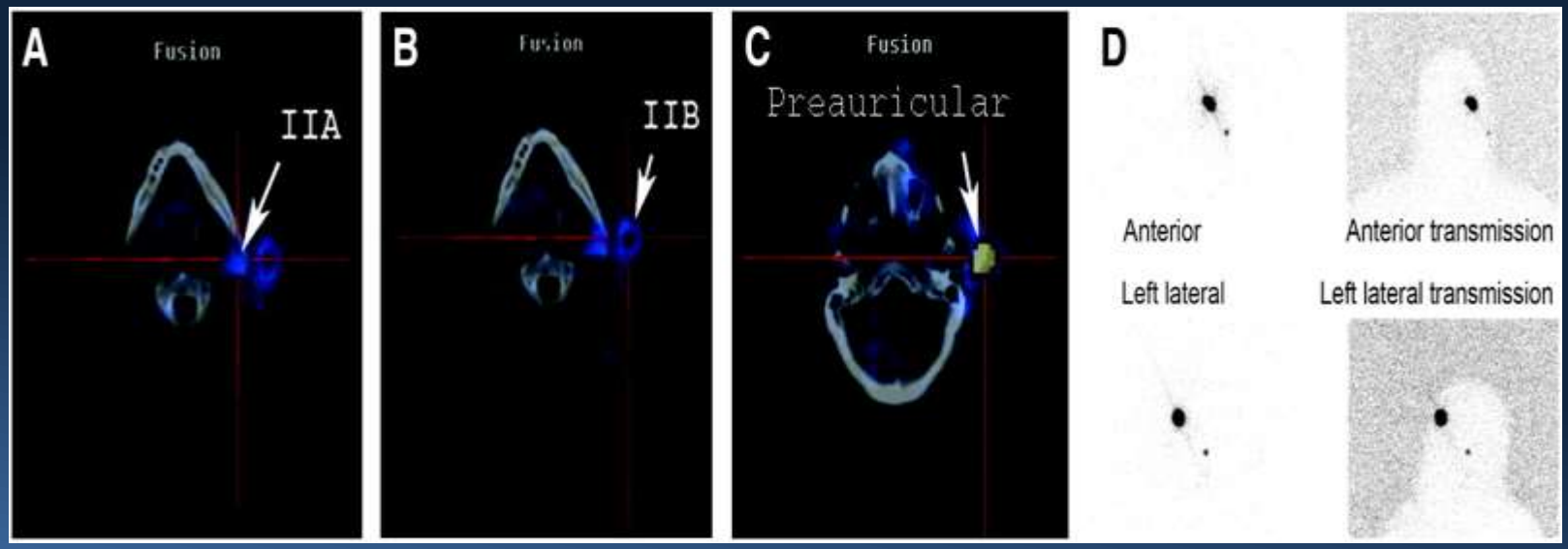
Hybrid Imaging with SPECT/CT Lymphoscintigraphic Imaging



- Higher diagnostic reliability
  - Anatomic correlation
  - Higher specificity
- Better image quality
  - Due to CT attenuation correction

Sebaceous cell carcinoma of left upper eyelid: Planar imaging (D) demonstrated only 1 node, whereas SPECT/CT demonstrated 4 nodes, possibly because of slight delay in imaging time. Level IIA (A), level IIB (B), and preauricular (C) lymphatic chains are shown.

Hybrid Imaging with SPECT/CT Lymphoscintigraphic Imaging



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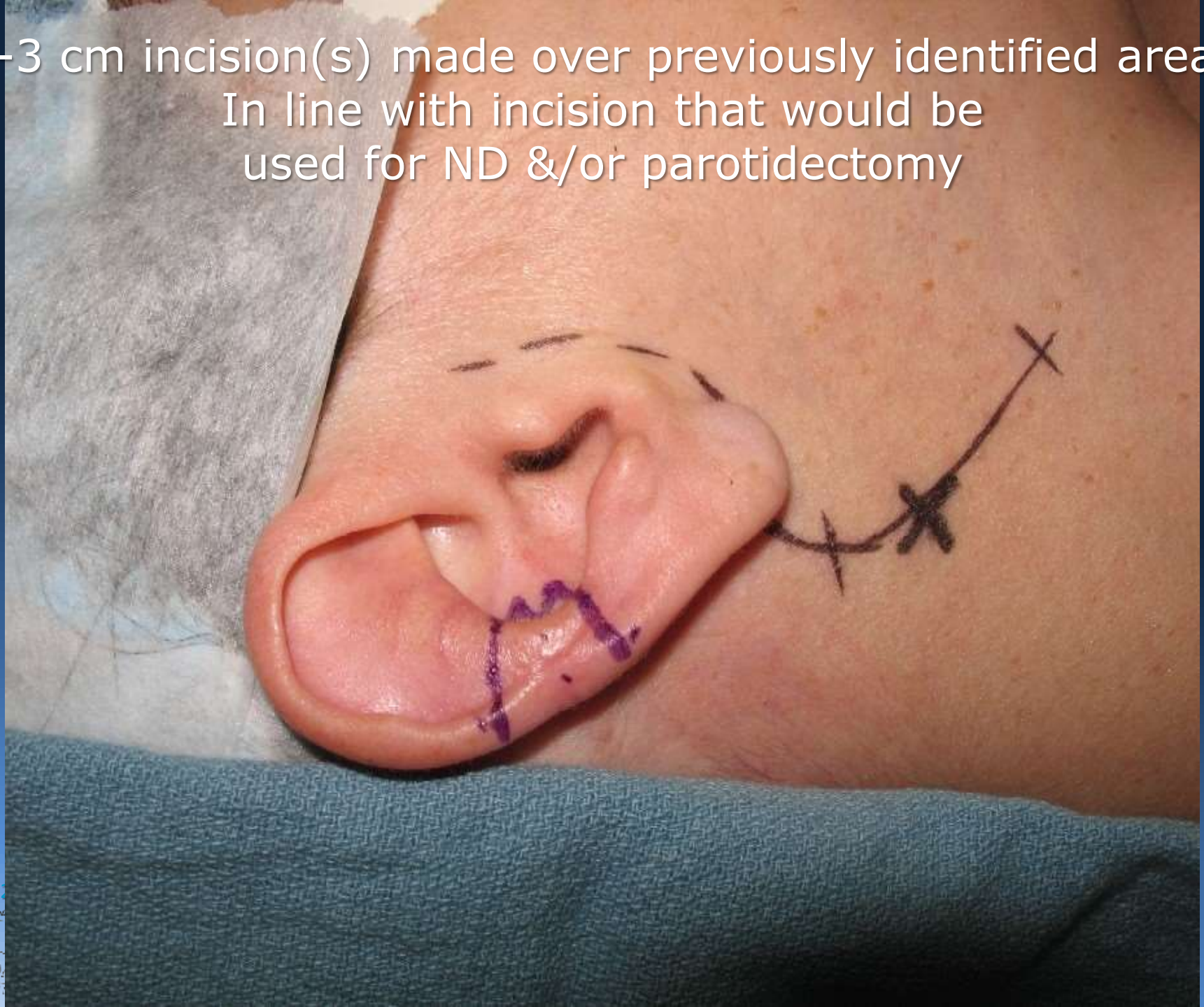
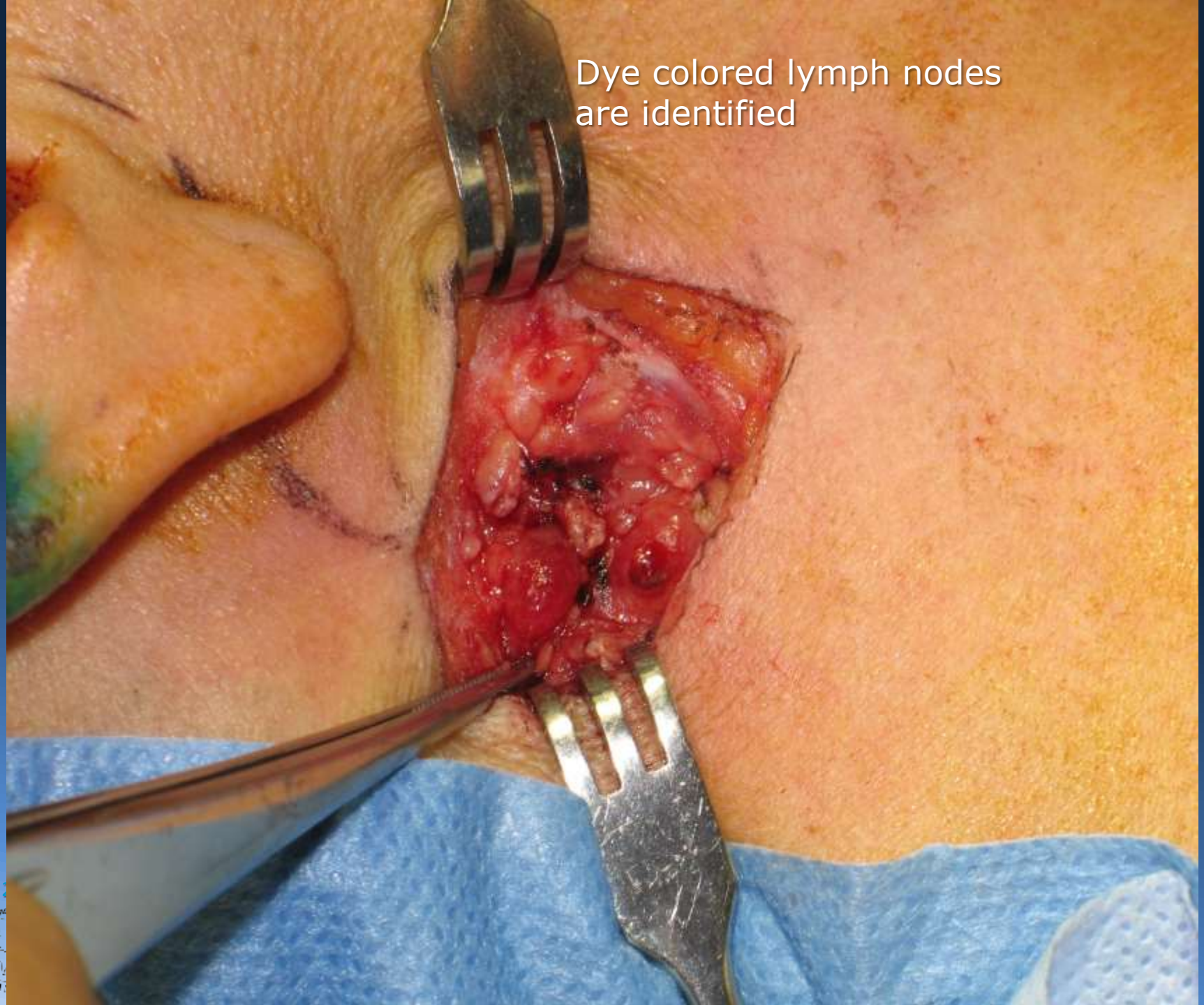
Sebaceous cell carcinoma of left upper eyelid: Planar imaging (D) demonstrated only 1 node, whereas SPECT/CT demonstrated 4 nodes, possibly because of slight delay in imaging time. Level IIA (A), level IIB (B), and preauricular (C) lymphatic chains are shown.

