Sentinel Node Biopsy and Completion Node Dissection in Melanoma

Time for a change?

Greg McKinnon MD FRCSC
SON Vancouver
Oct 2016

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- No disclosures

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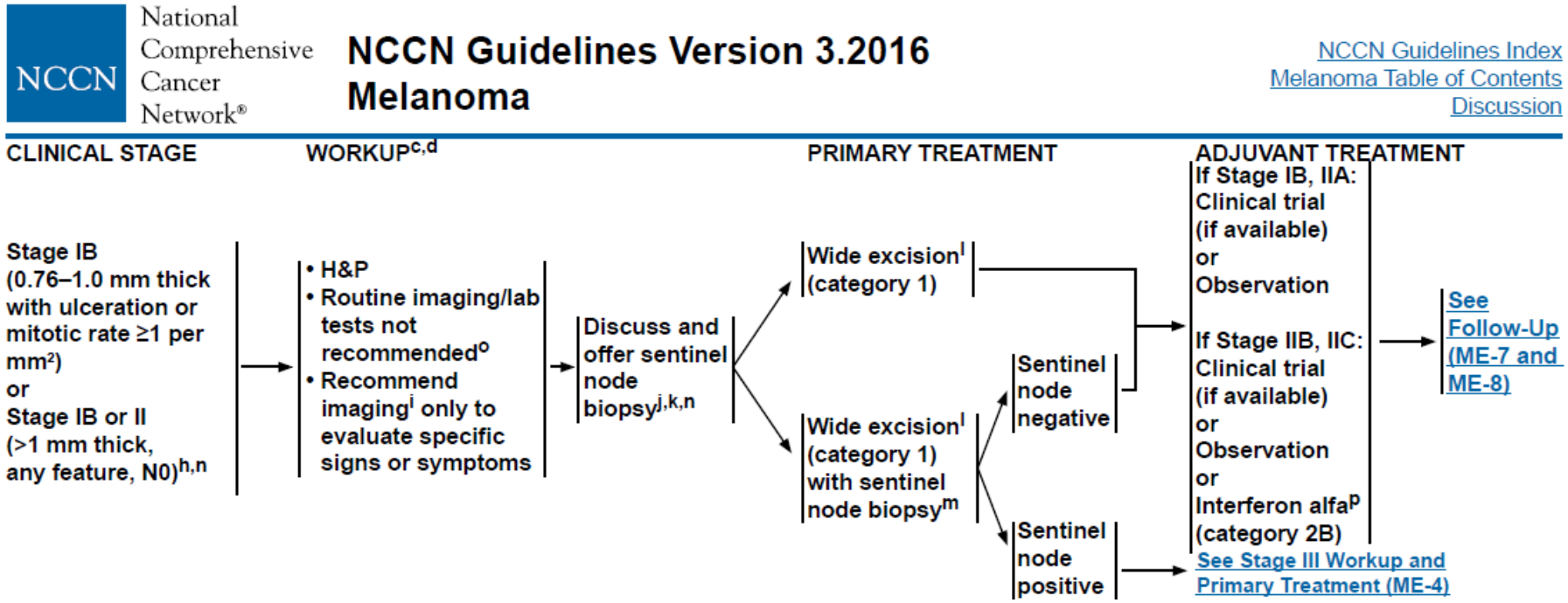
Objectives and Issues

- Is SNB still valuable?
- Who gets it?
- If it is positive is CLND necessary
- Where do new systemic agents fit in?

Most recent guidelines for SNB



SNB positivity rates in thin melanomas

Table 2. Effect of Thickness on Rate of Positive SLN in Thin Melanomas (≤1 mm)

	Primary Tumor Thickness			
	<0.75 mm		0.75–1.0 mm	
	Positive SLN		Positive SLN	
Study	**n/N**	**%**	**n/N**	**%**
Bleicher 2003[202]	2/118	1.7%	6/154	3.9%
Kesmodel 2005[19]	1/91[a]	1.1%	8/90[a]	8.9%
Puleo 2005[196]			20/409	4.9%
Ranieri 2006[191]	2/86	2.3%	10/98	10.2%
Wong 2006[192]	0/73	0%	8/150	5.3%
Wright 2008[186]	16/372	4.3%	15/259	5.8%
Vermeeren 2010[204]	0/39[b]	0%	5/39[b]	12.8%
Murali 2012[193]	3/113	2.7%	26/290	9.0%
Venna 2013[189]	7/170[c]	4.1%	27/280[c]	9.6%
Total	**31/1062**	**2.9%**	**125/1769**	**7.1%**

SLN, sentinel lymph node

[a]Subgroups were primary tumor thickness <0.76 mm, 0.76–1.0 mm; all had VGP

[b]Subgroups were primary tumor thickness ≤0.75 mm, 0.76–1.0 mm

[c]Subgroups were primary tumor thickness <0.8 mm, ≥0.8 mm

NCCN Guideline Manual 2016

Predictors

Table 2 Multivariate logistic regression modeling the association between SLN positivity and the clinicopathologic features of thin melanoma (n = 469)

Clinicopathologic feature	OR	95% CI	*P*
Ulceration	5.27	1.02–27.10	.047
Thickness	46.69	1.73–1260.61	.022
Clark level	1.90	.62–5.85	.264
Mitotic rate	1.24	.79–1.94	.352
Lymphatic response	.88	.24–3.25	.854
Regression	1.23	.39–3.85	.722
Vertical growth	.59	.14–2.40	.460
Satellitosis	1.81	.06–51.95	.728
Angiolymphatic spread	3.75	.32–43.95	.292
Margin status	.63	.20–2.02	.441
Nevus	.59	.16–2.13	.421
Melanoma score	2.82	1.42–5.61	.003

Predictors of positive sentinel lymph node in thin melanoma

David V. Yonick, M.D.,[a] Rana M. Ballo, M.D.,[a] Estelle Kahn, M.D.,[a,*] Madhu Dahiya, M.D.,[b] Katherine Yao, M.D.,[a] Constantine Godellas, M.D.,[a] Margo Shoup, M.D.,[a] Gerard V. Aranha, M.D.[a,*]

The American Journal of Surgery (2011) 201, 324–328

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- Should patients with thick melanoma get SNB?

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Sentinel Lymph Node Biopsy Is Indicated for Patients With Thick Clinically Lymph Node-Negative Melanoma

