Lymph Nodes and Melanoma

Changing Paradigm

Vancouver 2019

Disclosures

- none

Objectives

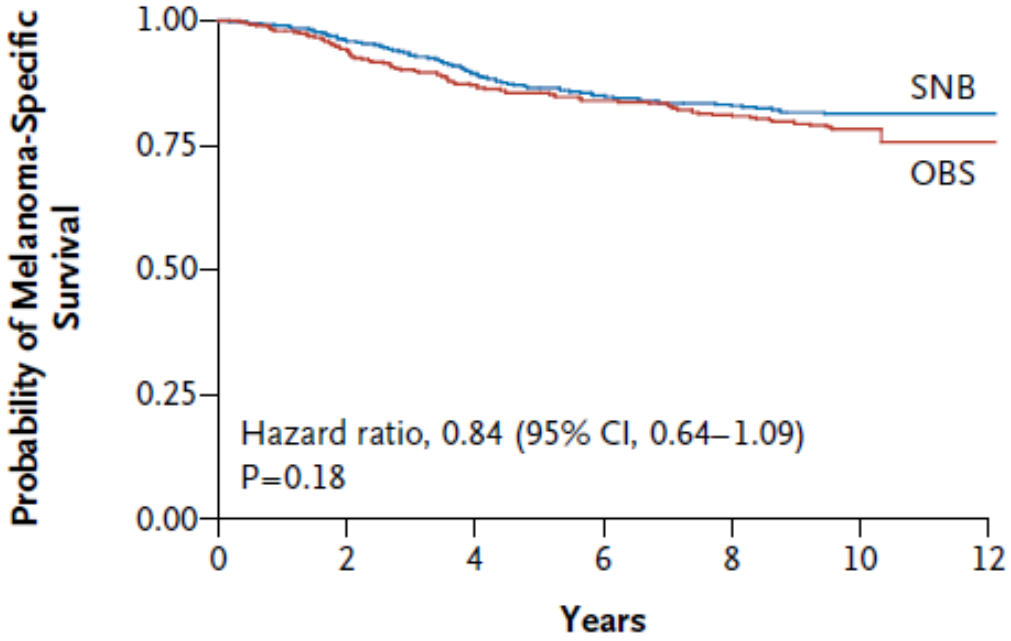
- Change in indications for SNB?
- What is the role of completion node dissection?

Change in indications for SNB?

MSLT-I 2014

A Melanoma-Specific Survival, Intermediate-Thickness Melanomas

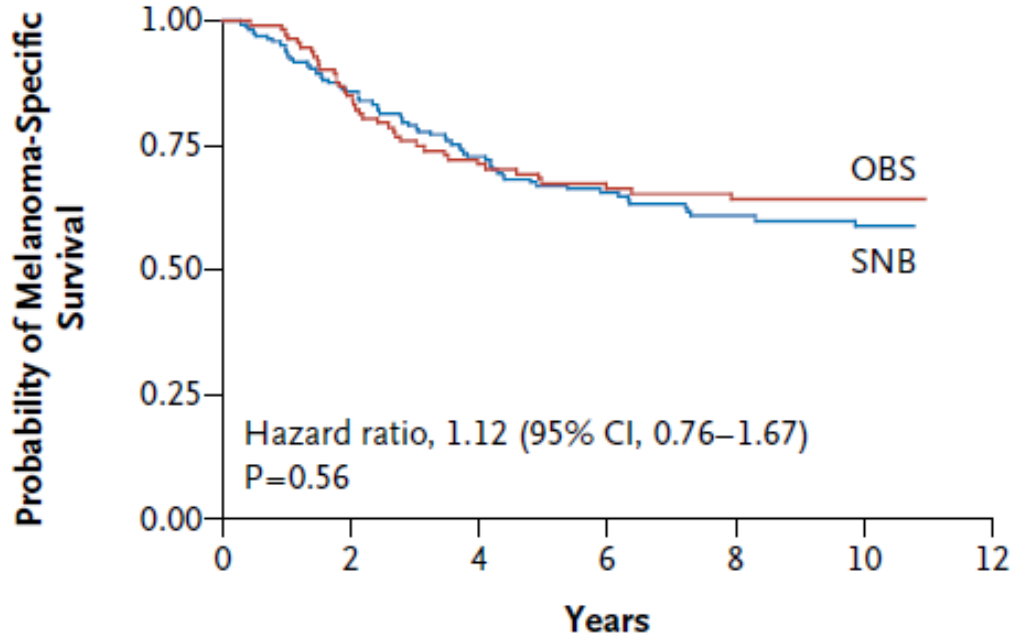
	No. of Events/ Total No.	Rate (%) Yr 5	Rate (%) Yr 10
OBS	97/500	85.7±1.6	78.3±2.0
SNB	125/770	86.6±1.3	81.4±1.5



No. at Risk							
OBS	500	448	390	351	318	191	4
SNB	770	700	611	530	467	282	5

B Melanoma-Specific Survival, Thick Melanomas

	No. of Events/ Total No.	Rate (%) Yr 5	Rate (%) Yr 10
OBS	39/117	67.5±4.5	64.4±4.6
SNB	64/173	67.0±3.7	58.9±4.1



No. at Risk							
OBS	117	94	76	68	57	34	0
SNB	173	143	115	91	70	41	0

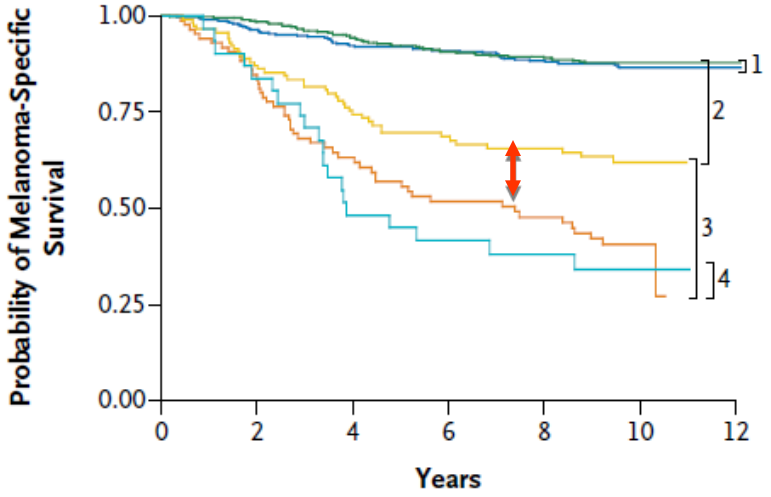
The NEW ENGLAND JOURNAL of MEDICINE

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

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

C Melanoma-Specific Survival, Intermediate-Thickness Melanomas

	No. of Events/ Total No.	Rate (%) Yr 5	Yr 10
OBS, no nodal recurrence	48/413	92.0±1.4	86.6±1.8
OBS, nodal recurrence	49/87	57.5±5.4	41.5±5.6
SNB, true neg.	63/612	92.3±1.1	88.0±1.4
SNB, pos.	41/122	69.8±4.4	62.1±4.8
SNB, false neg.	20/31	45.2±8.9	34.4±8.7

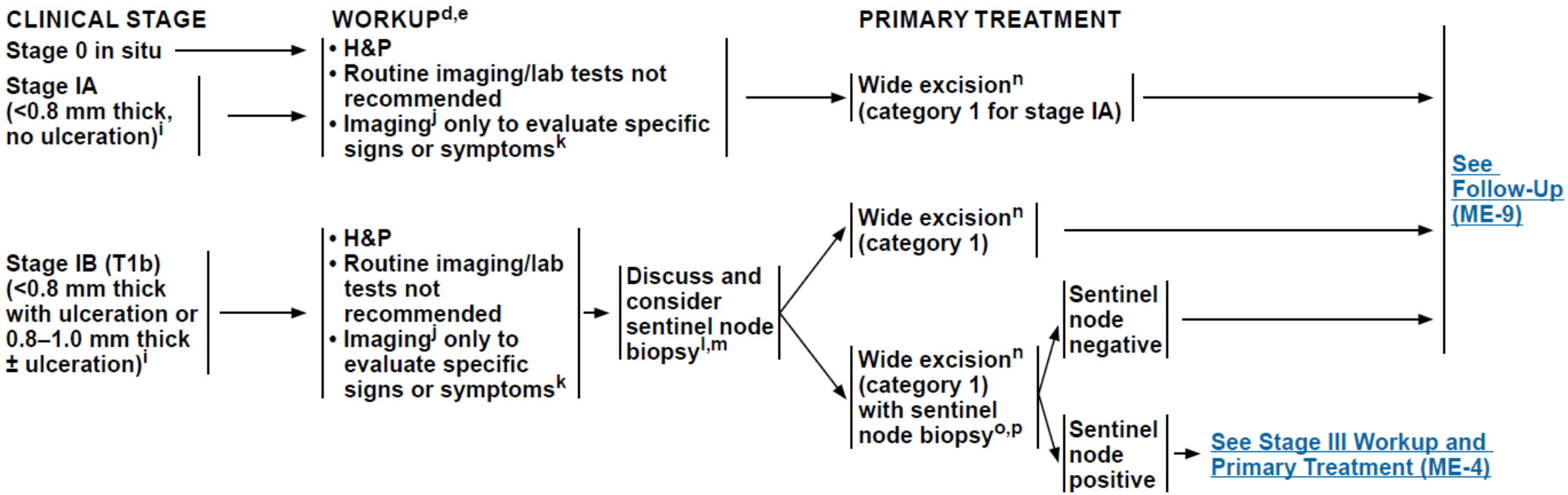


Indications for SNB in Melanoma

- Standard practice in most of the world
- Controversial issues relate to thin or thick melanomas
- Change in AJCC staging have confused the picture

NCCN Guidelines Version 2.2019
Cutaneous Melanoma

NCCN Guidelines Index
Table of Contents
Discussion



[i]If a patient's risk of a positive sentinel lymph node (SLN) is <5%, NCCN does not recommend SLNB. This would include clinical stage IA, T1a melanoma with Breslow depth of <0.8 mm without ulceration, or other adverse features, unless there is significant uncertainty about the adequacy of microstaging (positive deep margins). If a patient's risk of a positive SLNB is 5%–10%, NCCN recommends discussing and considering SLNB. This would include clinical stage IB, T1b melanoma (Breslow depth <0.8 mm with ulceration or 0.8–1 mm with or without ulceration), or T1a lesions with Breslow depth <0.8 mm and with other adverse features (eg, very high mitotic index ≥2/mm^2 [particularly in the setting of young age], lymphovascular invasion, or a combination of these factors).