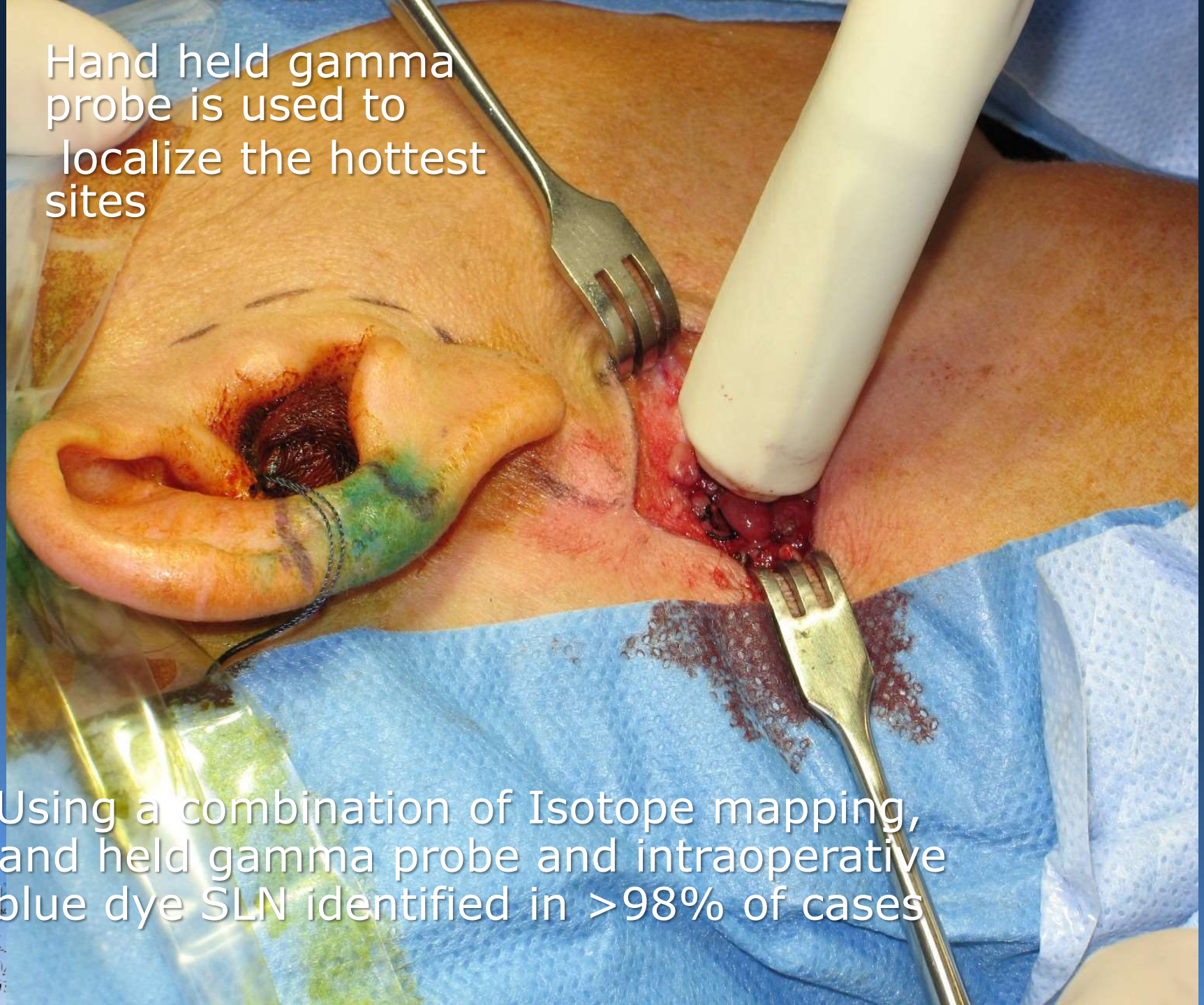
Intra-operative technique

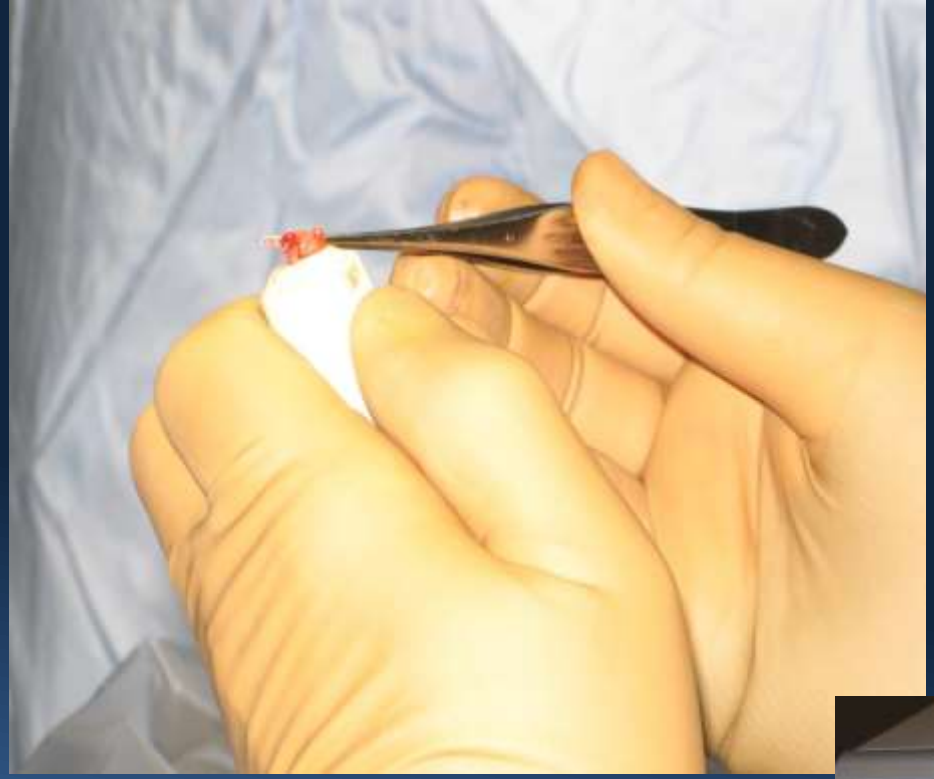
2-3 cm incision(s) made over previously identified areas
In line with incision that would be
used for ND &/or parotidectomy




Isosulfan blue (<1cc) is injected into the derm
at the biopsy margins


Dye colored lymph nodes
are identified


Hand held gamma probe is used to localize the hottest sites
Using a combination of Isotope mapping, hand held gamma probe and intraoperative blue dye SLN identified in >98% of cases



SLN shows radioactive uptake exceeding a 10:1 ratio of ex vivo to resection bed count or a 3:1 ratio of in vivo to resection bed count.

10% rule: Keep looking until bed count < 10% of initial in situ count

Formalin fixation and
Permanent Sections
Special micro-sectioning

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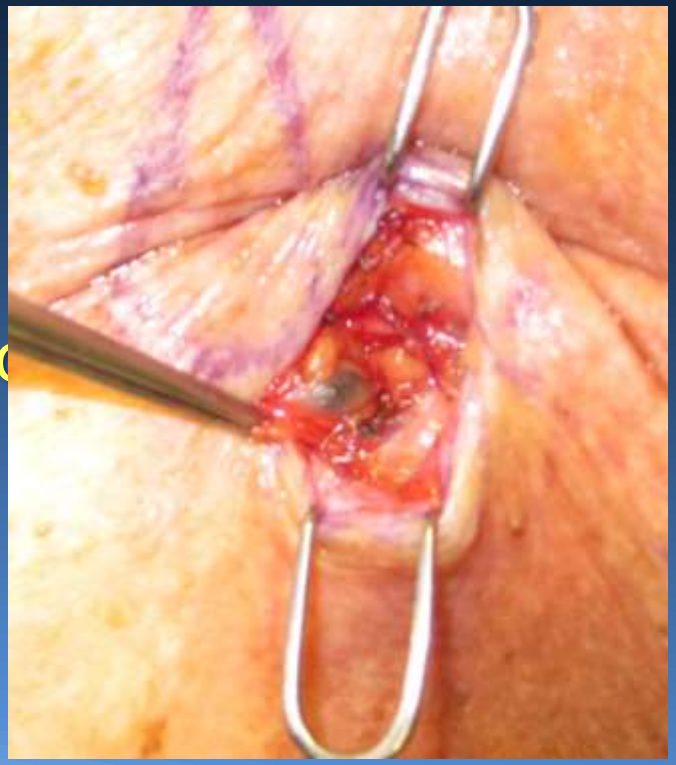
SPECT-CT for SLNB

- Single Photon Emission CT
- Primarily H&N melanoma
- Improves anatomic location of SLN
  - EJ vs IJ
  - Levels IIA vs IIB vs VA
  - Parotid nodes
  - Suboccipital nodes
- Shortens operative time
- Proper placement of incisi



If SNB *positive*…

- Neck dissection and consideration for systemic therapy +/- clinical trial

Management of +ve SN

- Therapeutic dissection
  - Based on pattern of drainage at LSG
  - Only 20% will have additional +ve nodes
- Is CLND-Complete Lymph node dissection necessary?