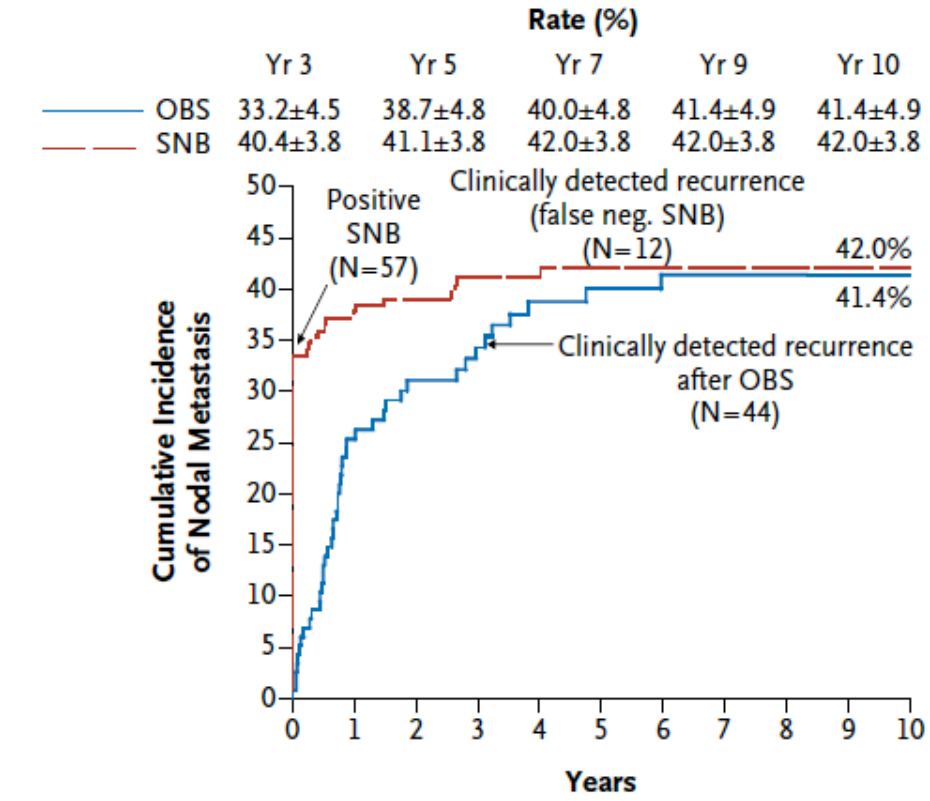
Maki Yamamoto, MD[1]; Kate J. Fisher, MS[2]; Joyce Y. Wong, MD[3]; Jonathan M. Koscso, BS[4]; Monique A. Konstantinovic, BS[4]; Nicholas Govsyeyev, BS[4]; Jane L. Messina, MD[5,6,7]; Amod A. Sarnaik, MD[6,7]; C. Wayne Cruse, MD[6,7]; Ricardo J. Gonzalez, MD[6,7,8]; Vernon K. Sondak, MD[6,7]; and Jonathan S. Zager, MD[6,7,8]

With a relative high risk of lymph node disease, an acceptably low FNR, and significant prognostic information relative to survival, we believe that SLNB is indicated in patients with clinically lymph node-negative, thick, cutaneous melanoma.

Cancer May 15, 2015

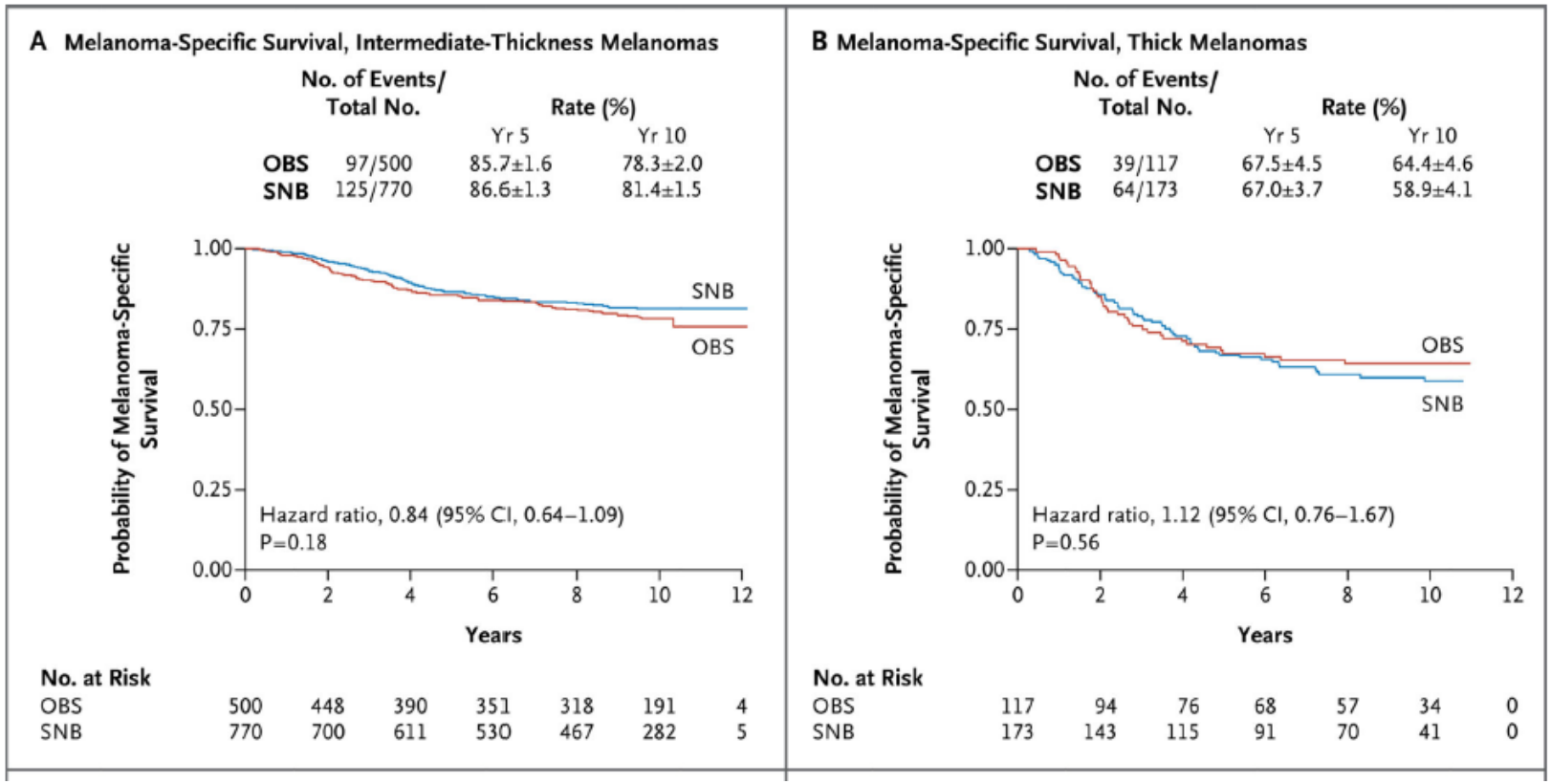
MSLT I – how many positive nodes?

B Cumulative 10-Yr Incidence of Nodal Metastasis, Thick Melanomas



No. at Risk						
OBS	117	63	50	47	39	25
SNB	173	86	68	53	43	26

MSLT I: SNB plus CLND



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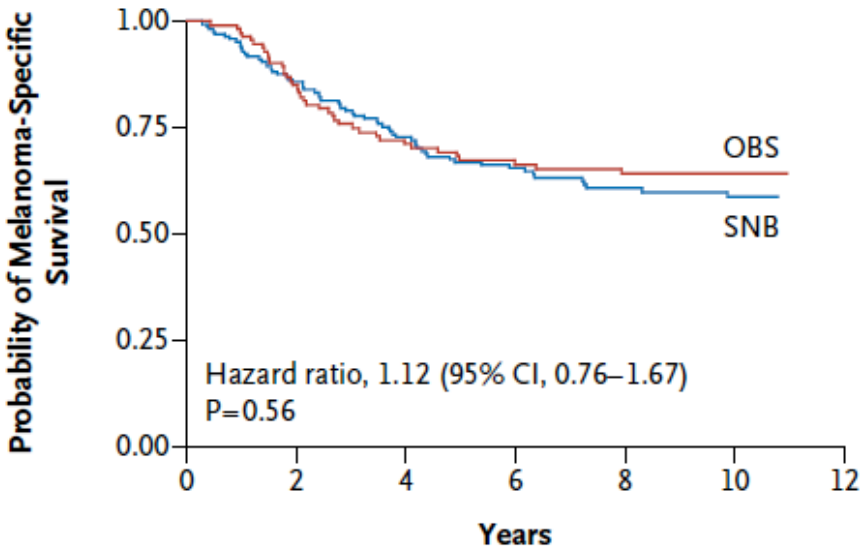
B Melanoma-Specific Survival, Thick Melanomas