[d]While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate melanomas at low versus high risk for metastasis, routine (baseline) prognostic genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside of a clinical study (trial). Newer prognostic molecular techniques should not replace standard staging procedures. See Principles of Molecular Testing (ME-C).

[e]Mutational analysis for *BRAF* or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma who are without evidence of disease (NED), unless required to guide adjuvant or other systemic therapy or consideration of clinical trials. See Principles of Molecular Testing (ME-C).

[k]Consider nodal basin ultrasound (US) prior to SLNB for melanoma patients with an equivocal regional lymph node physical exam. Nodal basin US is not a substitute for SLNB. Negative nodal basin US is not a substitute for biopsy of clinically suspicious lymph nodes. Abnormalities or suspicious lesions on nodal basin US should be confirmed histologically.

[l]Decision not to perform SLNB may be based on significant patient comorbidities, patient preference, or other factors.

[m]SLNB is an important staging tool. While SLNB itself has not been shown to improve disease-specific survival (DSS), a positive SLNB would upstage a patient to stage III. Adjuvant therapy has been shown to improve recurrence-free survival

CURRENT ONCOLOGY
A Canadian Cancer Research Journal

PRACTICE GUIDELINE

Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline

F.C. Wright MEd MD,* L.H. Souter PhD,† S. Kellett MEnvSc,† A. Easson MD MSc,‡ C. Murray MD,§ J. Toye MD,|| D. McCready MD MSc,‡ C. Nessim MD,# D. Ghazarian MD,** N.J. Look Hong MD MSc,†† S. Johnson MD,# D.P. Goldstein MD,** T. Petrella MD,* and the Melanoma Disease Site Group

Recommendation 3—SLNB for Melanoma Located on the Trunk and Extremities

Patients with a clinically node-negative stage I or II melanoma 0.8 mm in thickness and located on the trunk or extremities should be given the opportunity to discuss SLNB to provide staging and prognostic information (Table IV).

Curr Oncol. 2019 August;26(4):e541-e550

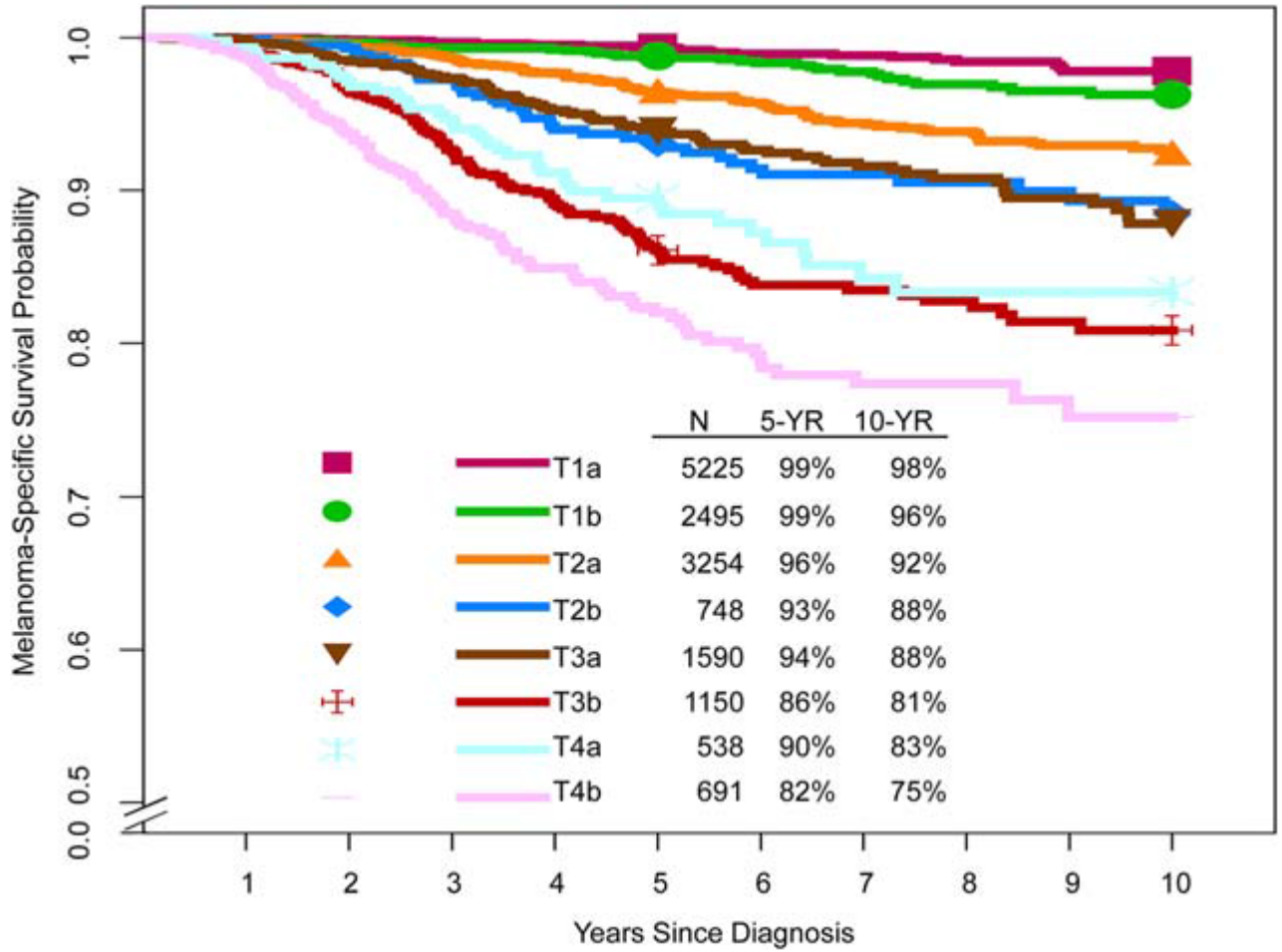
AJCC 8th Edition

- T1A is <0.8 mm
- T1B is 0.8-1.0 or ulcerated
- Mitotic rate is removed from staging system

Changes in T1 status

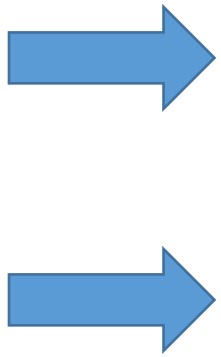
- T1b now defined as 0.8 – 1.0 mm or <0.8 ulcerated
- 70% of new diagnoses are T1
- T1 cause @29% of melanoma deaths

AJCC data 8th edition



8th Edition N staging

- N1a = one clinically occult positive SN
- N2a = more than one positive SN



AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions

(1) Select patient's N category at left chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID

Survival with positive SNB in T1 tumors

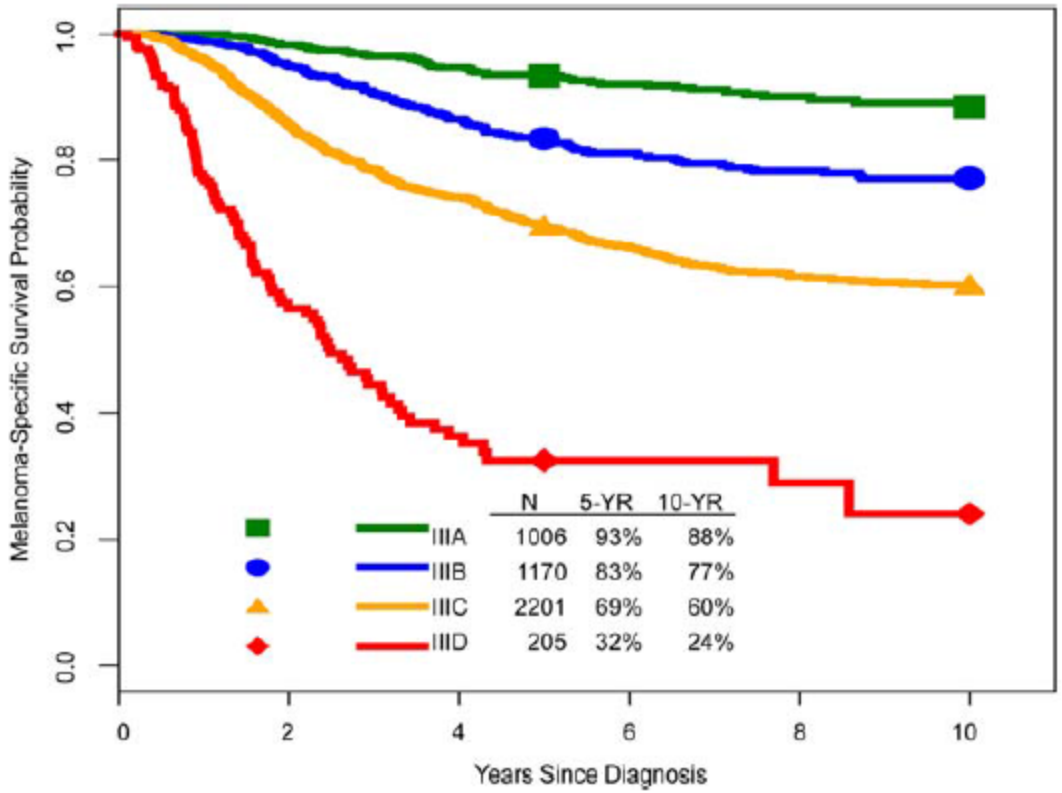
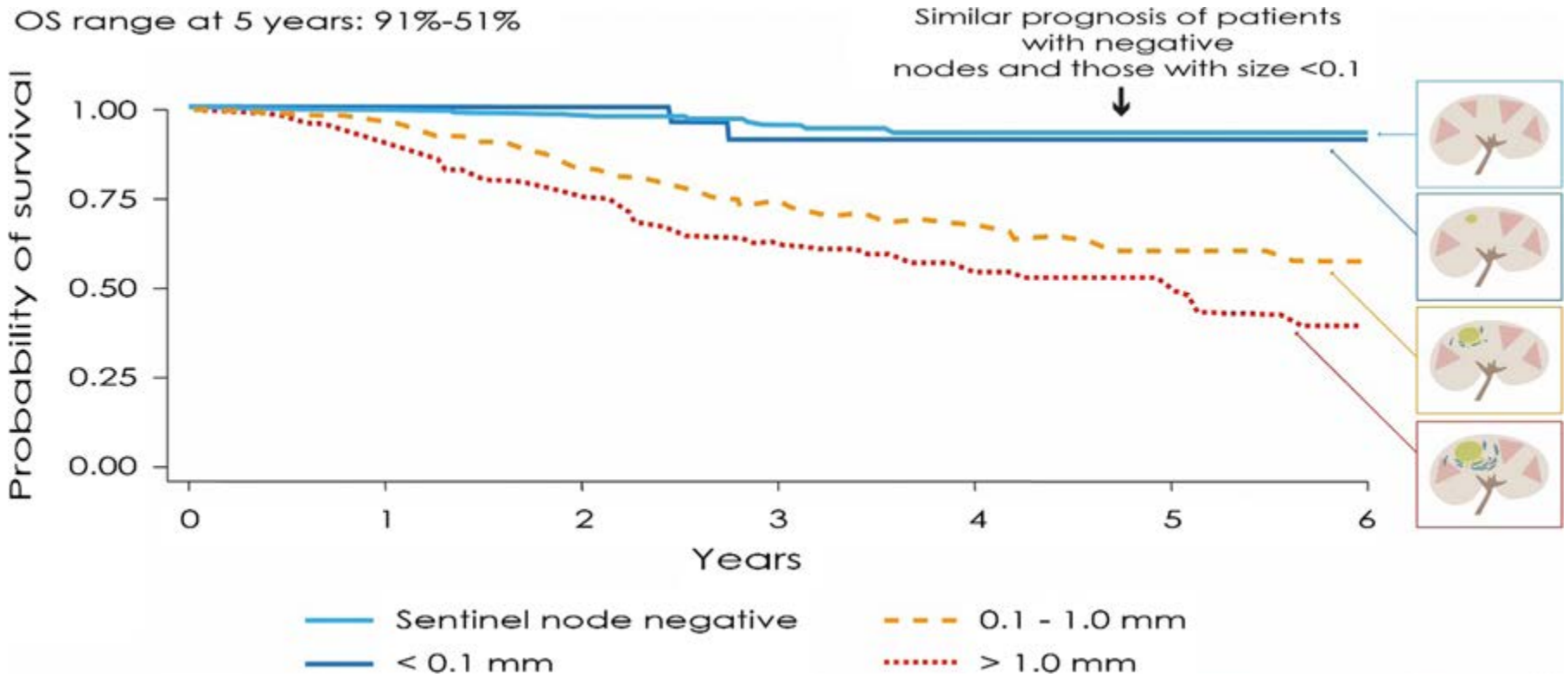