  MSLT II

Why is Head and Neck site different from all other sites?

- Cosmetic issues in the head and neck
- Technically challenging
  - Complex anatomy:
    - nerves and vessels at risk
    - Intraparotid nodes
  - Incision(s) need to be planned based on potential for neck dissection
- Radionucleotide overlap between primary and drainage

Arguments Against SNB

- Micromets may be clinically irrelevant
- False negative rates
  - Can still have regional recurrence following SNB and SNB w/ND
  - Drainage not predictable
  - Number of sentinel nodes generally greater than elsewhere- may miss
- ?? Survival benefit

Summary

- SNB improves locoregional control of head and neck melanoma
- Sentinel-node biopsy has staging and prognostic value in atients with intermediate thickness melanoma
- But there is no clear survival benefit

Current Role for SNB

- To identify patients with poor prognosis that can be offered adjuvant immunotherapy and/or chemotherapeutic agents
  - Very limited benefit
- Or to be enrolled in a clinical trial investigating systemic therapies

MSLT-I

The NEW ENGLAND JOURNAL of MEDICINE

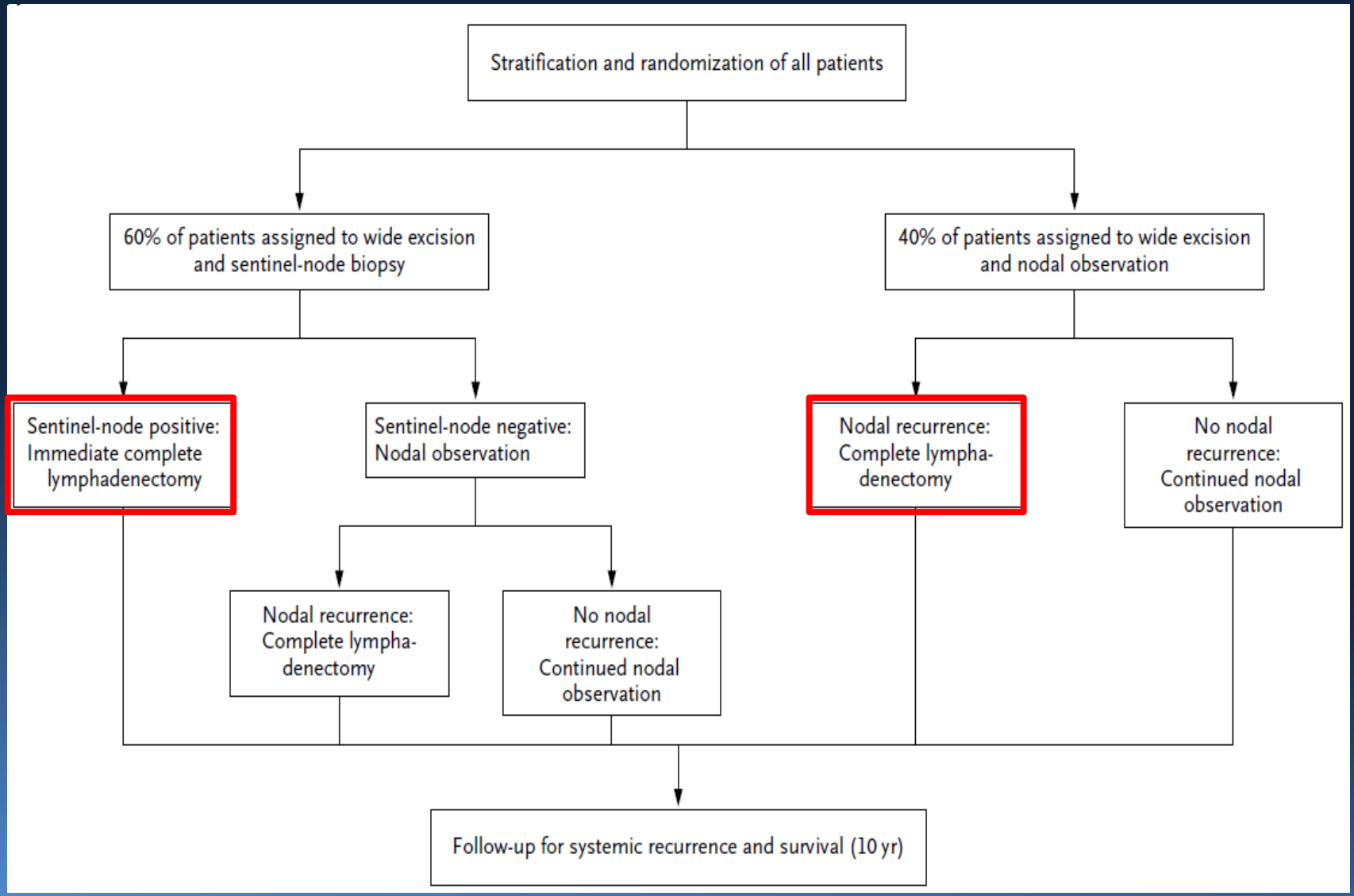
ESTABLISHED IN 1812 FEBRUARY 13, 2014 VOL. 370 NO. 7

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*

MSLT-1: Rationale

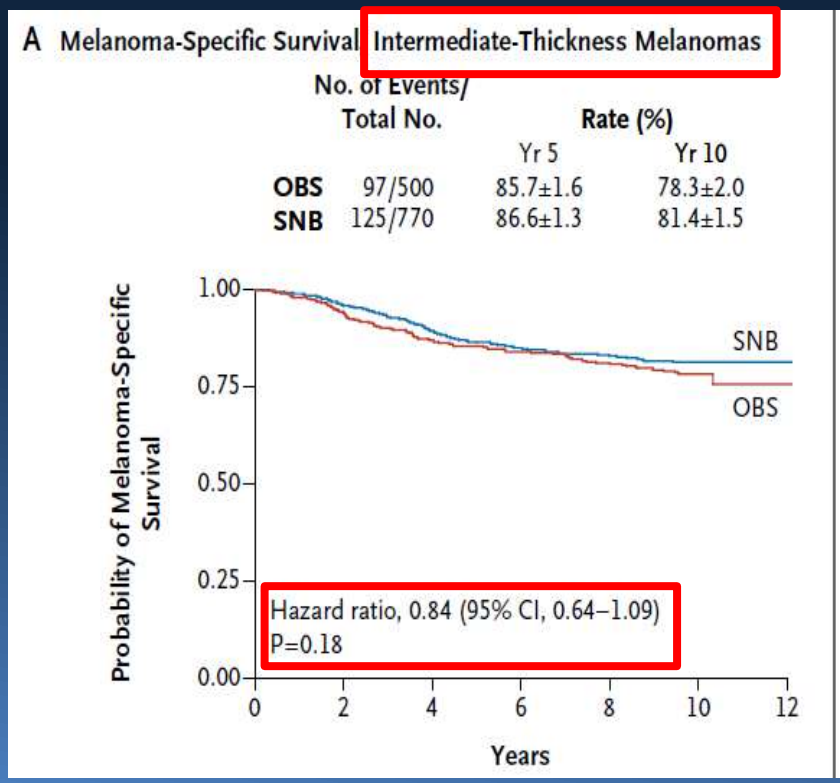
- Phase 3 Trial to assess the role of SNLBx in melanoma staging (identification of occult nodal metastases)
- Why?
  - Authors were unsatisfied with the other options:
    - Lymphadenectomy (procedure related risk)
    - Observation
- Results previously reported but only for intermediate thickness melanomas at 5 years (2006)

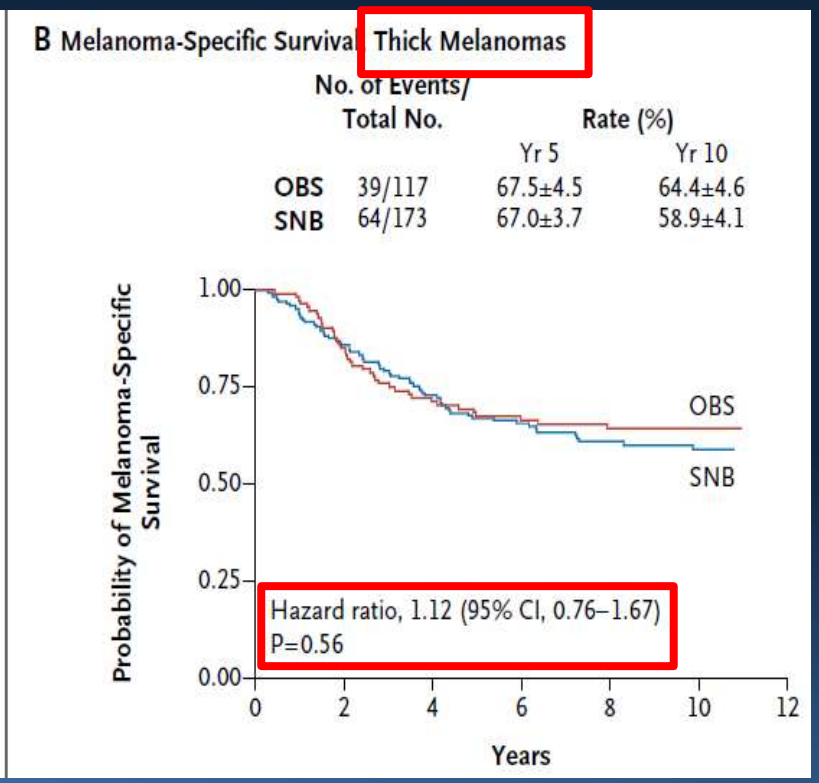

Stratification and randomization of all patients
60% of patients assigned to wide excision and sentinel-node biopsy
40% of patients assigned to wide excision and nodal observation
Sentinel-node positive: Immediate complete lymphadenectomy
Sentinel-node negative: Nodal observation
Nodal recurrence: Complete lympha-denectomy
No nodal recurrence: Continued nodal observation
Nodal recurrence: Complete lympha-denectomy
No nodal recurrence: Continued nodal observation
Follow-up for systemic recurrence and survival (10 yr)