	No. of Events/ Total No.	Rate (%) Yr 5	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

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

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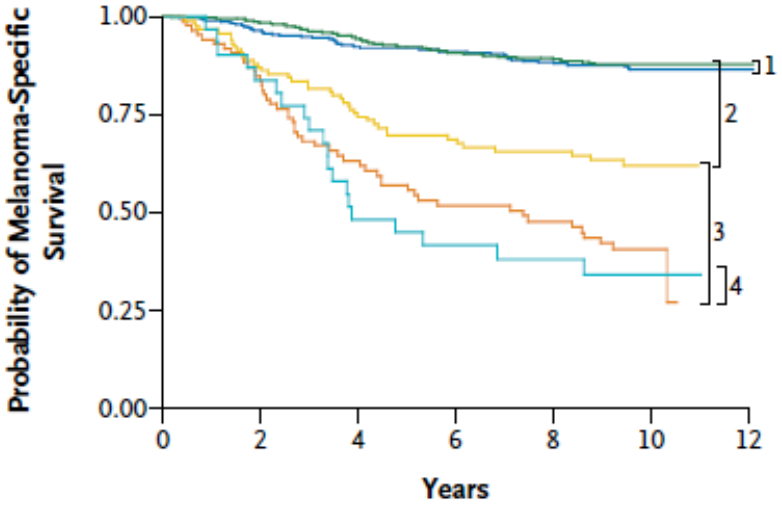
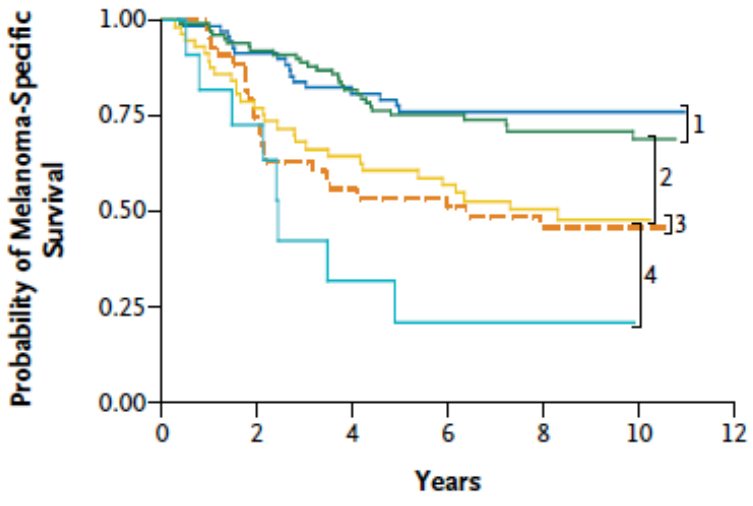
C Melanoma-Specific Survival, Intermediate-Thickness Melanomas

	No. of Events/ Total No.	Rate (%) Yr 5	Rate (%) 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	Rate (%) 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	—



The NEW ENGLAND JOURNAL of MEDICINE
FEBRUARY 13, 2014

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

Prognostic Value

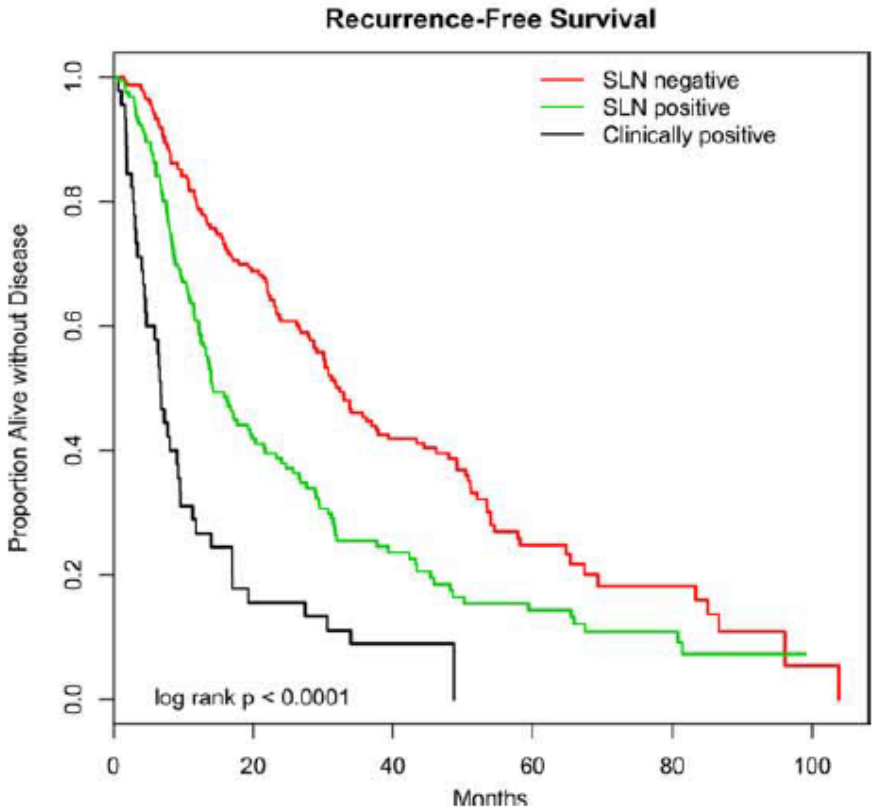


Figure 2. Kaplan-Meier curves are shown for (*Top*) overall survival, (*Middle*) disease-specific survival, and (*Bottom*) recurrence-free survival. Clinically positive indicates patients with clinically positive regional disease at the time of presentation who underwent therapeutic lymph node dissection; SLN, sentinel lymph node.

N = 458

Sentinel Lymph Node Biopsy Is Indicated for Patients With Thick Clinically Lymph Node-Negative Melanoma

Maki Yamamoto, MD[1]; Kate J. Fisher, MS[2]; Joyce Y. Wong, MD[3]; Jonathan M. Koscso, BS[4]; Monique A. Konstantinovic, BS[4]; Nicholas Govsyeyev, BS[4]; Jane L. Messina, MD[5,6,7]; Amod A. Sarnaik, MD[6,7]; C. Wayne Cruse, MD[6,7]; Ricardo J. Gonzalez, MD[6,7,8]; Vernon K. Sondak, MD[6,7]; and Jonathan S. Zager, MD[6,7,8]

Cancer May 15, 2015

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- What about regional control for thick melanomas?