FIGURE 7. Kaplan-Meier Melanoma-Specific Survival Curves According to Stage III Subgroups From the Eighth Edition International Melanoma Database.



J Transl Med (2019) 17:266

What about likelihood of positivity?

had a sentinel lymph node biopsy or who have enlarged lymph nodes in proximity to the melanoma on physical examination. **more...**

Enter Your Information

Clear Calculate

All fields are required unless noted optional

How old are you?

55 years (20 to 95)

What was the thickness of your melanoma?

0.8 mm (0.1 to 10)

Note: If the tumor thickness is less than 0.1 mm, enter as 0.1 mm.

What was your Clark level?

Level IV

Note: This prediction tool applies only to Clark levels II to V.

▸ More on Clark levels:

Where was your melanoma located?

Extremity

Was there ulceration reported in your pathology report?

Yes No

▸ What is ulceration?

Melanoma Information

Learn more about melanoma, including skin melanoma and eye (ocular) melanoma, and find out how MSK is improving the outlook for people with these cancers.

Learn more »

Melanoma Screening Information

Each year more than a million people in the United States are diagnosed with the most common forms of skin cancer. Fortunately there are ways to detect most non-melanoma skin cancers early, when they are curable.

Learn more »

New Patient Appointments

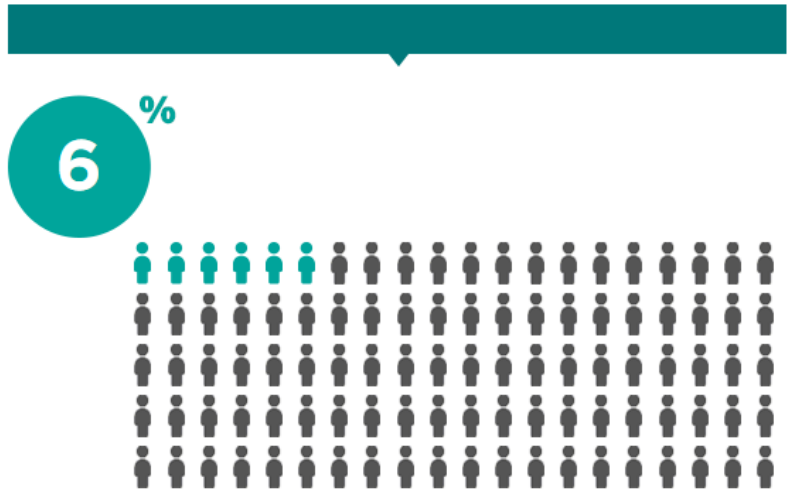
Risk of Sentinel Lymph Node Metastasis

Your Results

Edit Information

PROBABILITY OF SENTINEL LYMPH NODE METASTASIS

6 %



This number shows, as a percentage, the probability that your skin melanoma has metastasized (spread) to the sentinel lymph node (the first lymph node to which cancer cells are likely to spread from the primary tumor). This probability means that for every 100 patients like you, we expect that 6 have

Your Information Worksheet

If you are a patient, print the Risk of Sentinel Lymph Node Metastasis Worksheet and bring it with you to your next appointment. The worksheet contains a list of what you need to use this prediction tool.

Print worksheet »

Melanoma Information

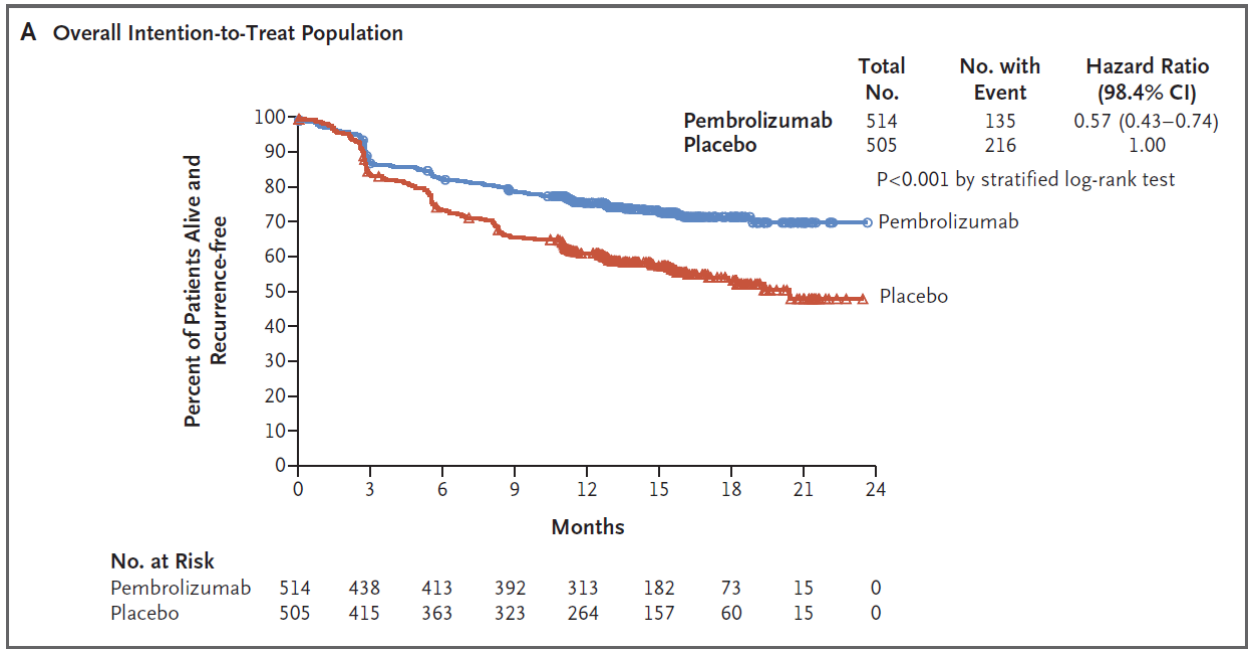
Learn more about melanoma, including skin melanoma and eye (ocular) melanoma, and find out how MSK is improving the outlook for people with these cancers.