Outcomes

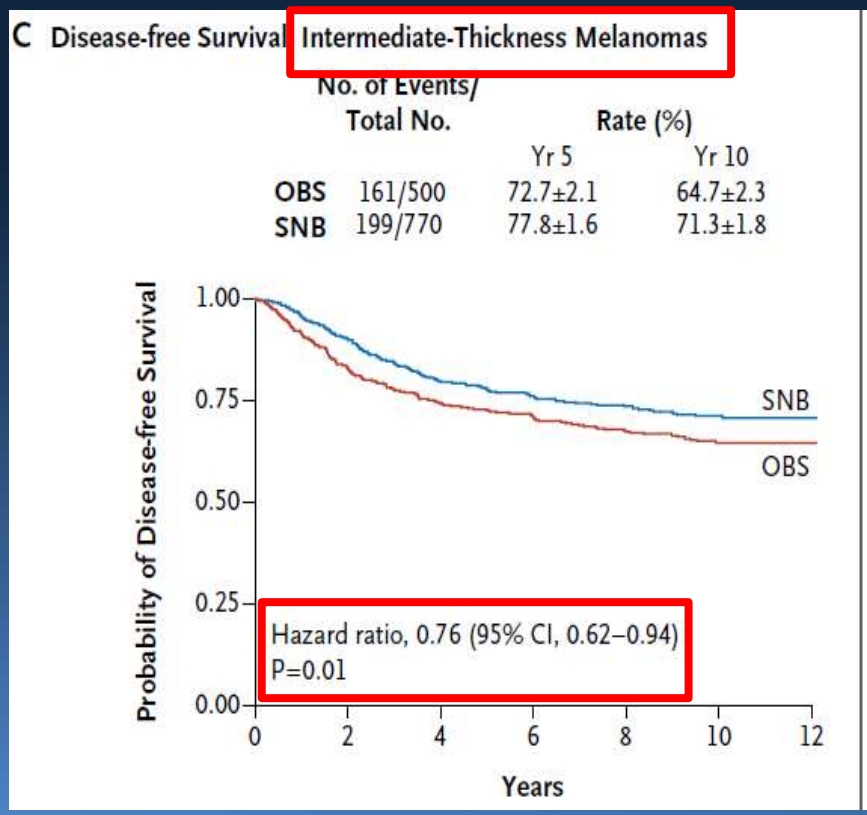
- Primary
  - Melanoma Specific Survival (DSS)
- Secondary
  - Disease Free Survival (DFS)

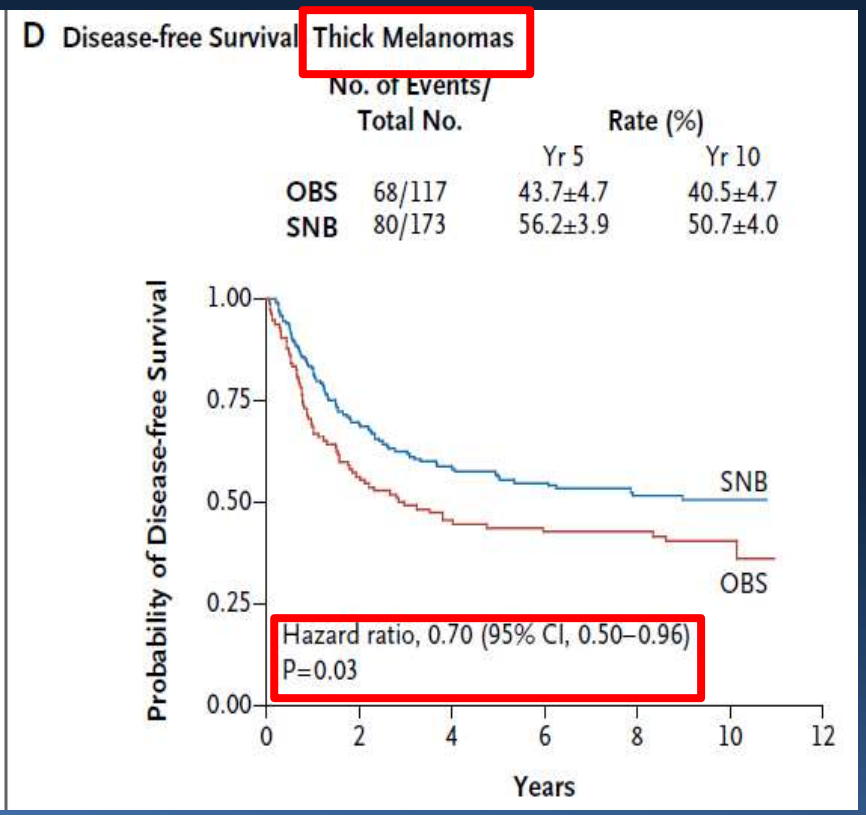
Primary Outcome (DSS)





Secondary Outcome (DFS)





MSLT – I Conclusions

- "Our long-term results confirm that sentinel-node biopsy correctly determines the pathologic status of the nodal basin in 96% of cases and is the most powerful **prognostic indicator**."
- "These long-term results clearly validate the use of sentinel-node biopsy in patients with intermediate-thickness or thick primary melanomas. The procedure provides accurate and important staging information, **enhances regional disease control, and, among patients with nodal metastases, appears to improve melanoma-specific survival substantially**."

Bias

- Despite the consistent strength of the data from the MSLT-I, there has been some reluctance to accept the results of **comparisons between node-positive patients in the biopsy group and those in the observation group**, because of concern about *ascertainment (surveillance) bias*. Latent-subgroup analysis methods were used to address this statistical consideration.

VOLUME 30 · NUMBER 23 · AUGUST 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Sentinel Lymph Node Biopsy for Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Joint Clinical Practice Guideline

Sandra L. Wong, Charles M. Balch, Patricia Hurley, Sanjiv S. Agarwala, Timothy J. Akhurst, Alistair Cochran, Janice N. Cormier, Mark Gorman, Theodore Y. Kim, Kelly M. McMasters, R. Dirk Noyes, Lynn M. Schuchter, Matias E. Valsecchi, Donald L. Weaver, and Gary H. Lyman

Recommendations

SLN biopsy is recommended for patients with intermediate-thickness melanomas (Breslow thickness, 1 to 4 mm) of any anatomic site; use of SLN biopsy in this population provides accurate staging. Although there are few studies focusing on patients with thick melanomas (T4; Breslow thickness, > 4 mm), SLN biopsy may be recommended for staging purposes and to facilitate regional disease control. There is insufficient evidence to support routine SLN biopsy for patients with thin melanomas (T1; Breslow thickness, < 1 mm), although it may be considered in selected patients with high-risk features when staging benefits outweigh risks of the procedure. Completion lymph node dissection (CLND) is recommended for all patients with a positive SLN biopsy and achieves good regional disease control. Whether CLND after a positive SLN biopsy improves survival is the subject of the ongoing Multicenter Selective Lymphadenectomy Trial II.

2013 NCCN Updated

- "There is consensus that the procedure should be discussed and offered to patients with primary melanomas greater than 1.0 mm thick."

- For melanomas 0.76 to 1.0 mm thick, SLNB should be discussed and considered. The discussion about SLNB in this group of patients should include the recognition that the yield of a positive SLNB is low and the clinical significance of a positive SLN is modest.
  - Ulceration
  - High mitotic rate
  - Lymphovascular invasion

MSLT – II

- SLN+ randomized to:
  - Completion lymphadenectomy
  - Observation
- Outcomes
  - Primary: DSS
  - Secondary: DFS and Recurrence at 10 years
- Estimated completion date 2022

The New England Journal of Medicine June 8 th2017

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. Hoefer, 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