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Table S1b. Baseline Characteristics of the Patients, Breslow >3.5 mm

Characteristic	All Patients		
	Biopsy (N=173)	Observation (N=117)	p-value
Nodal Metastasis - % (no./total no.)	32.9 (57/173)	37.6 (44/117)	
Median time to nodal metastasis (mos)			
No. of positive nodes – mean ± SE‡			
p-values comparing means			
Site of first recurrence – no. (%)[c]			
Nodal	15 (8.7)	40 (34.2)	
Distant	43 (24.9)	19 (16.2)	
Local or intransit	22 (12.7)	9 (7.7)	
No Recurrence – no. (%)	93 (53.8)	49 (41.9)	

Supplement to: Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 2014;370:599-609. DOI: 10.1056/NEJMoa1310460

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RCT: post dissection RT

- Non-RT group: 26/108 patients relapsed in nodal basin after TLND
- Median time 7 months
- 20 treated with surgery + RT
- One treated with RT only
- Four treated with surgery only
- 23 of 26 successfully salvaged

100 biopsies in patients with thick melanoma

- 100 procedures
- 66 will be negative, 34 positive
- At 2 years 25 would have become palpable
- 40% mortality by 2 years leaves 15 for TLND
- 70% regional control with TLND leaves 5 patients
- Four of those will be salvaged
- 1 patient benefits from improved regional control
- Improved systemic therapy will modify these numbers

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- What about intermediate thickness?

C **Melanoma-Specific Survival, Intermediate-Thickness Melanomas**

	No. of Events/ Total No.	Rate (%)	
		Yr 5	Yr 10
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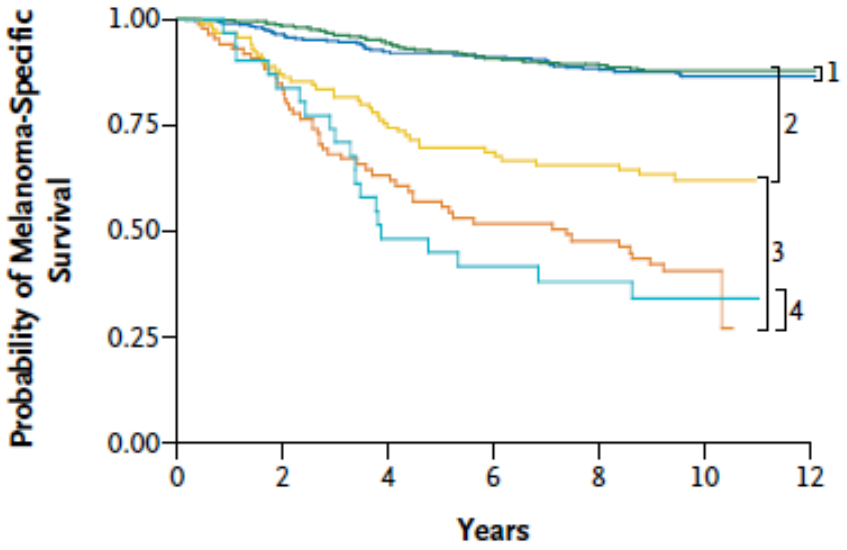

The NEW ENGLAND JOURNAL of MEDICINE
FEBRUARY 13, 2014

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

Recommendations for SNB in Melanoma

- Rare need for the procedure < 1 mm thick melanoma
- 1 – 4 mm: prognostic, improves regional control, helps avoid CLND, allows adjuvant therapy, may improve survival
- > 4 mm: improves regional control without extensive surgery and RT

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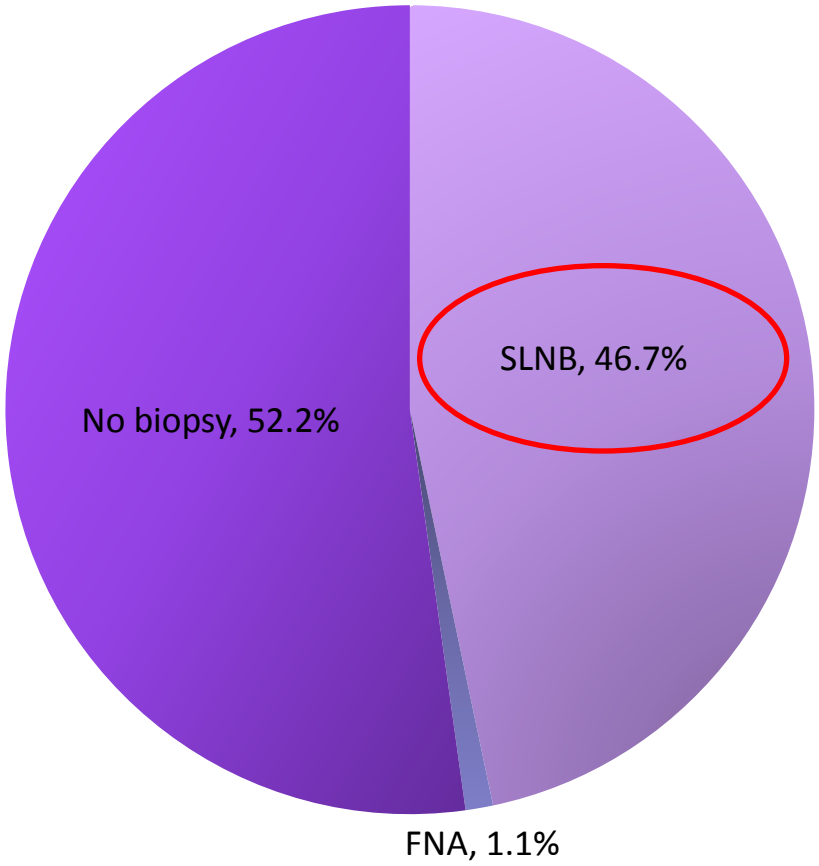
- Is a completion node dissection required?

Alberta data over 2 years: nodal management



→ POSITIVITY = 18.2% (47 ÷ 258)

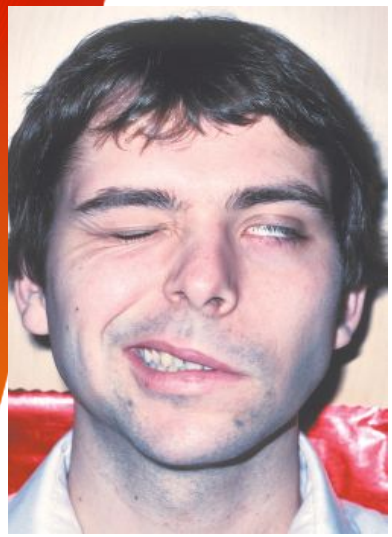
Rate of adherence:

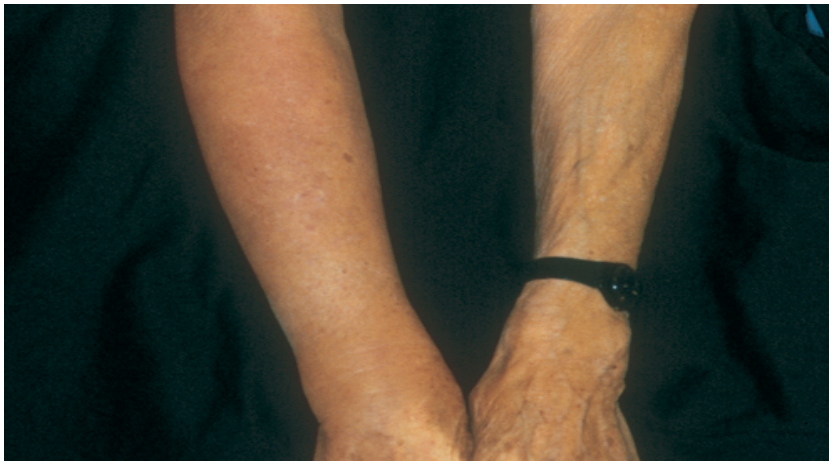
pts who underwent CLND ÷
pts with positive SLNB