Learn more »

Melanoma Screening Information

Each year more than a million people in the United States are

Adjuvant in high risk resected melanoma



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

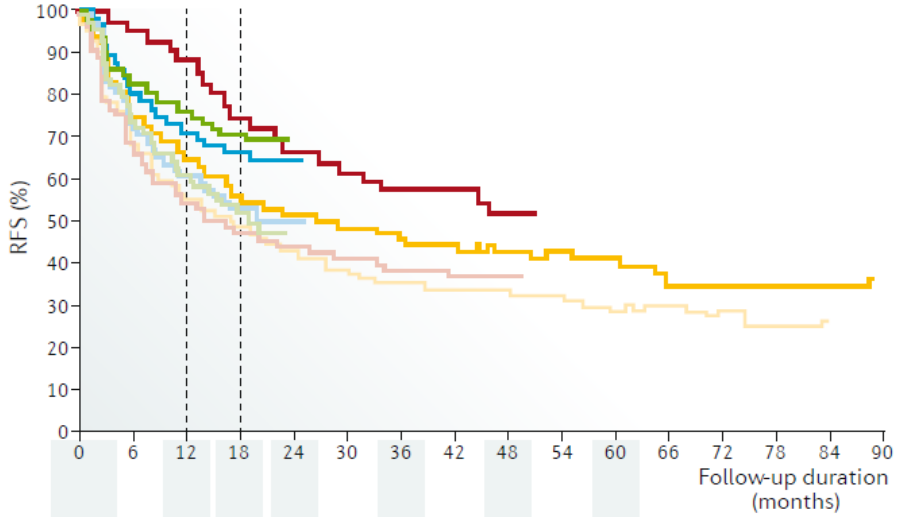
Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

April 2018

Adjuvant therapies summary

NATURE REVIEWS | CLINICAL ONCOLOGY

VOLUME 15 | SEPTEMBER 2018 | 535



Placebo (EORTC 18071)	100%	56%	49%	–	–	–	30%	HR 0.76, 95% CI 0.64–0.89
Ipilimumab (EORTC 18071)	100%	65%	57%	–	–	–	41%	
Placebo (COMBI-AD)	100%	56%	49%	44%	39%	–	–	HR 0.47, 95% CI 0.39–0.58
Dabrafenib + trametinib (COMBI-AD)	100%	88%	73%	67%	58%	–	–	
Ipilimumab (CheckMate 238)	100%	61%	53%	–	–	–	–	HR 0.65, 97.6% CI 0.51–0.83
Nivolumab (CheckMate 238)	100%	71%	66%	–	–	–	–	
Placebo (KEYNOTE-054)	100%	61%	53%	–	–	–	–	HR 0.57, 98.4% CI 0.43–0.74
Pembrolizumab (KEYNOTE-054)	100%	75%	71%	–	–	–	–	

Fig. 1 | **Kaplan–Meier curves of estimated RFS in key trials of adjuvant therapies for melanoma**[2–5]. RFS, relapse-free survival.

Regional control after SNB

- MSLT-I clearly showed that microscopic disease will eventually become macro
- MSLT-II observation group did not recur in the nodal basin in 80% of cases (n = 855)
- SND in itself provides regional control in the majority of patients

M Faries: personal communication

What about morbidity of SNB?

Ann Surg Oncol (2017) 24:2071–2079
DOI 10.1245/s10434-017-5842-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEALTH SERVICES RESEARCH AND GLOBAL ONCOLOGY

Quality of Life Following Sentinel Node Biopsy for Primary Cutaneous Melanoma: Health Economic Implications

Rachael L. Morton, PhD, MScMed (Clin Epi) (Hons)[1], Anh Tran, PhD[1], Johan Yusof Vessey, BSc (Hons), MBBS[2], Nick Rowbotham, BEcon[1], Julie Winstanley, PhD, MSc, CStat[3], Kerwin Shannon, MBBS, FRACS[4,5,6], Andrew J. Spillane, MBBS, MD, FRACS[5,6], Jonathan Stretch, MBBS, DPhil, FRACS[4,5,6], John F. Thompson, MBBS, MD, FRACS, FACS[4,5,6], and Robyn P.-M. Saw, MBBS, MS, FRACS[4,5,6]

TABLE 2 Mean perometer measurements of ipsilateral and contralateral limbs ($n = 694$)

	Difference, in mL [mean (SD)]	Difference, in mL [median (IQR)]	% difference [mean (SD)]
Upper limbs	−8.5 (160.5)	−4.0 (−104 to 83)	0.0 (0.05)
Lower limbs	141.3 (320.2)	110 (−68 to 291.5)	0.02 (0.04)
$n \geq 10\%$ increase in limb volume	14		

SD standard deviation, *IQR* interquartile range

Morbidity of SNB versus CLND in MSLT-II

- Lymphedema after SNB = 6.3%
- Lymphedema after CLND = 24.1%

Argument for SNB

Node status is important for prognosis

Majority of node positive patients will be spared a CLND

Node positive patients may be eligible for effective adjuvant therapy

SNB for T1b?

- 6-15% positive
- Of those, most will be spared a regional recurrence
- Of those, many will be eligible for adjuvant therapy (indications will likely broaden to <1 mm size)
- Highest morbidity is in inguinal nodes
- Decision is individualized

Example 1

- 31 year old male otherwise healthy
- 0.9 mm melanoma over upper scapula, non-ulcerated, MR =2, Clark IV
- Probability of positive node is 8% in axilla or neck
- If positive could be maximum potential benefit of 20% survival = 1.6%
- If met > 1mm will be eligible for adjuvant – approx. benefit similar
- If positive but no SNB then **will** need therapeutic node dissection
- Peace of mind?

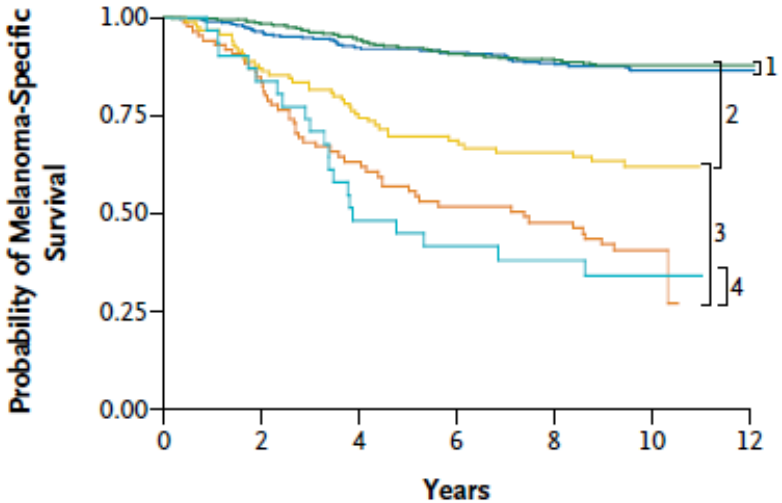
Example 2

- 25 year old male otherwise healthy
- 0.9 mm melanoma over upper scapula, ulcerated, MR =2, Clark IV
- Probability of positive node is 14% in axilla or neck
- If positive could be maximum potential benefit of 20% survival = 2.8%
- If met > 1mm will be eligible for adjuvant – approx. benefit similar
- If positive but no SNB then **will** need therapeutic node dissection
- Peace of mind?

What about melanomas > 4mm thick?

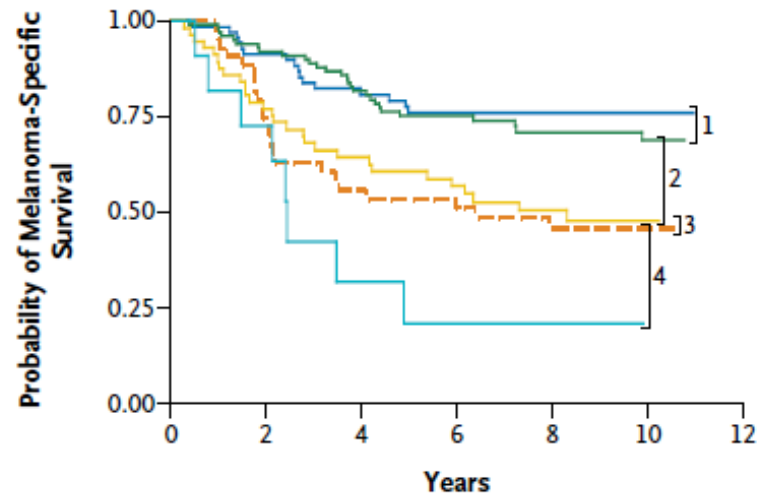
C Melanoma-Specific Survival, Intermediate-Thickness Melanomas

	No. of Events/ Total No.	Rate (%) Yr 5	Yr 10
OBS, no nodal recurrence	48/413	92.0±1.4	86.6±1.8
OBS, nodal recurrence	49/87	57.5±5.4	41.5±5.6
SNB, true neg.	63/612	92.3±1.1	88.0±1.4
SNB, pos.	41/122	69.8±4.4	62.1±4.8
SNB, false neg.	20/31	45.2±8.9	34.4±8.7



D Melanoma-Specific Survival, Thick Melanomas

	No. of Events/ Total No.	Rate (%) Yr 5	Yr 10
OBS, no nodal recurrence	16/73	76.1±5.2	76.1±5.2
OBS, nodal recurrence	23/44	53.8±7.6	45.8±7.8
SNB, true neg.	27/104	76.0±4.4	69.8±5.0
SNB, pos.	28/57	60.8±6.6	48.0±7.0
SNB, false neg.	9/12	19.4±12.2	—



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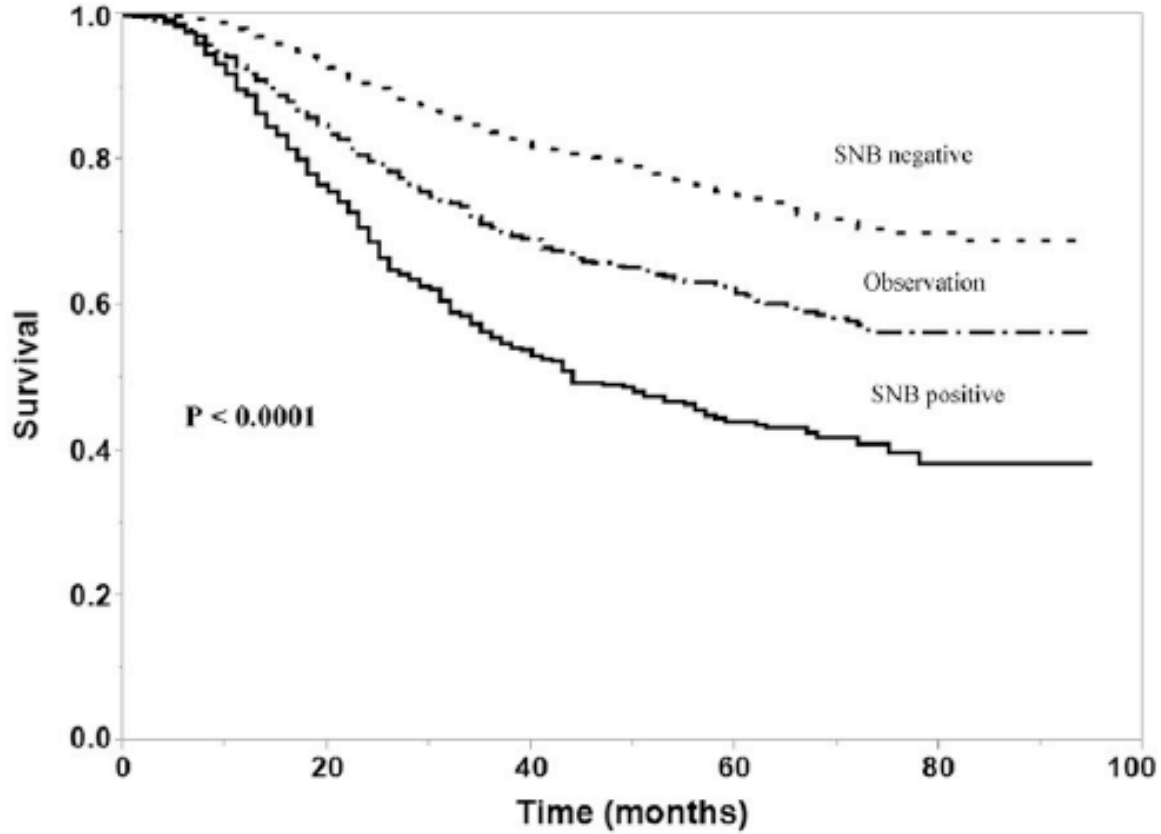


Figure. Disease-specific survival for positive versus negative sentinel lymph node biopsy (SNB), Surveillance Epidemiology and End Results 2003–2010.