2017

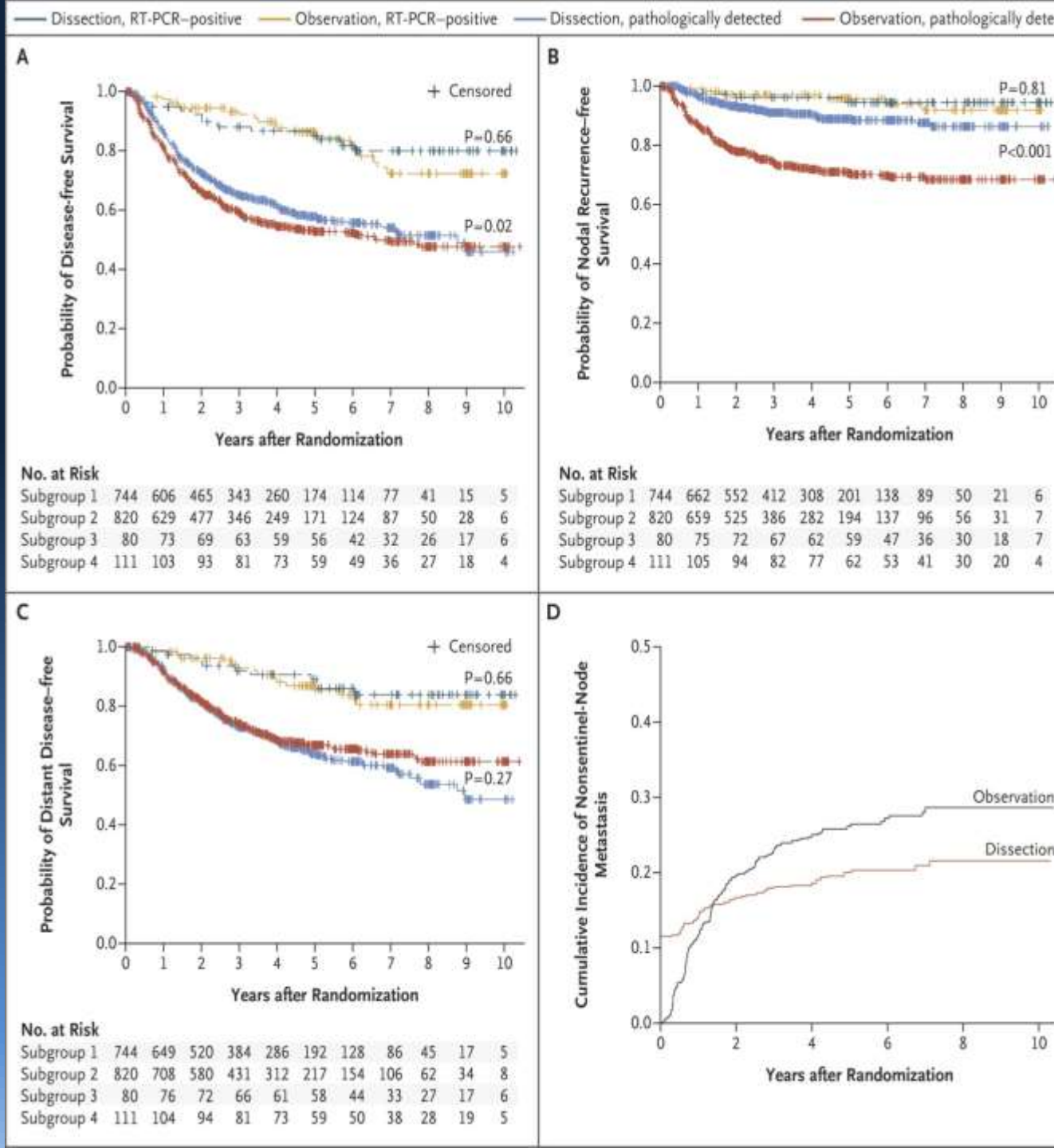
A. **A. Disease-free Survival**

B. **B. Survival without Nodal Recurrence**

C. **C. Distant Metastasis–free Survival**

D. **D. Cumulative Rate of Non-sentinel-**

E. **Node Metastasis.**



The NEW ENGLAND JOURNAL of MEDICINE

Faries MB et al. N Engl J Med 2017;376:2211-2222

2017 International Federation of Head and Neck Oncologic Societies

MSLT II - Conclusions

Immediate completion lymph-node dissection:

- Increased the rate of regional disease control
- Provided prognostic information

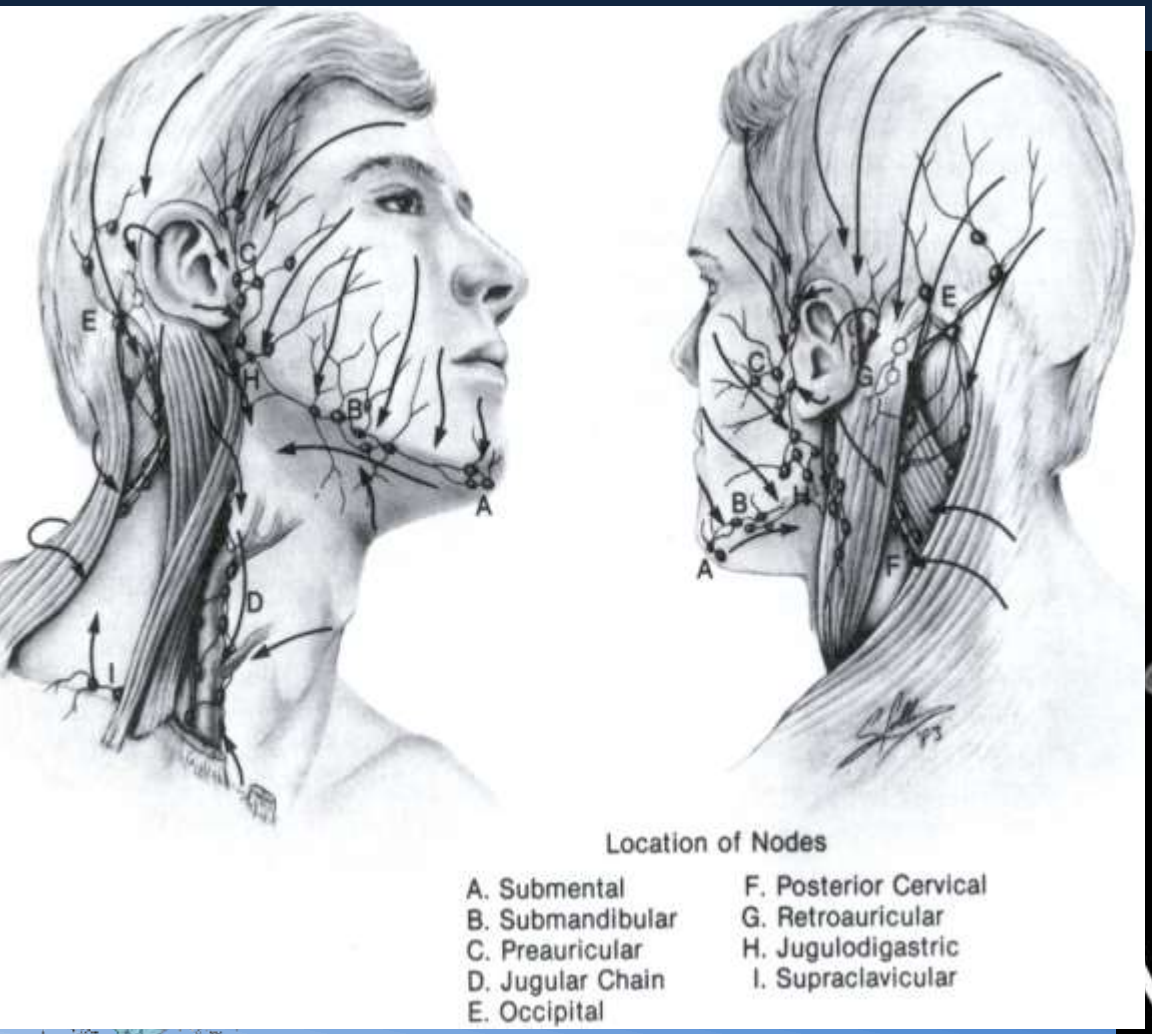
But

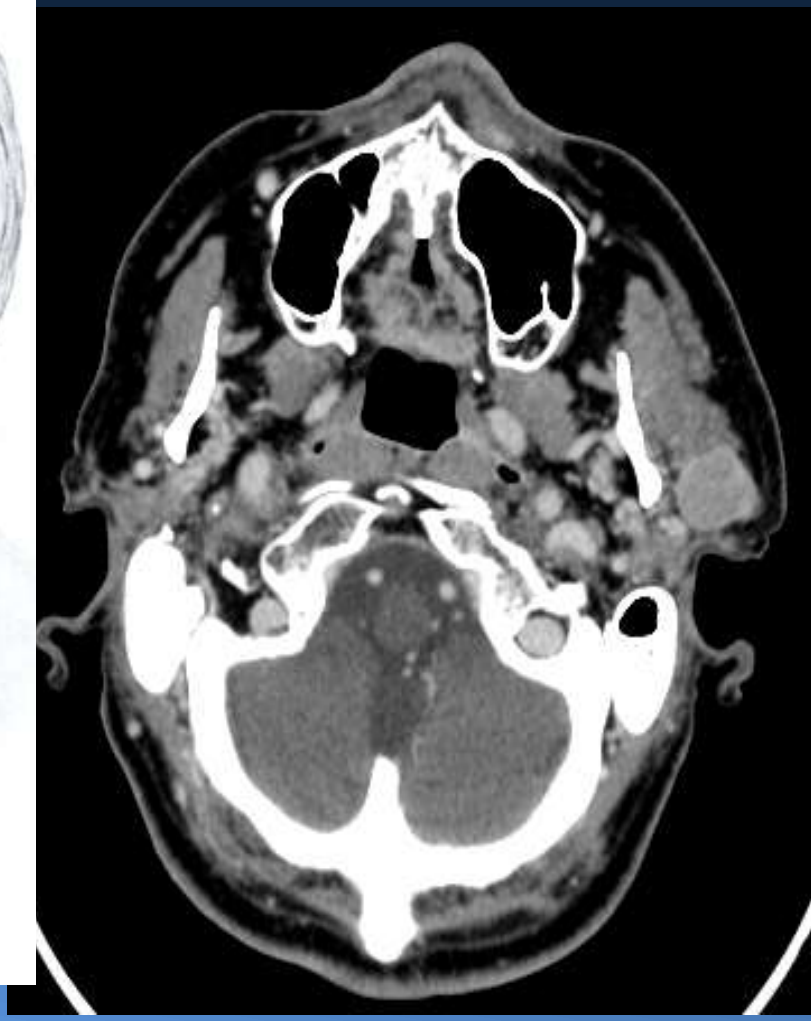
Did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases.