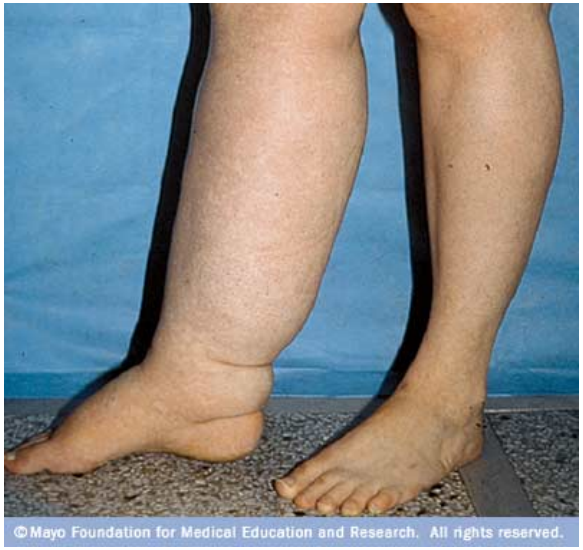
= 42 ÷ 47

= 89.4%

Complications of CLND







Overall rate of non-sentinel node metastases

- 2335 patients with melanoma
- 347 patients had positive sentinel nodes
- 51 had positive non-sentinel nodes (14.7%)

Ann Surg Oncol (2010) 17:3330–3335

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Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial

Ulrike Leiter, Rudolf Stadler*, Cornelia Mauch, Werner Hohenberger, Norbert Brockmeyer, Carola Berking, Cord Sunderkötter, Martin Kaatz, Klaus-Werner Schulte, Percy Lehmann, Thomas Vogt, Jens Ulrich, Rudolf Herbst, Wolfgang Gehring, Jan-Christoph Simon, Ulrike Keim, Peter Martus, Claus Garbe, for the German Dermatologic Cooperative Oncology Group (DeCOG)*

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DeCOG trial

Identical follow-up schedules were applied for both study groups, according to the current German guidelines in patients with stage III melanoma. Physical examinations (whole body and palpation of primary scar to and including the regional lymph node basin), lymph node sonography (primary scar to and including regional lymph node basin), and blood tests with serum S100b were done every 3 months. Every 6 months, patients received section diagram imaging, such as whole body CT scan, MRI, or PET-CT, or a chest x-ray and abdomen sonography at minimum. This procedure was done during the entire 3-year follow-up from the date of randomisation. For patients allocated to the complete

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DeCOG trial

	Observation group (n=233)	Complete lymph node dissection group (n=240)
Median follow-up time (months)	35·5 (22·7–57·0)	33·0 (17·0–50·0)
Total patients with recurrences	67 (29%)	59 (25%)
Satellite/in-transit recurrences	9 (4%)	9 (4%)
Regional lymph node without distant recurrences	15 (7%)	8 (3%)
Regional and distant recurrences	19 (8%)	12 (5%)
Distant without regional lymph node recurrences	24 (10%)	30 (13%)
Total deaths	44 (19%)	40 (17%)
Melanoma	38 (16%)	36 (15%)
Other malignancy	1 (<1%)	0
Other disease	5 (2%)	4 (2%)

Data are median (IQR) or n (%). For recurrences, more than one type of recurrence could occur in one patient. Distribution of recurrences and cause of death is given purely descriptively.

Table 2: **Follow-up time, recurrences, and cause of death in the intention-to-treat population**

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DeCOG trial

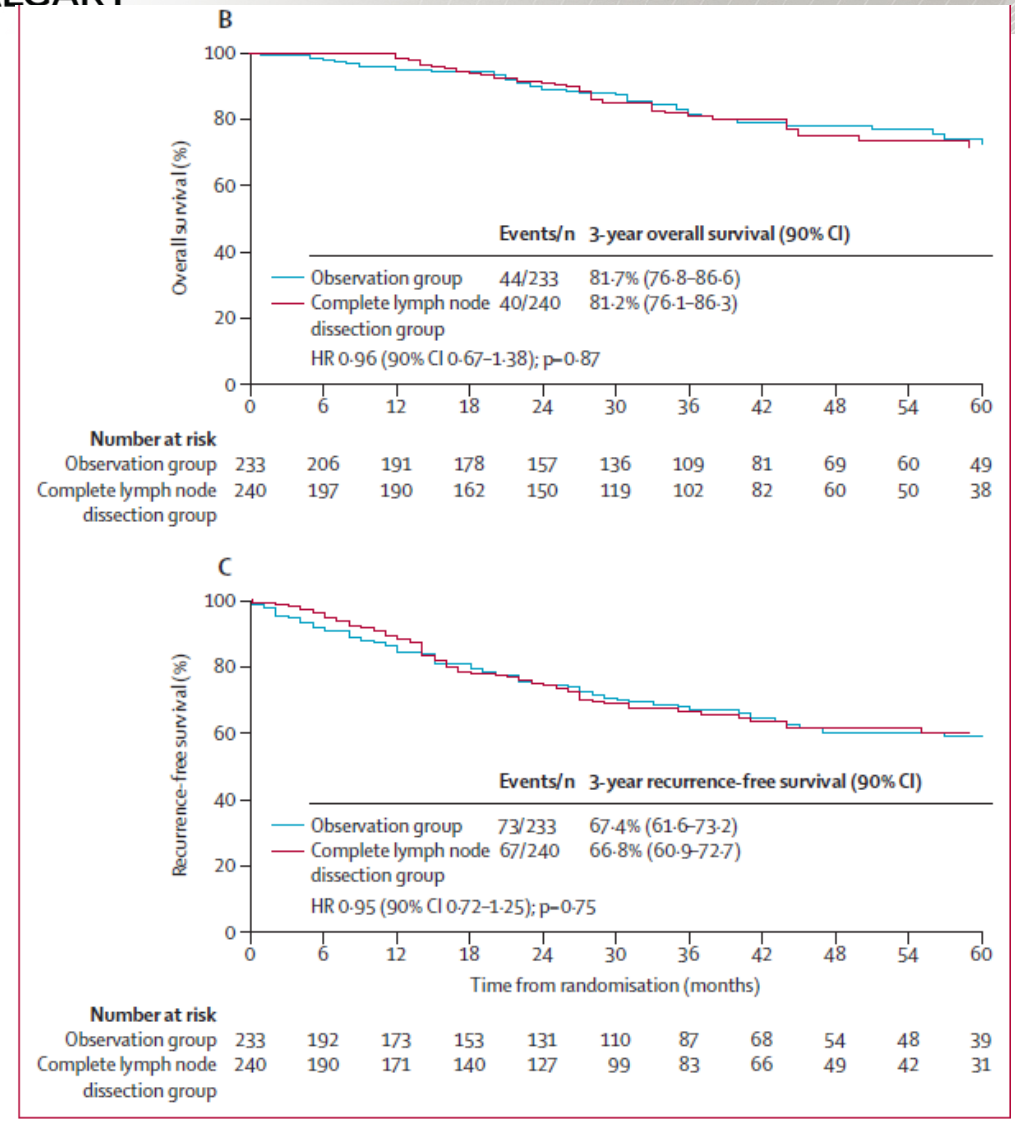

Figure 2: **Analysis of distant metastasis-free survival (A), overall survival (B), and recurrence-free survival (C) in the intention-to-treat population**