Sentinel lymph node biopsy
is prognostic but not therapeutic
for thick melanoma

Swapnil D. Kachare, MD, MBA,[a,b] Patreek Singla, BS,[a] Nasreen A. Vohra, MD,[a,b]
Emmanuel E. Zervos, MD,[a,b] Jan H. Wong, MD,[a,b] *and* Timothy L. Fitzgerald, MD,[a,b] *Greenville, NC*

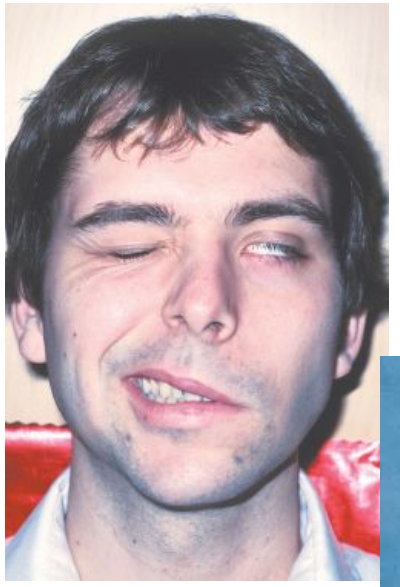
Surgery
Volume 158, Number 3

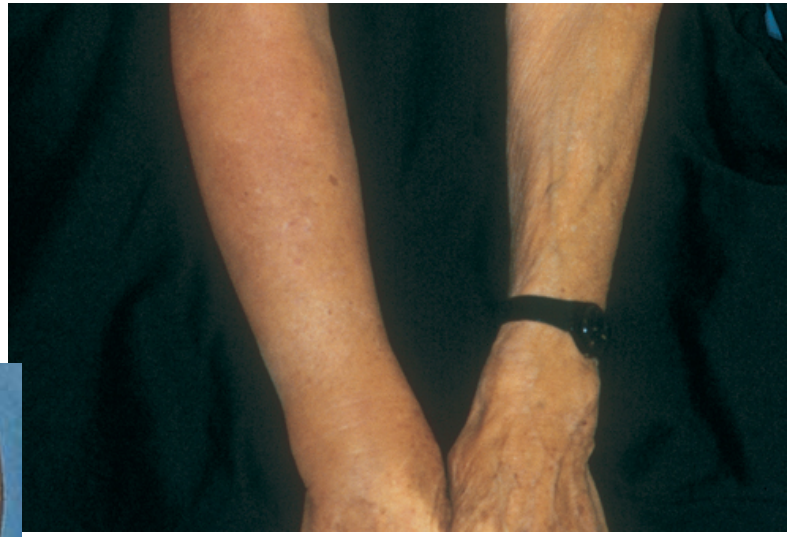
SNB in thick melanoma

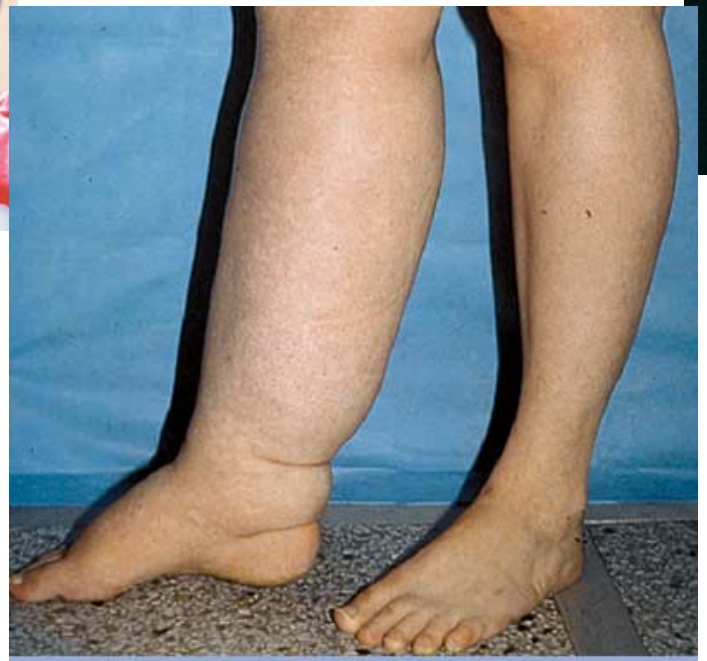
- Prevents CLND in majority of patients
- Allows access to effective adjuvant therapy

Completion Node Dissection?

Consequences of CLND







Ann Surg Oncol (2011) 18:1453–1459
DOI 10.1245/s10434-010-1450-0

Annals of
SURGICAL ONCOLOGY
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ORIGINAL ARTICLE – MELANOMAS

Regional Control and Morbidity After Superficial Groin Dissection in Melanoma

Amber L. Shada, MD and Craig L. Slingluff Jr, MD

Department of Surgery, University of Virginia, Charlottesville, VA

TABLE 3 Complications after superficial groin dissection

Complication	Patients, no. (%)	Published range, %[6,7,12,14–16,19]
Seroma/lymphocele	9 (17)	5–39
Wound breakdown	12 (23)	7–65
Wound infection	22 (42)	13–33
Lymphedema	21 (40)	14–51
Prolonged drain use	19 (36)	N/A