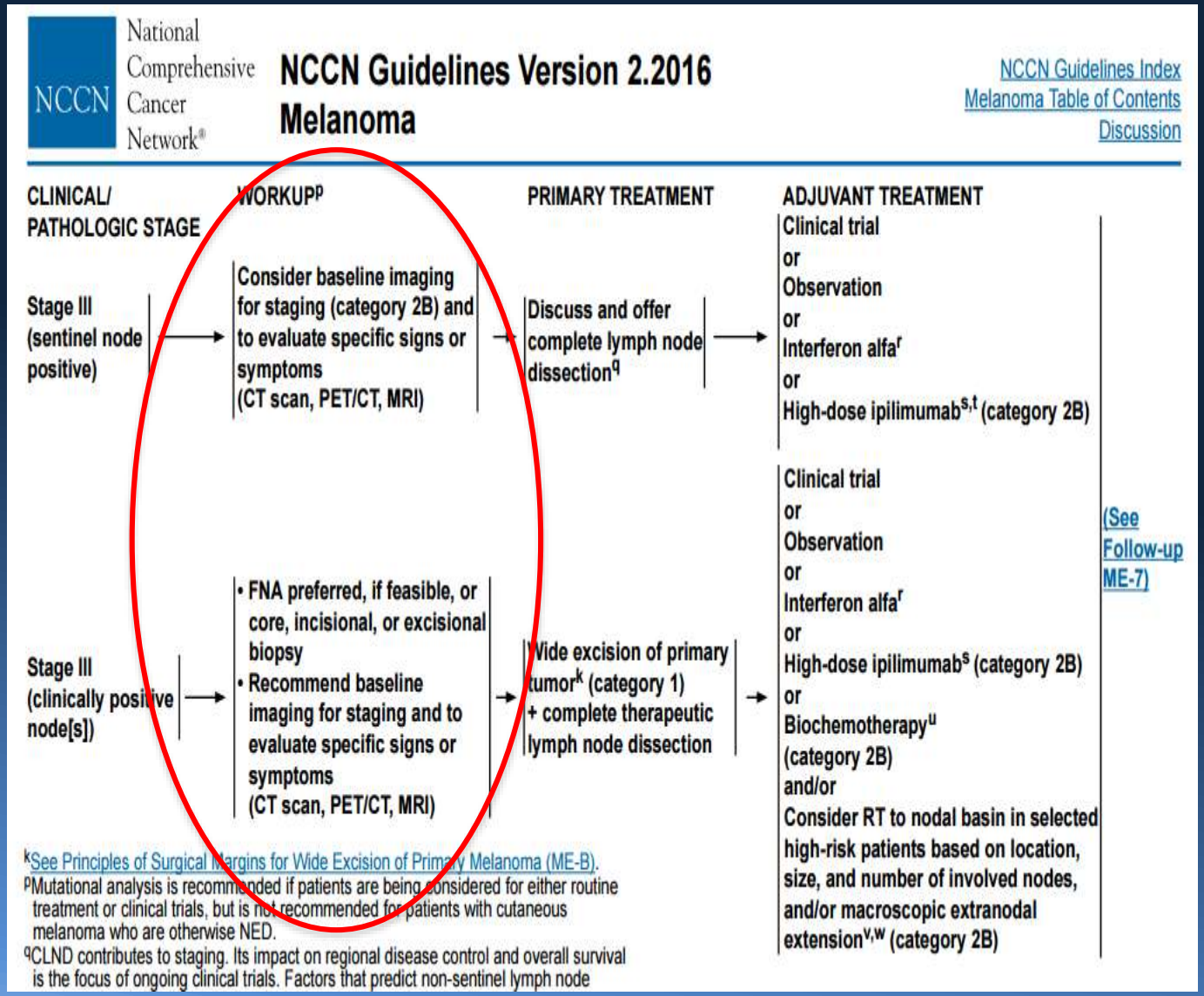
Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

- **Conclusions:**
- Immediate completion lymph-node dissection increased the rate of regional disease control
- and provided prognostic information but did not increase melanoma-specific survival
- among patients with melanoma and sentinel-node metastases. (Funded by the National
- Cancer Institute and others; MSLT-II ClinicalTrials.gov number, NCT00297895.)

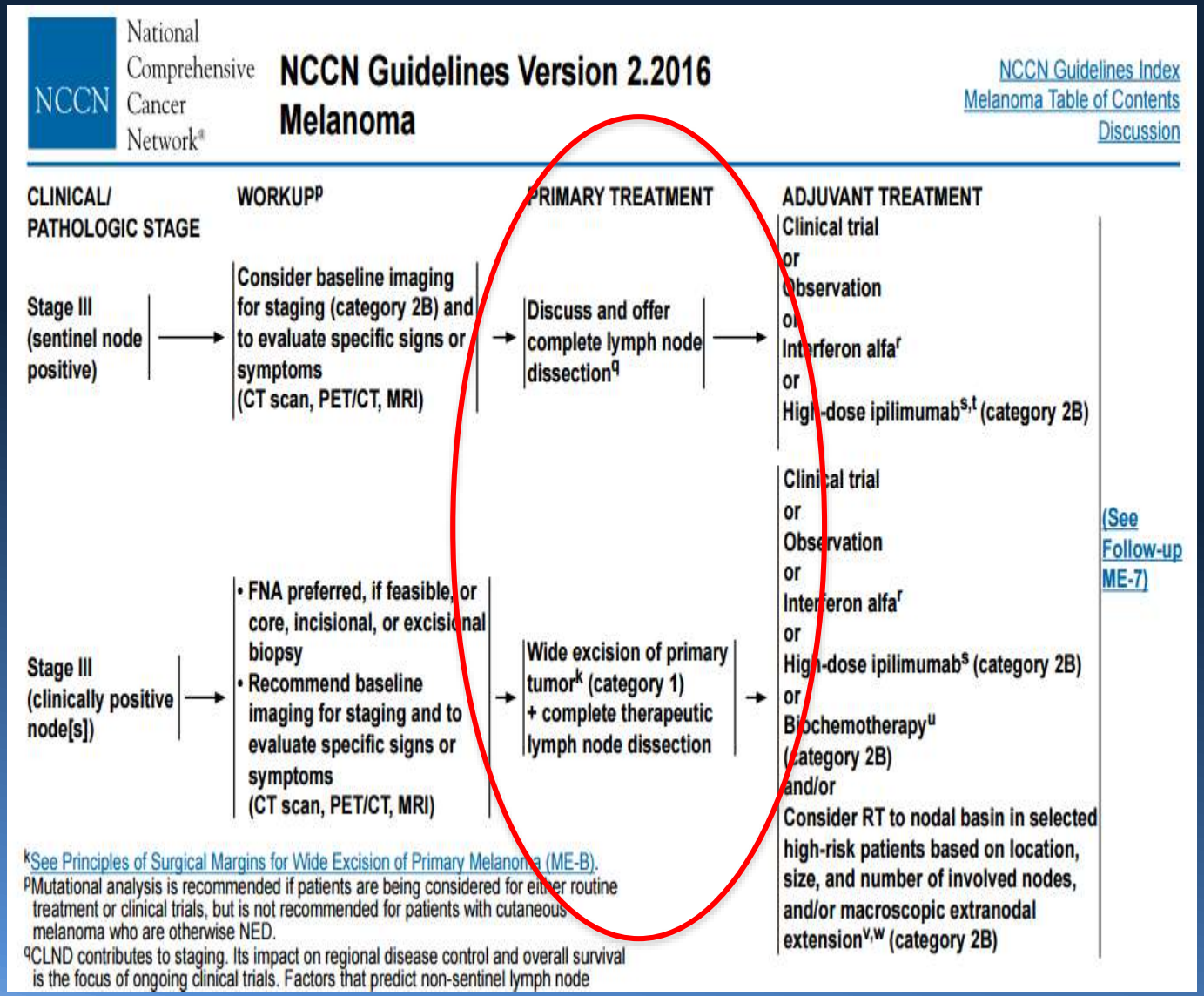
Management of the PN+ Neck Surgery: What levels to dissect






National Comprehensive Cancer Network
NCCN Guidelines Version 2.2016
Melanoma
NCCN Guidelines Index
Melanoma Table of Contents
Discussion
CLINICAL/ PATHOLOGIC STAGE
WORKUP[p]
PRIMARY TREATMENT
ADJUVANT TREATMENT
Stage III (sentinel node positive)
Consider baseline imaging for staging (category 2B) and to evaluate specific signs or symptoms (CT scan, PET/CT, MRI)
Discuss and offer complete lymph node dissection[q]
Clinical trial
or
Observation
or
Interferon alfa[r]
or
High-dose ipilimumab[s,t] (category 2B)
Stage III (clinically positive node[s])
• FNA preferred, if feasible, or core, incisional, or excisional biopsy
• Recommend baseline imaging for staging and to evaluate specific signs or symptoms (CT scan, PET/CT, MRI)
Wide excision of primary tumor[k] (category 1) + complete therapeutic lymph node dissection
Clinical trial
or
Observation
or
Interferon alfa[r]
or
High-dose ipilimumab[s] (category 2B)
or
Biochemotherapy[u] (category 2B)
and/or
Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, and/or macroscopic extranodal extension[v,w] (category 2B)
(See Follow-up ME-7)
[k]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[p]Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended for patients with cutaneous melanoma who are otherwise NED.
[q]CLND contributes to staging. Its impact on regional disease control and overall survival is the focus of ongoing clinical trials. Factors that predict non-sentinel lymph node