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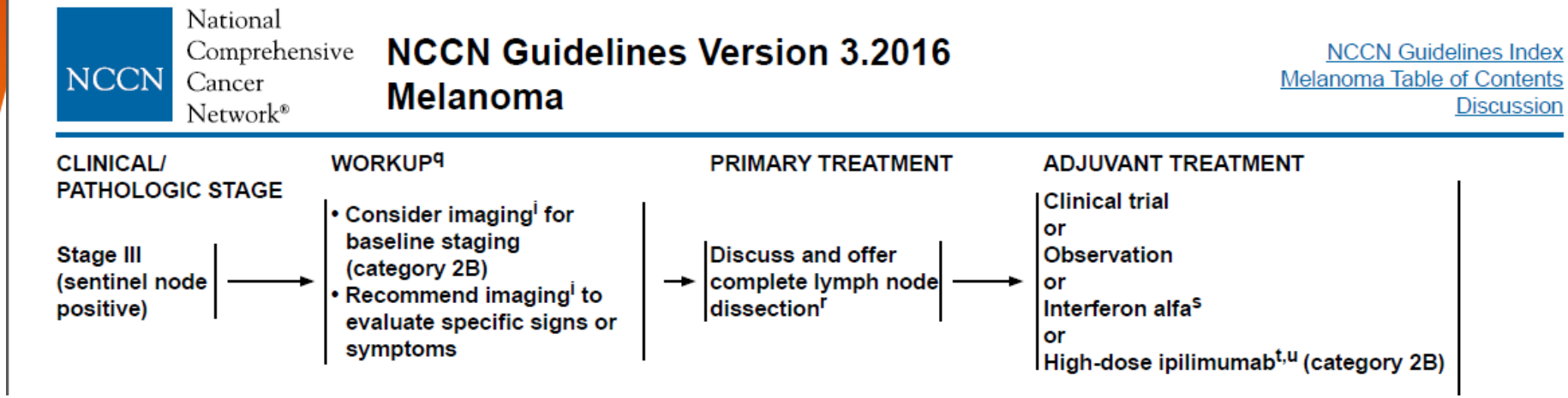
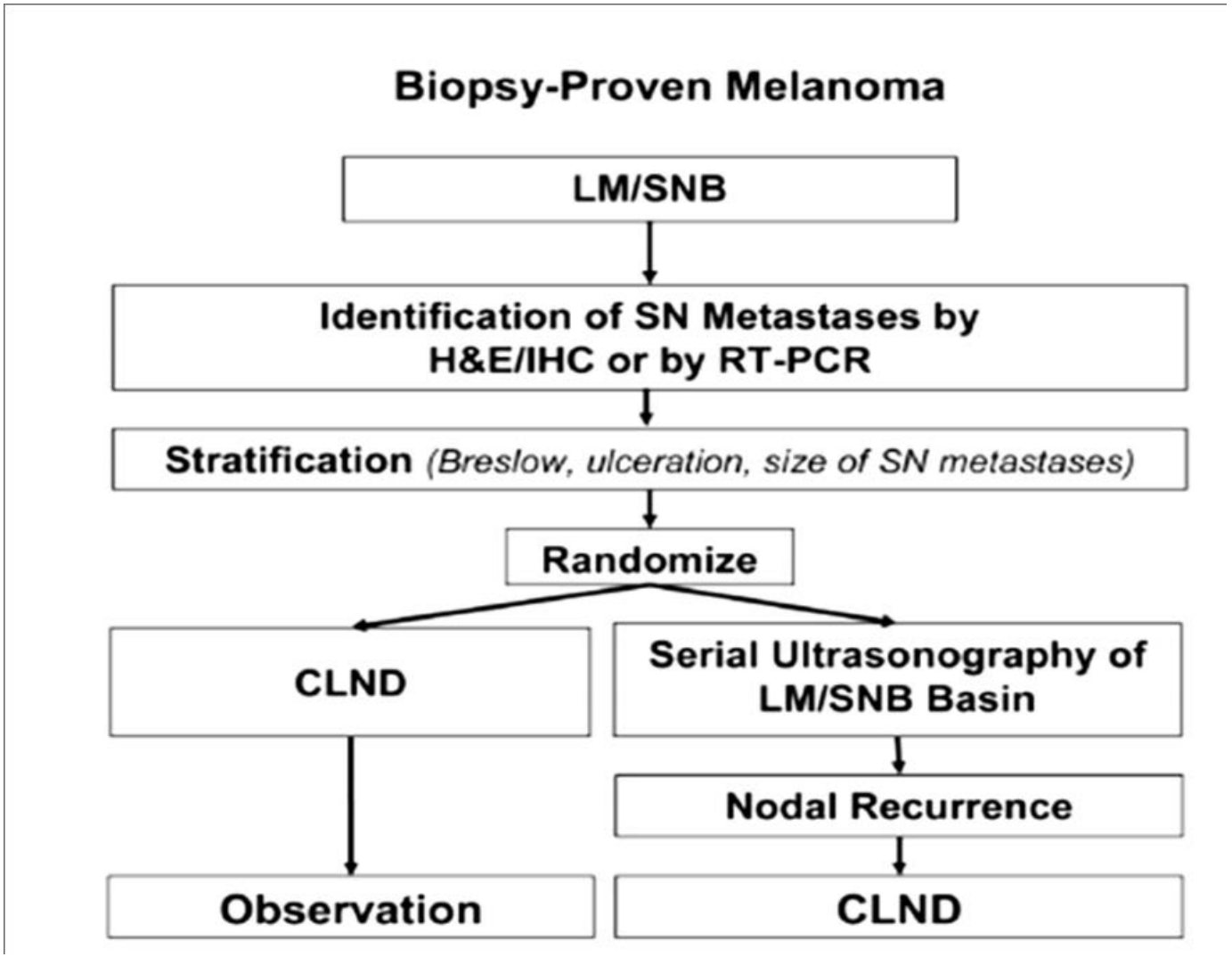


MSLT-II


Biopsy-Proven Melanoma
LM/SNB
Identification of SN Metastases by H&E/IHC or by RT-PCR
Stratification (Breslow, ulceration, size of SN metastases)
Randomize
CLND
Serial Ultrasonography of LM/SNB Basin
Nodal Recurrence
Observation
CLND

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Conclusions

- Completion node dissection is no longer mandatory
- If no CLND, patient should be followed closely for nodal recurrence
- SNB alone provides good regional control

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- What about adjuvant therapy?