N/A not available

DeCOG trial

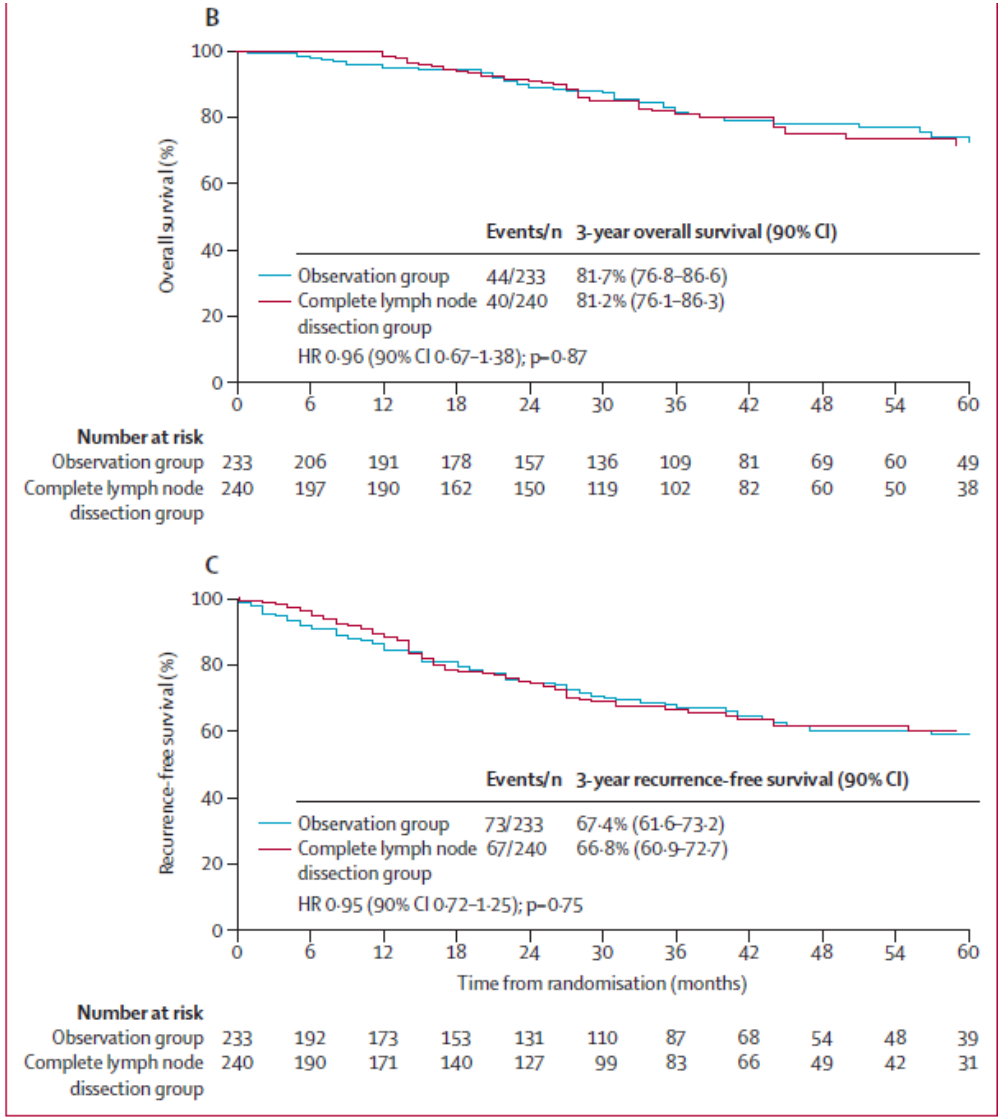


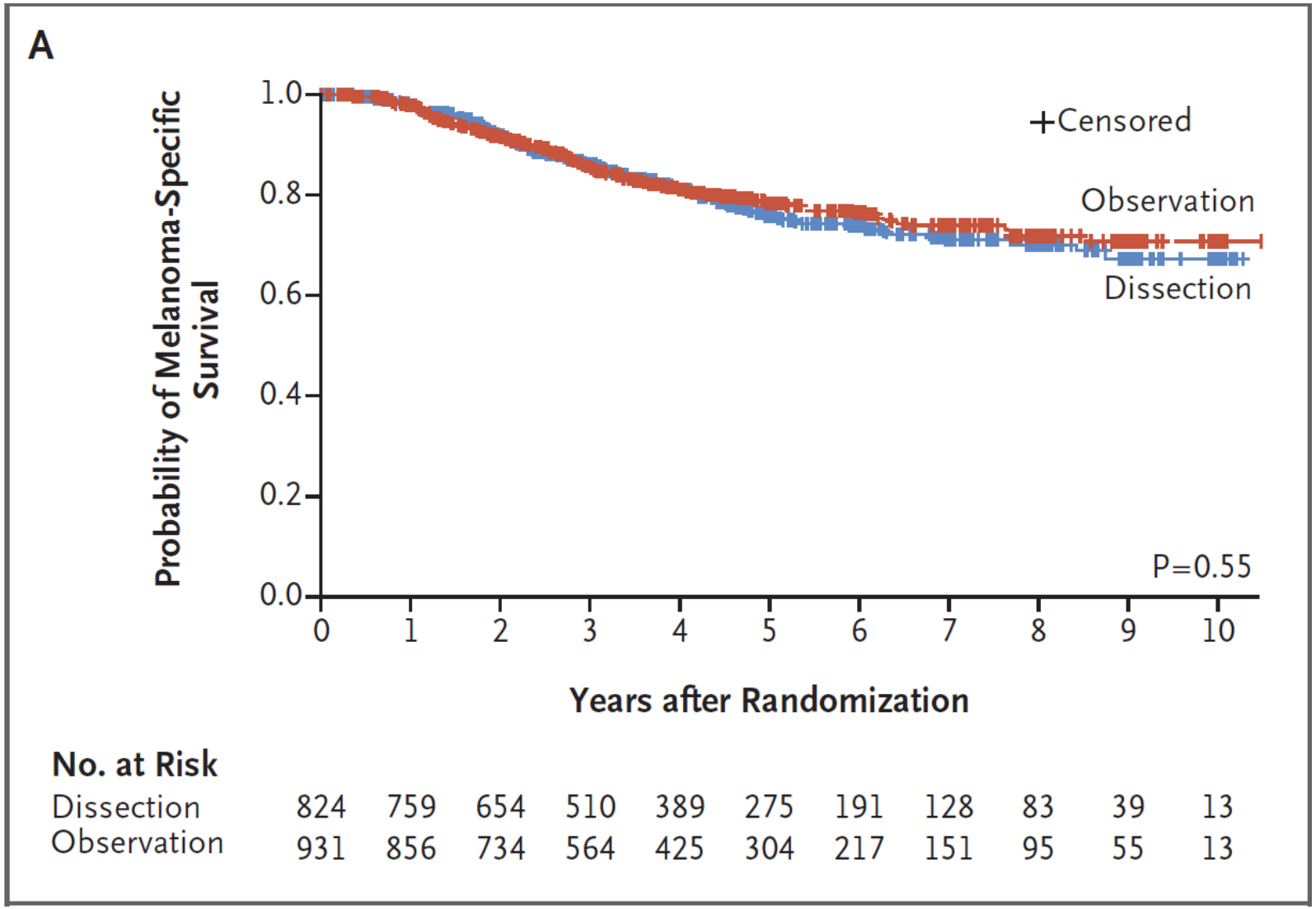
Figure 2: **Analysis of distant metastasis-free survival (A), overall survival (B), and recurrence-free survival (C) in the intention-to-treat population**

MSLT-II Trial for Sentinel node positive patients

- Randomized between completion node dissection versus observation
- 740 v.s. 820 patients

Follow up of observation group

- Visit with ultrasound of nodal basin
- Visit every 4 months for 2 years
- Every six months for 3 years
- Annual visit no ultrasound to 10 years



MSLT-II

The NEW ENGLAND JOURNAL of MEDICINE
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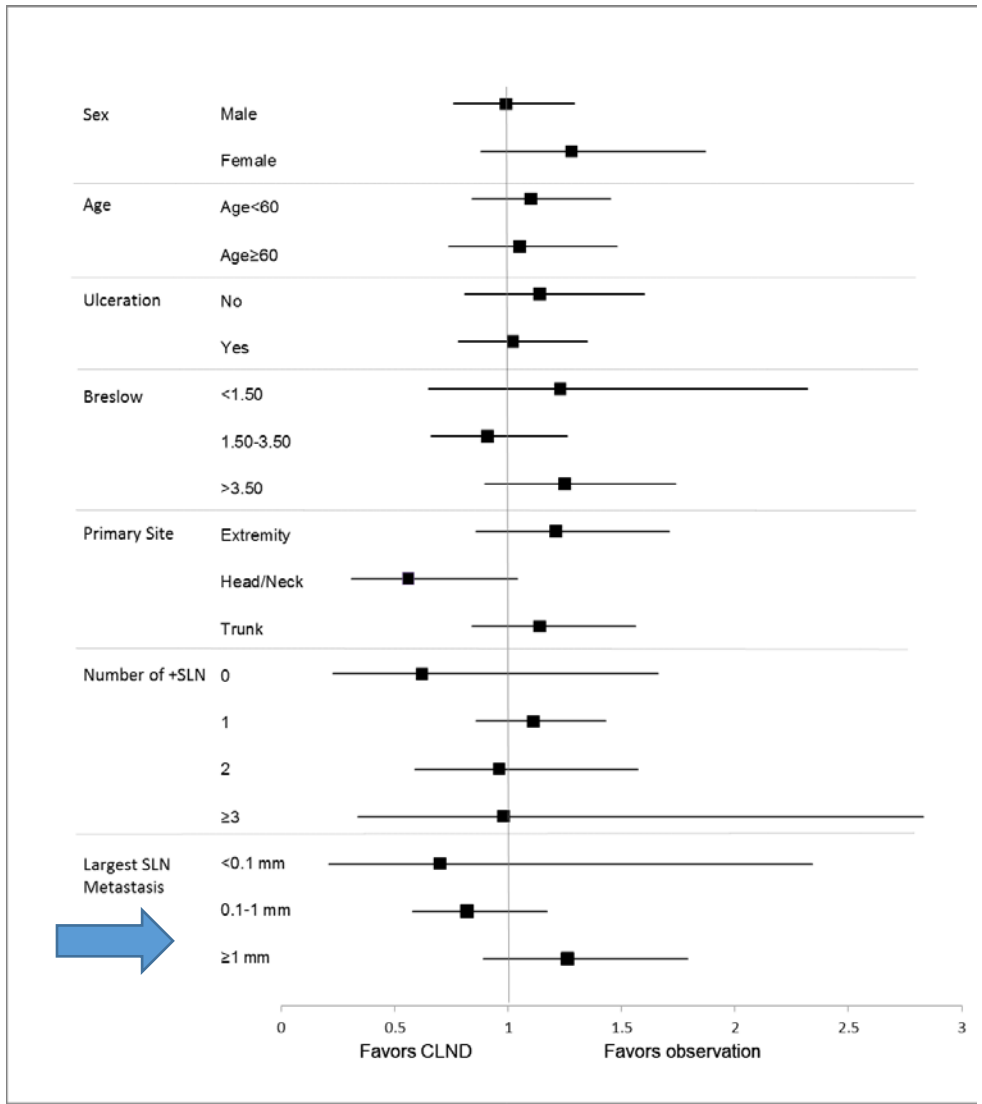
Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

Melanoma-specific survival hazard ration: univariate analysis



What about regional control?

MSLT-II appendix – types of recurrence

Table S4 Initial recurrence types (Per protocol, Pathology positive)

Recurrence status	CLND (n=744)	OBS (n=820)	Total (n=1564)
Without recurrence	465	472	937
With recurrence(s)	279	348	627
Local-regional recurrence only	32	25	57
Nodal recurrence only	10	63	73
Distant recurrence only	128	84	212
Local-regional and Nodal	4	26	30
Local and distant recurrences	51	31	82
Nodal and distant recurrences	31	73	104
Local-regional, nodal and distant	23	46	69
With local-regional recurrence	110	128	238
With nodal recurrence	68	208	286
With distant recurrence	233	234	467