2017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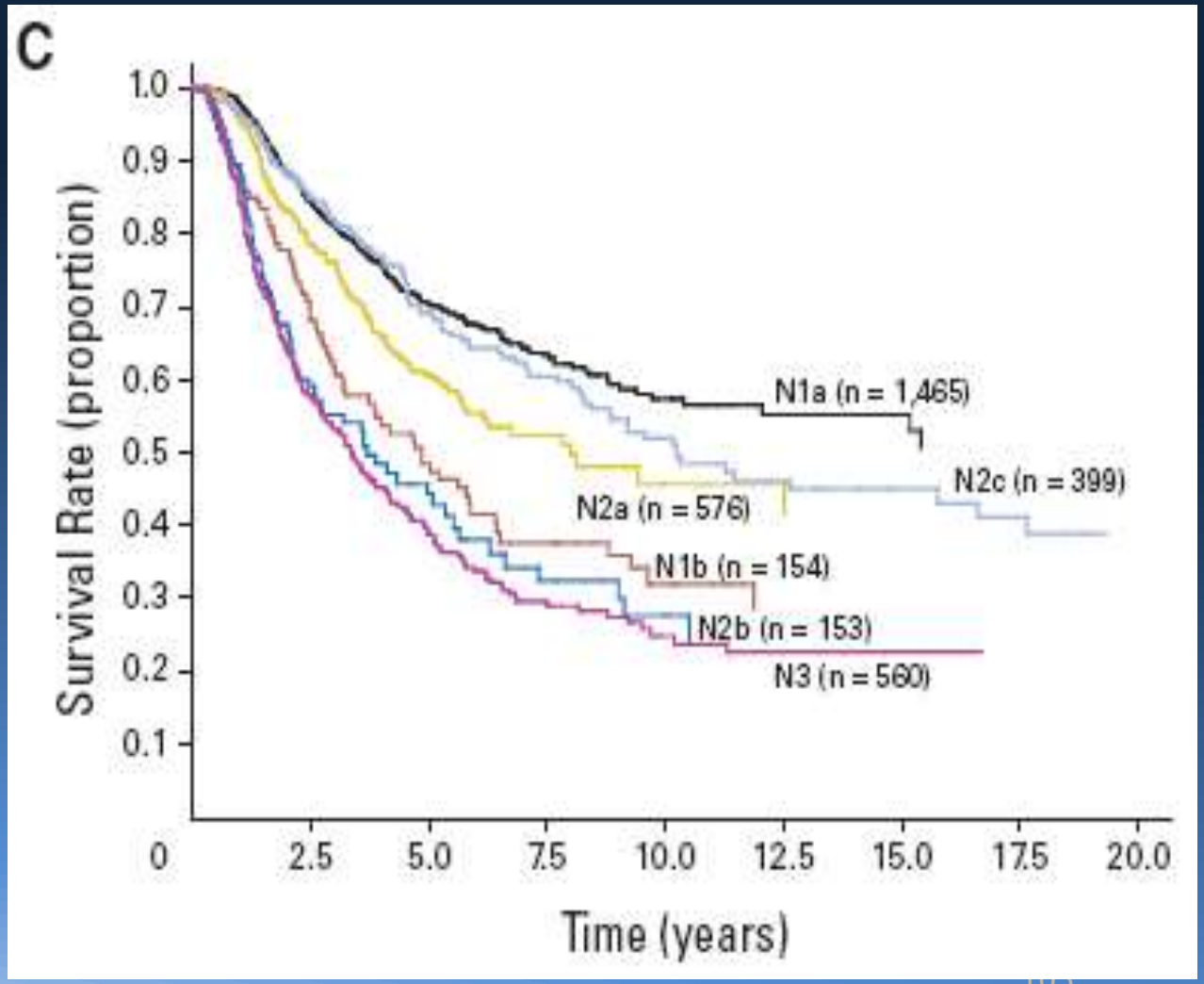
CLINICAL/ PATHOLOGIC STAGE
WORKUP[p]
PRIMARY TREATMENT
ADJUVANT TREATMENT
Stage III (sentinel node positive)
Consider baseline imaging for staging (category 2B) and to evaluate specific signs or symptoms (CT scan, PET/CT, MRI)
Discuss and offer complete lymph node dissection[q]
Clinical trial
or
Observation
or
Interferon alfa[r]
or
High-dose ipilimumab[s,t] (category 2B)
Stage III (clinically positive node[s])
• FNA preferred, if feasible, or core, incisional, or excisional biopsy
• Recommend baseline imaging for staging and to evaluate specific signs or symptoms (CT scan, PET/CT, MRI)
Wide excision of primary tumor[k] (category 1) + complete therapeutic lymph node dissection
Clinical trial
or
Observation
or
Interferon alfa[r]
or
High-dose ipilimumab[s] (category 2B)
or
Biochemotherapy[u] (category 2B)
and/or
Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, and/or macroscopic extranodal extension[v,w] (category 2B)
(See Follow-up ME-7)
[k] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[p] Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended for patients with cutaneous melanoma who are otherwise NED.
[q] CLND contributes to staging. Its impact on regional disease control and overall survival is the focus of ongoing clinical trials. Factors that predict non-sentinel lymph node

2017

Nodal Burden vs Outcome



ROLE OF RADIOTHERAPY

- 36 patients N+ cMMHN
  - 20 primary
  - 16 recurrent
- N+ with local excision of LN only + XRT
- 5 yr actuarial regional control 93%
- 5 yr actuarial DFS 59%

Ballo MT (2005) Head&Neck 27(8):718

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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Consider RT in the following situations:[1]

PRIMARY DISEASE

- Adjuvant treatment in selected patients with factors including, but not limited to deep desmoplastic melanoma with narrow margins, extensive neurotropism, or locally recurrent disease.

REGIONAL DISEASE[2]

- Adjuvant treatment in selected patients following resection of clinically appreciable nodes (category 2B)[3] if
  - Extranodal tumor extension AND/OR
    - Parotid: ≥1 involved node, any size of involvement
    - Cervical: ≥2 involved nodes and/or ≥3 cm tumor within a node
    - Axillary: ≥2 involved nodes and/or ≥4 cm tumor within a node
    - Inguinal: ≥3 involved nodes and/or ≥4 cm tumor within a node
- Palliative
  - Unresectable nodal, satellite, or in-transit disease

METASTATIC DISEASE

- Brain metastases (See NCCN Guidelines for Central Nervous System Cancers)
  - Stereotactic radiosurgery either as adjuvant or primary treatment
  - Whole brain radiation therapy, either as adjuvant (category 2B) or primary treatment[4]
- Other symptomatic or potentially symptomatic soft tissue and/or bone metastases[2]

Adjuvant RT

- Aim: improves regional control without unacceptable complications
- ? survival benefit
- Indications based on histopathological findings

Published data on role of adjuvant RT

- Only randomized data: Creagan et al. 1978
- 56 pts
- Sx vs Sx + RT (unusual split course)
- Trend toward better DFS
- No comment on locoregional control

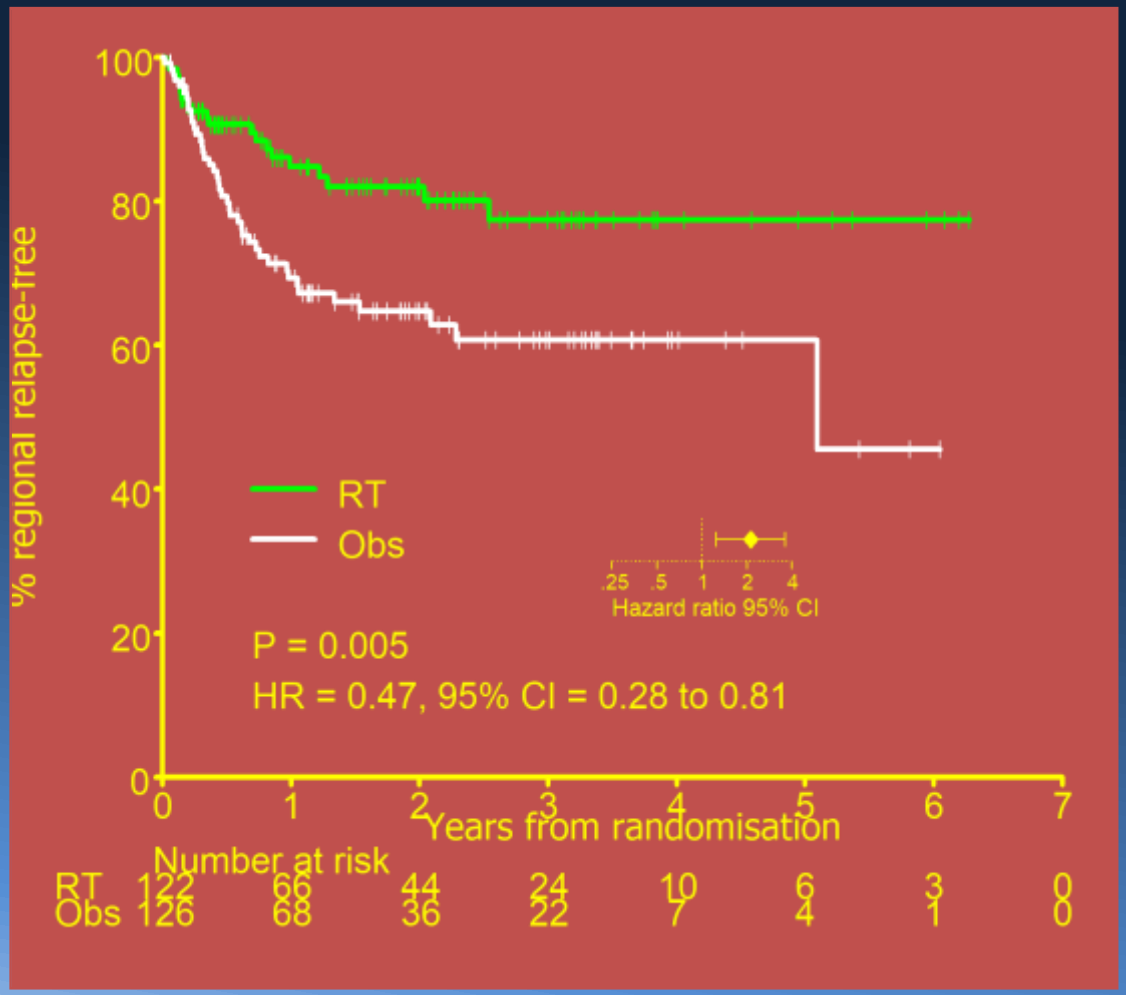
TROG 96.06: Single arm phase II trial of adjuvant radiotherapy after lymphadenectomy

- 234 patients
- Radiotherapy: 48 Gy in 20 fraction given 5 days per week
- Lymph node field relapse rate 7%
- Late grade 3 toxicity (fibrosis, lymphoedema)
  - Axilla 9%
  - Groin 19%