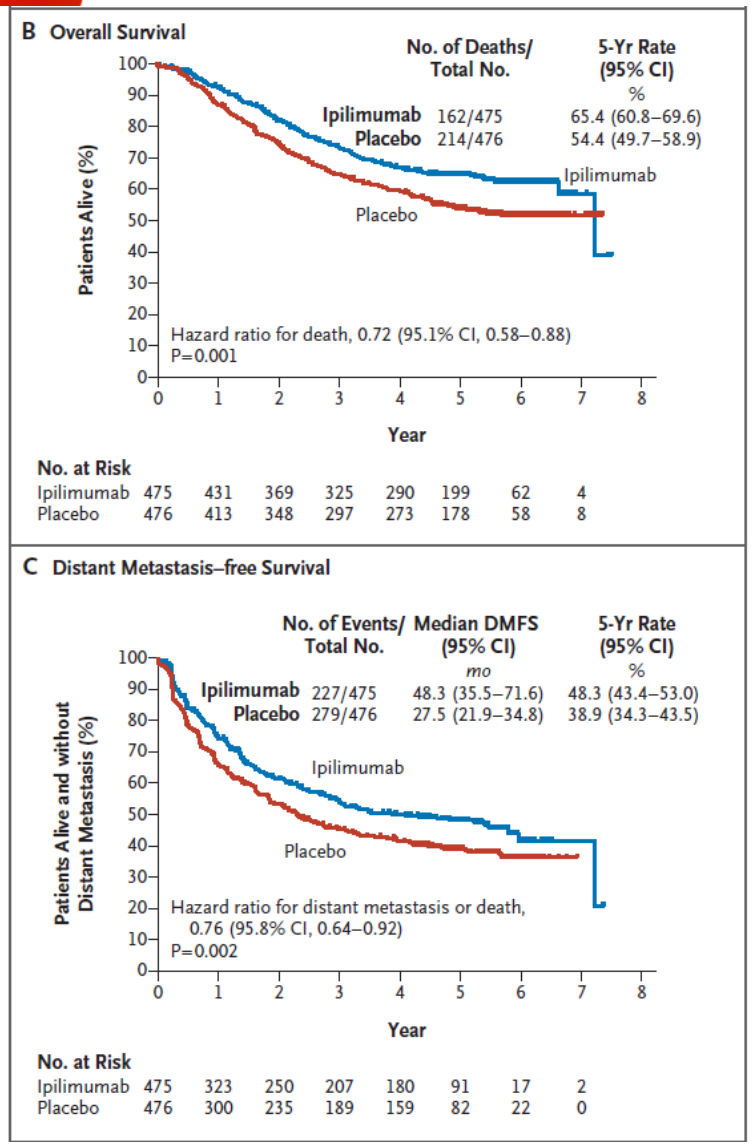
Ongoing adjuvant trials

Table 1
Ongoing or finished phase III trials on adjuvant systemic therapy in high-risk melanoma.

Clinicaltrials.gov#	Study ID	Disease-stage	Estimated enrolment	Intervention	Comparison	Main outcomes	Status	Completion
NCT01502696	EORTC-18081	T(2-4)bN0M0	1200	PEG IFN-α 2b for 2 years	Observation	OS, RFS, QoL, toxicity	R	2020
NCT01274338	ECOG-E1609	IIIB/C or IV	1545	High- or low-dose ipilimumab for 1 year	High dose recombinant IFN-α-2b for 1 year	OS, RFS, QoL, toxicity	C	2018
NCT00636168	EORTC-18071	III[a]	951	Ipilimumab for 3 years	Placebo	OS, RFS, QoL, toxicit	F	2015
NCT02506153	untitled	III or IV	1378	Pembrolizumab for 1 year	High dose recombinant IFN-α-2b for 1 year	OS, RFS, QoL, toxicity	R	2020
NCT02362594	KEYNOTE-054	III[a]	900	Pembrolizumab for 1 year	Placebo	OS, RFS	R	2023
NCT02388906	CheckMate 238	IIIB/C or IV	800	Ipilimumab and placebo matching nivolumab for 1 year	Nivolumab and placebo matching ipilimumab for 1 year	OS, RFS	C	2019
NCT01667419	BRIM-8	III[a]	475	Vemurafenib for 1 year	Placebo	OS, RFS, QoL, safety	C	2020
NCT01682083	COMBI-AD	III[a]	852	Dabrafenib and trametinib for 1 year	Placebo	OS, RFS, safety	C	2018

R – recruiting, C – closed, F – finished, PEG – pegylated, IFN – interferon, OS – overall survival, RFS – recurrence-free survival, QoL – quality of life.
[a] Lymph node metastasis of >1 mm is required for stage IIIA melanoma.

M.C.T. van Zeijl et al. / EJSO xx (2016) 1–10



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ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

Stage IV – surgery and after

- 61 y.o. male
- Oct 2013 axillary met unknown primary
- Jan 2014 Axillary node dissection followed by adjuvant RT

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- Tested for BRAF mutation – negative
- Adjuvant immunotherapy trial
- Combination Nivolumab and Ipilimumab
- Well tolerated
- October 2016 NED

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- What about neoadjuvant therapy

Conclusions

- Awkward but exciting point of determining the best sequence of treatment for unresectable Stage III and Stage IV disease

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Summary

- Fewer indications for routine sentinel node biopsies (1-4 mm)
- CLND need not be done routinely (provided you follow the patient)
- Adjuvant is promising but still not routine
- Therapy for Stage IV is getting a lot more complicated

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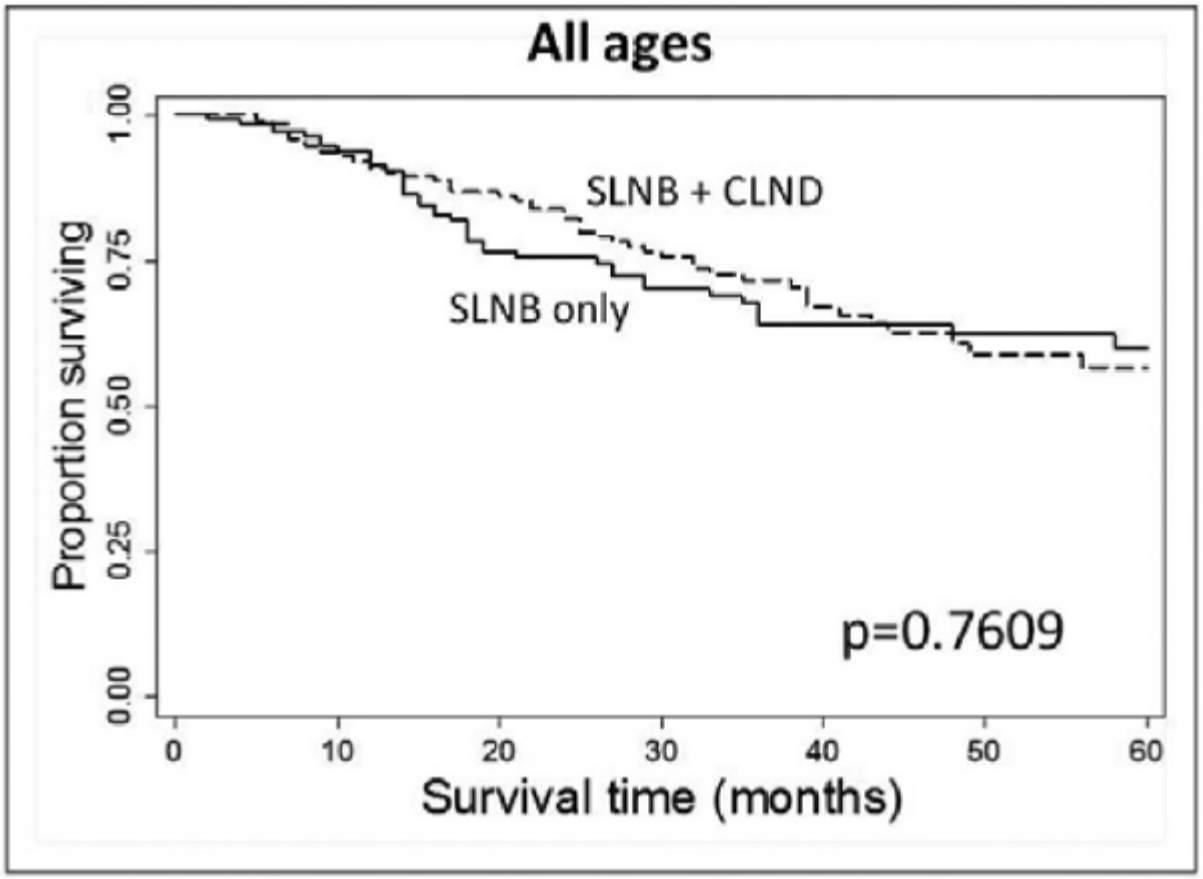
Questions?