* Local-regional recurrence includes satellite and in-transit metastases

MSLT-II appendix – types of recurrence

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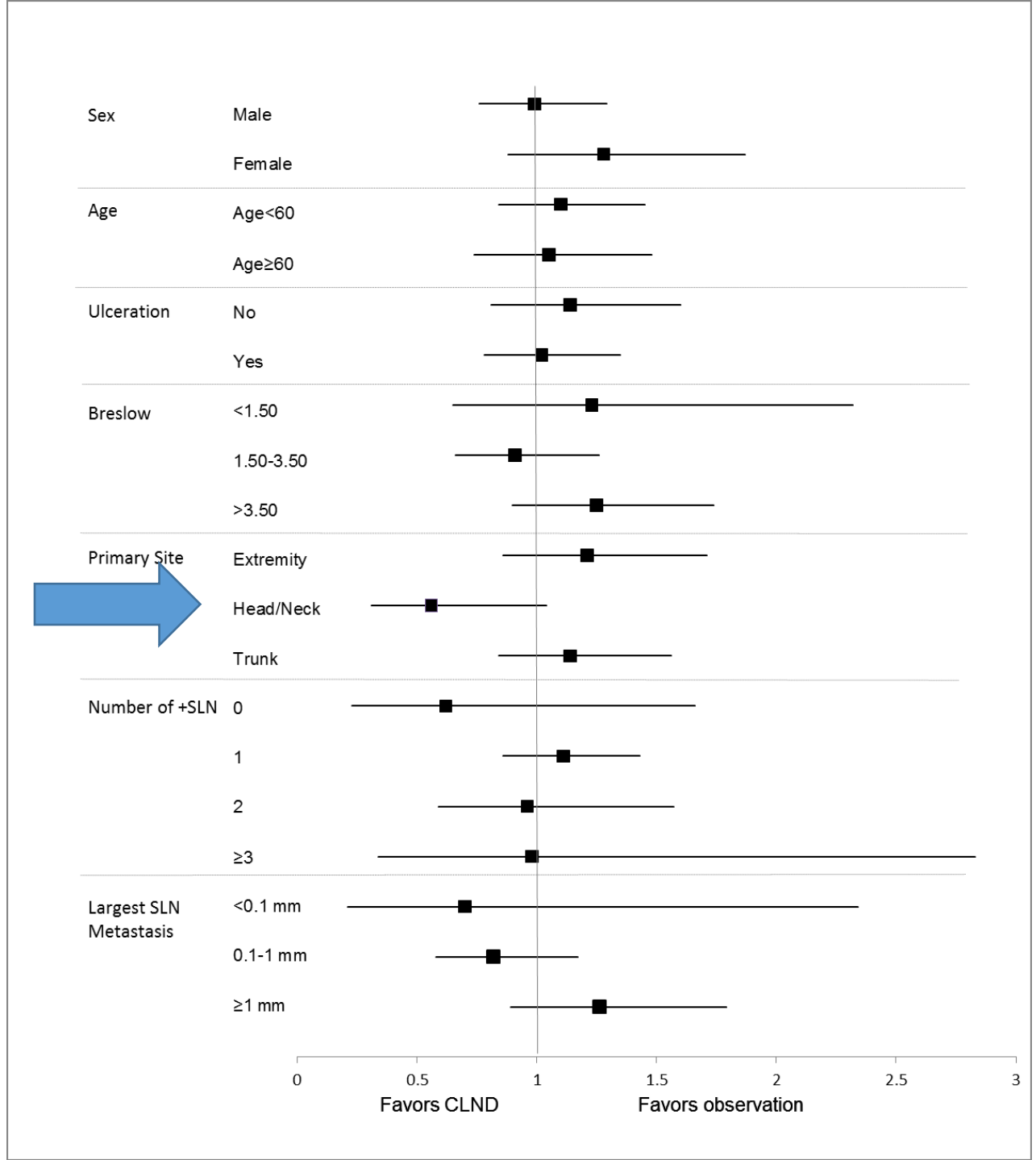
Extra capsular extension

- Any SN with ECE excluded from both MSLT-II and DECOG trials
- Currently still an indication for CLND

What about head and neck patients?

- Lymphedema is not a problem
- Close to survival benefit



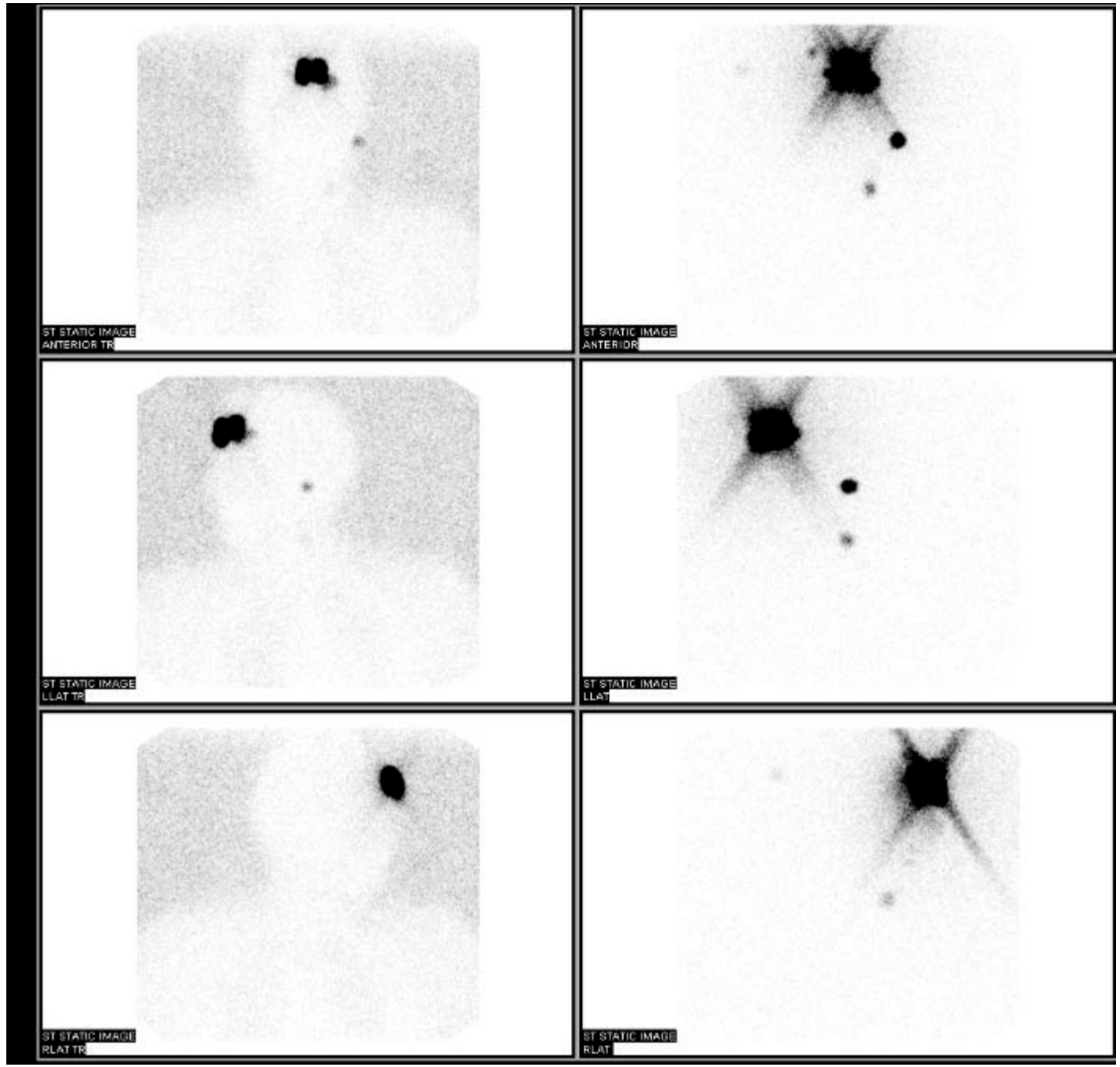
MSLT-II Univariate analysis

The Laryngoscope

Cranial Nerve Outcomes in Regionally Recurrent Head & Neck Melanoma After Sentinel Lymph Node Biopsy

John E. Hanks, MD; Pratyusha Yalamanchi, MD, MBA; Kevin J. Kovatch, MD; S. Ahmed Ali, MD; Joshua D. Smith, MD; Alison B. Durham, MD; Carol R. Bradford, MD, MS; Kelly M. Malloy, MD; Scott A. McLean, MD, PhD

Overall, our 25% incidence of CN injury following delayed regional macrometastases after SLNB-guided management argues against the MSLT-II authors' advocacy for delayed excision of post-observation regional recurrences.[7] Instead we contend that iCLND should be performed for at-risk basins whenever possible in HNCM. Furthermore, we assert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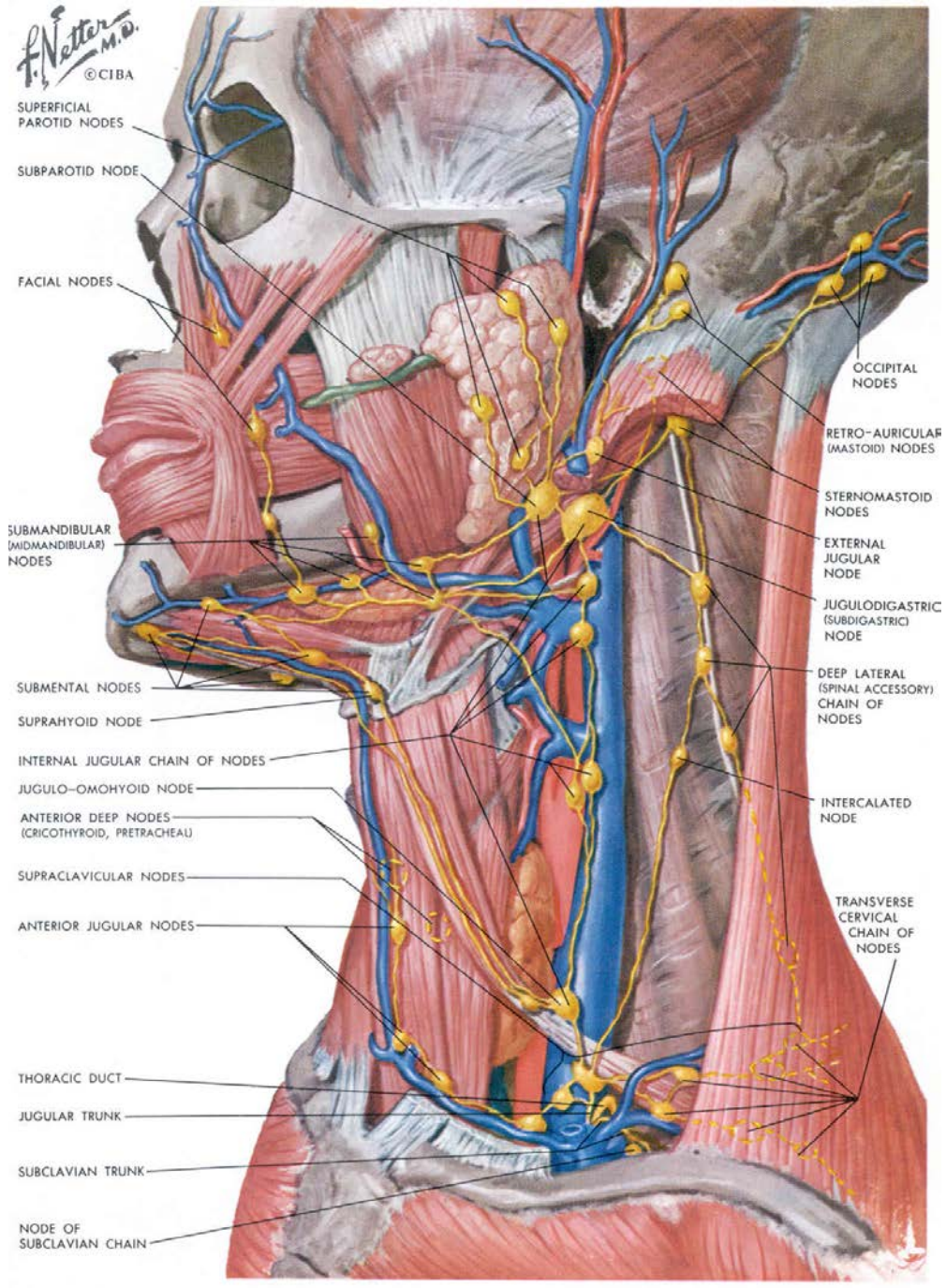
F. Netter M.D.
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SUPERFICIAL PAROTID NODES
SUBPAROTID NODE
FACIAL NODES
SUBMANDIBULAR (MIDMANDIBULAR) NODES
SUBMENTAL NODES
SUPRAHYOID NODE
INTERNAL JUGULAR CHAIN OF NODES
JUGULO-OMOHYOID NODE
ANTERIOR DEEP NODES (CRICOTHYROID, PRETRACHEAL)
SUPRACLAVICULAR NODES
ANTERIOR JUGULAR NODES
THORACIC DUCT
JUGULAR TRUNK
SUBCLAVIAN TRUNK
NODE OF SUBCLAVIAN CHAIN
OCCIPITAL NODES
RETRO-AURICULAR (MASTOID) NODES
STERNOMASTOID NODES
EXTERNAL JUGULAR NODE
JUGULODIGASTRIC (SUBDIGASTRIC) NODE
DEEP LATERAL (SPINAL ACCESSORY) CHAIN OF NODES
INTERCALATED NODE
TRANSVERSE CERVICAL CHAIN OF NODES