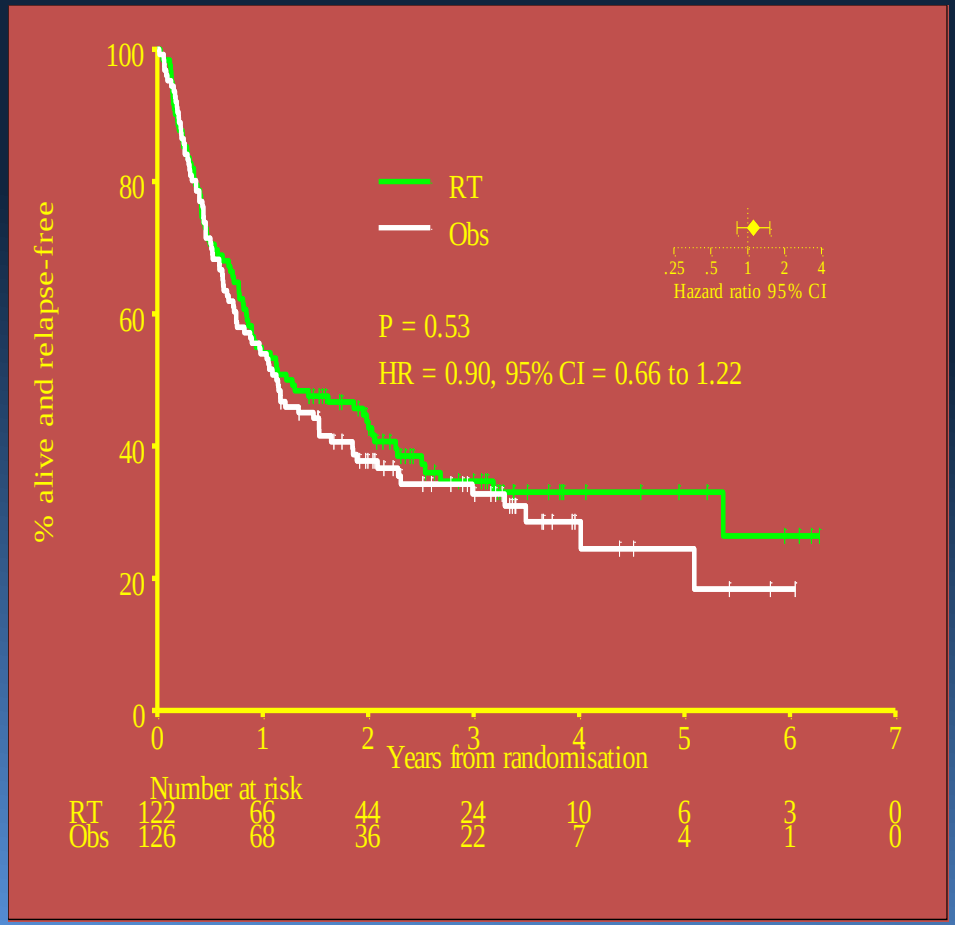
Burmeister et al., ANZ J Surg 72: 344-48; 2002

Burmeister et al., Radiotherapy and Oncology 81: 136-42; 2006

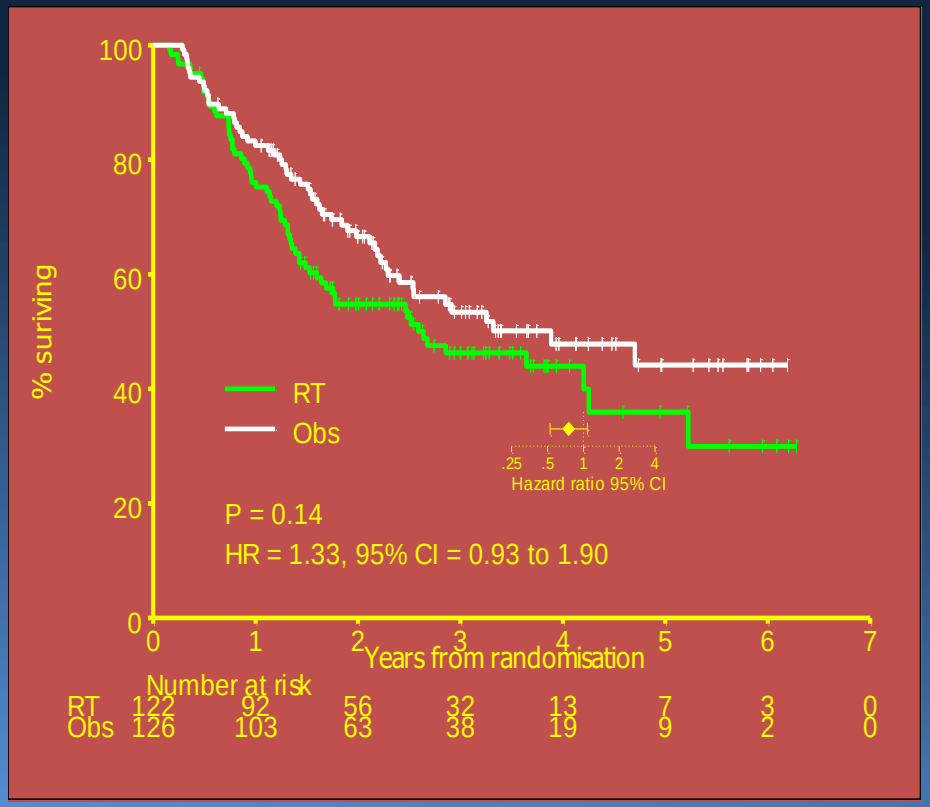
Time to LN field relapse by arm



No significant difference in relapse free survival (2 yr 44% vs 38%, p=0.53)



No significant difference in overall Survival (2yr 55% vs 67%, p=0.14)



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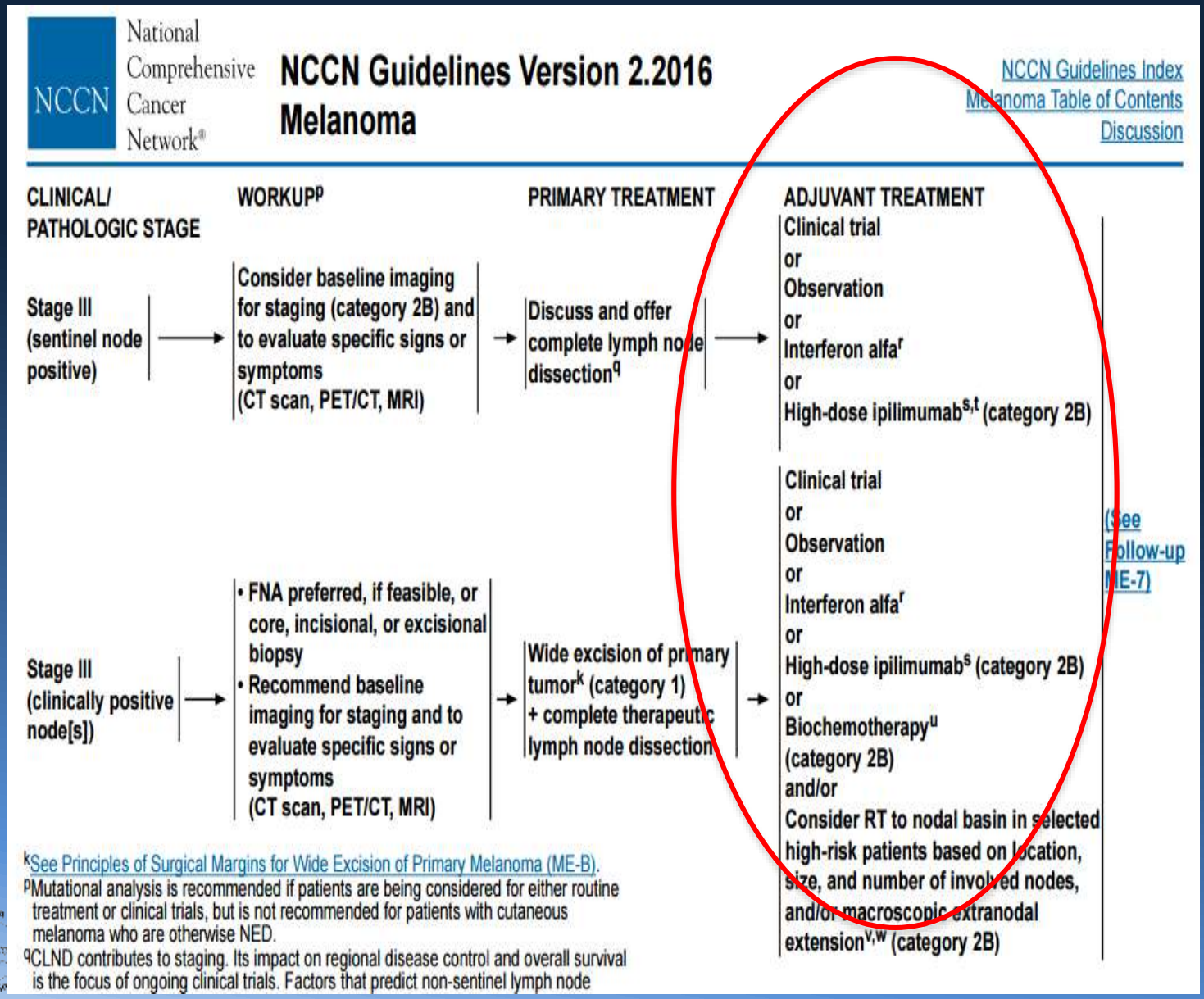
Systemic Therapy



CONCLUSIONS

- A new era in systemic treatment for advanced stage melanoma
  - Targeted therapy: BRAF and MEK mutations
    - Some remarkable responses but resistance develops rapidly
  - Immunotherapy
    - Targets PD-1 and CTLA 4
    - 30% response, durable remissions in some patients
    - Need predictive biomarkers
    - Expensive
  - In the future patients at high risk will receive biomarker driven combinatorial therapy

Adjuvant Therapy

- Chemotherapy
  - Dacarbazine (DTIC)
- Interferon
  - 1% survival benefit approx
- Immunotherapy
- Postoperative Radiation Therapy

Conclusions

- Adjuvant RT improves nodal control
- Acceptable early toxicities
- No overall survival benefit
- Await QoL and lymphoedema data

Conclusions

- Nodal status most significant predictor of disease free and overall survival
- SNB standard of care
- Better outcomes with therapeutic dissection for microscopic disease, but era of ELND over
- Therapeutic dissection may be selective
- Surgery remains the mainstay of regional metastatic melanoma treatment

CONCLUSIONS

- Challenging disease with early metastasis
- Imperative for accurate staging
  - Pre-op: pathology, nodal staging
  - Intra-op: WLE + SLNB
  - Post-op: Pathologic staging, margin status, reconstruction