- Thank you!

CLND in H&N patients with positive SNB

Melanoma-Specific Survival by Scope of Lymph Node Surgery



Otolaryngology–Head and Neck Surgery 146(4)

Retrospective study of patients without CLND

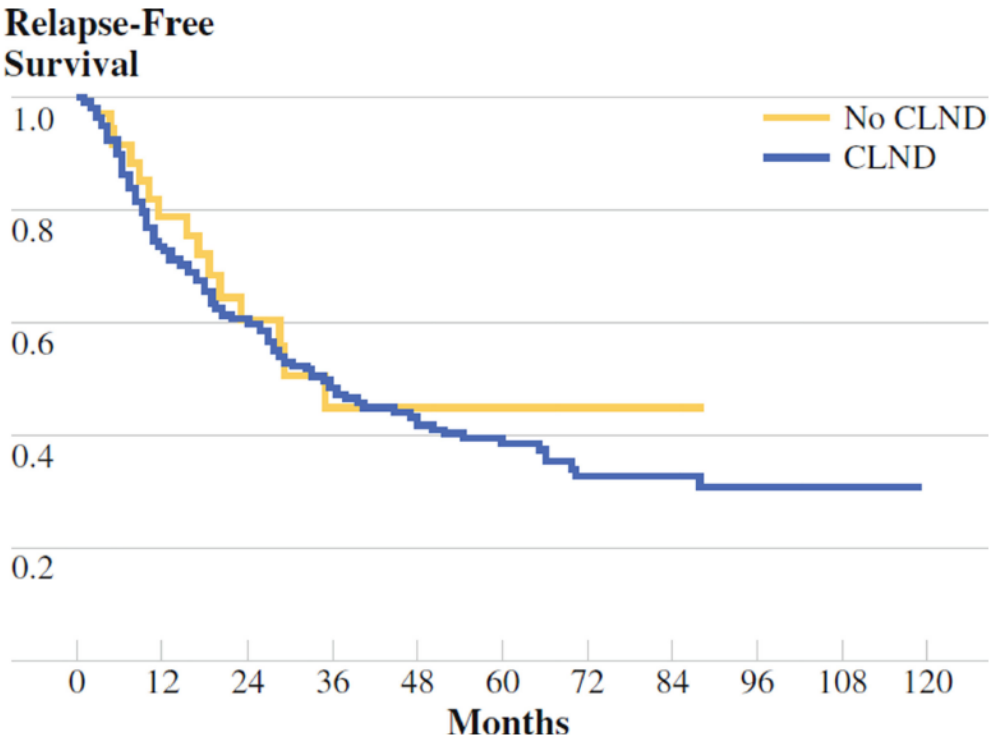
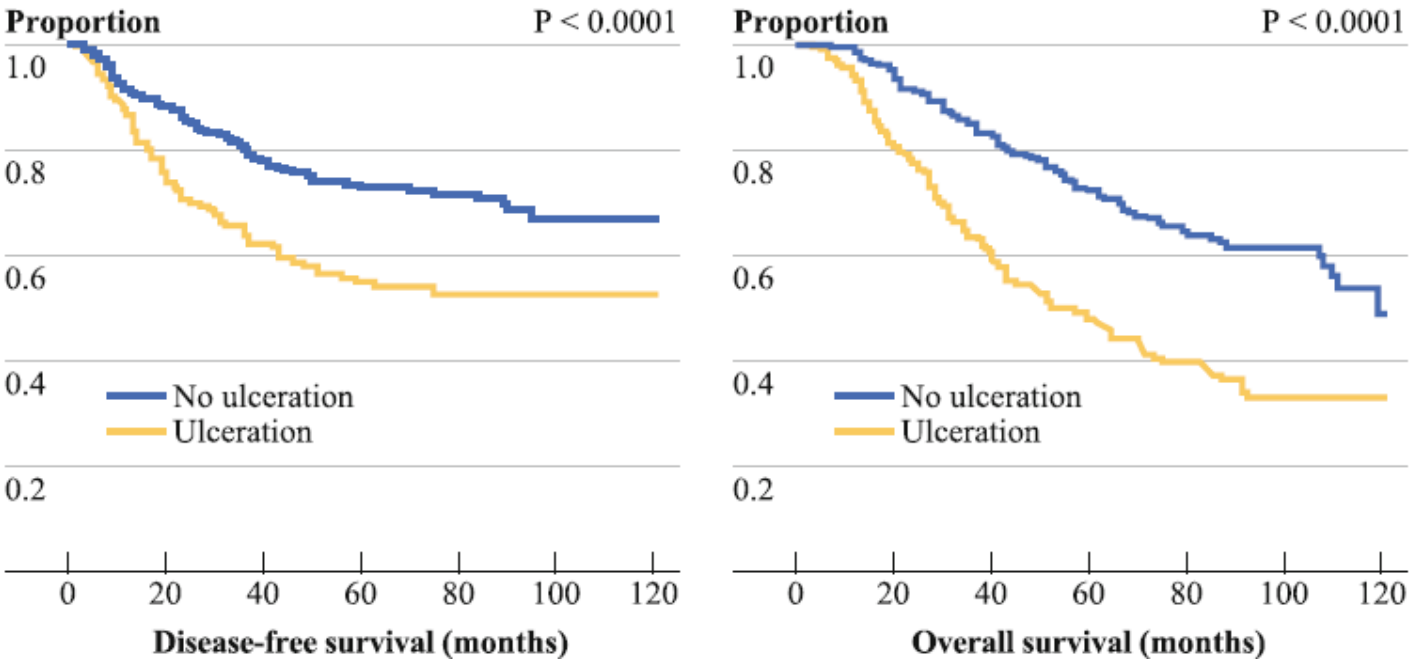


FIG. 2.
Recurrence-free survival (RFS) no-completion lymph node dissection (CLND) ($n = 37$) vs. CLND ($n = 271$). Median RFS was 35 months for the no-CLND group and 36 months for the CLND group ($P = .63$)

Outcome of Patients with a Positive Sentinel Lymph Node who do not Undergo Completion Lymphadenectomy

T. Peter Kingham, MD[1], Katherine S. Panageas, DrPH[2], Charlotte E. Ariyan, MD, PhD[1], Klaus J. Busam, MD[3], Mary Sue Brady, MD[1], and Daniel G. Coit, MD[1]

Sunbelt Study: Survival of node positive patients



Ann Surg Oncol (2013) 20:956–963