Facial Nerve Monitoring during Parotidectomy: A Systematic Review and Meta-analysis

Amit J. Sood, MD[1], Jeffrey J. Houlton, MD[1,2], Shaun A. Nguyen, MD, MA[1], and M. Boyd Gillespie, MD[1]

Otolaryngology–Head and Neck Surgery
2015, Vol. 152(4) 631–637

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http://otojournal.org
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Table 4. Incidence of Facial Nerve Weakness in FNM vs Unmonitored Patients, No. (%).

	FNM			Unmonitored		
Author	PAROT	IMMED	PERM	PAROT	IMMED	PERM
Deneuve[21]	46	3 (6.5)	0 (0.0)	41	5 (12.1)	1 (2.4)
Yuan[22]	65	4 (6.1)	0 (0.0)	44	9 (20.4)	2 (4.5)
Pons[23]	42	11 (26.1)	3 (7.1)	23	6 (26.1)	2 (8.7)
Grosheva[6]	50	19 (38.0)	4 (8.0)	50	22 (44.0)	2 (4.0)
López[24]	25	18 (36.0)	1 (4.0)	27	19 (70.4)	8 (29.6)
Witt[25]	20	4 (20.0)	0 (0.0)	33	5 (15.2)	0 (0.0)
Terrell[26]	40	13 (33.0)	4 (10.0)	40	23 (57.5)	3 (7.5)
Weighted total	288	22.5%	3.9%	258	34.2%	7.1%

Abbreviations: FNM, facial nerve monitoring; IMMED, immediate postoperative weakness; PAR, parotidectomies; PERM, permanent outcome weakness.

In head and neck patients:

- Completion node dissection is still highly morbid
- Almost 1/3 of MSLT-II patients had head and neck primaries
- Survival not significantly different
- Regional recurrence is reduced by adjuvant therapy (preliminary results)

Who gets complete lymph node dissection?

- Clinical nodes (palpable or image detected)
- Extra capsular extension in the SN
- Head and Neck patients? No!

Conclusions – Sentinel node biopsy

- “Discussed” for T1B melanomas
- Still important prognostic indicator
- CLND now unusual
- adequate regional control by itself in majority of patients
- stratification for effective adjuvant therapy
- Can be done with minimal morbidity

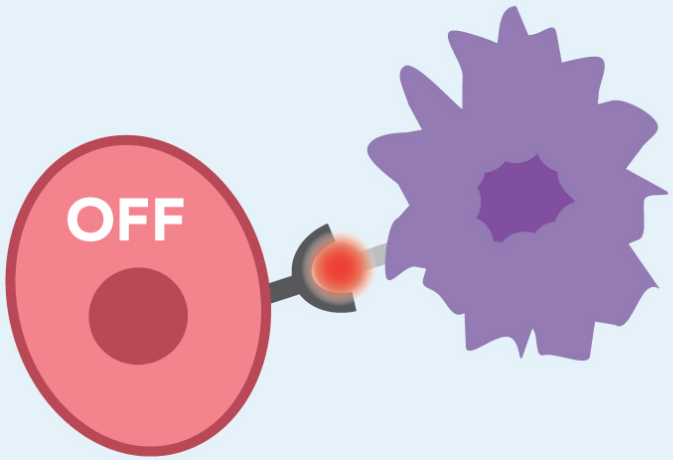
Conclusions: Completion node dissection

- Completion node dissection is no longer mandatory
- If no CLND, patient should be followed closely for nodal recurrence
- **Recurrence in the nodal basin mandates therapeutic node dissection**

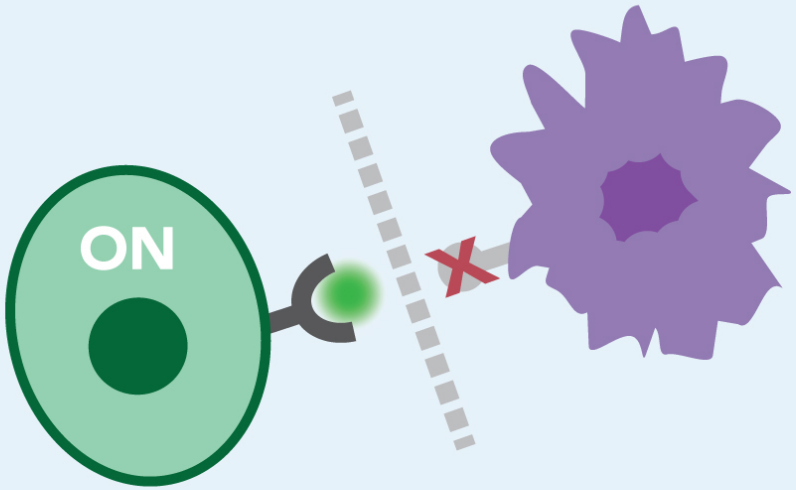
"We'd now like to open the floor to shorter speeches disguised as questions."

How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

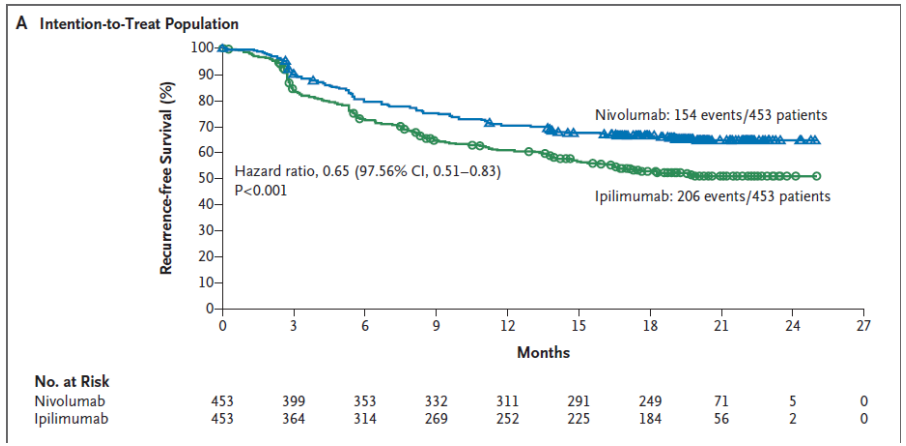


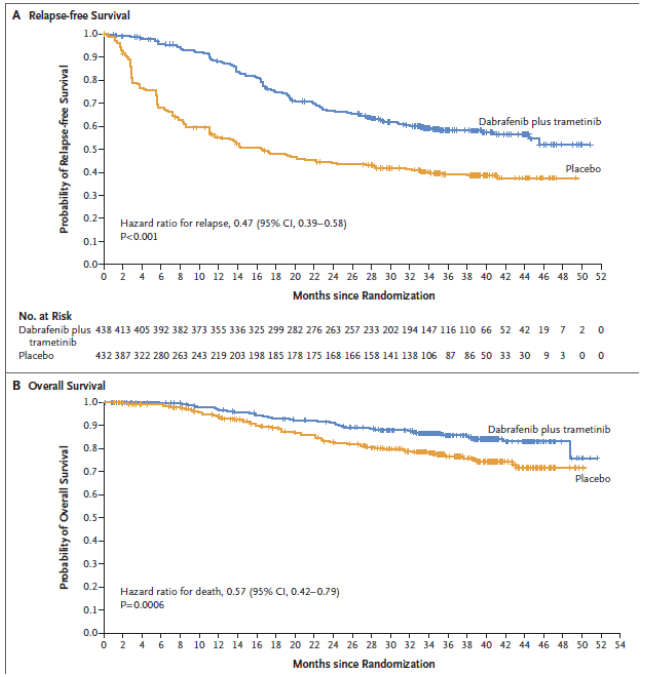
Immunotherapy drugs can block tumor cells from deactivating T-cells



Columbia University Medical Center

Adjuvant therapy





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 9, 2017 VOL. 377 NO. 19

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 8, 2017 VOL. 376 NO. 23

Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

Table S4 Initial recurrence types (Per protocol, Pathology positive)

Recurrence status	CLND (n=744)	OBS (n=820)	Total (n=1564)
Without recurrence	465	472	937
With recurrence(s)	279	348	627
Local-regional recurrence only	32	25	57
Nodal recurrence only	10	63	73
Distant recurrence only	128	84	212
Local-regional and Nodal	4	26	30
Local and distant recurrences	51	31	82
Nodal and distant recurrences	31	73	104
Local-regional, nodal and distant	23	46	69
With local-regional recurrence	110	128	238
With nodal recurrence	68	208	286
With distant recurrence	233	234	467

* Local-regional recurrence includes satellite and in-transit metastases

AJCC 8th Edition

- Mitotic rate removed in staging because less predictive than thickness
- 0.8-1.0 no included as Tib –Large modern dataset used for 8th edition shows a 5%-12% positivity range for SN in Tib primaries
- is SNB necessary??