VII SIMPÓSIO INTERNACIONAL DE Melanoma

HOTEL PULLMAN VILA OLÍMPIA

29 E 30 DE NOVEMBRO 2019

Em que situações clínicas a dissecção linfonodal ainda é necessária?

Eduardo Bertolli – MD, PhD

TCBC, TSBCO

Membro da Diretoria do GBM – 2017 / 2019

Conflito de interesses

De acordo com a resolução do **Conselho Federal de Medicina nº 1595/2000 e Resolução da Diretoria Colegiada da ANVISA nº 96/2008**, eu declaro que:

- Apresentações Científicas – Como palestrante: BMS, MSD, Roche, Scav Medical
- Atividades de Consultoria – Como membro de *Advisory Boards*: BMS, MSD

Declaro não ter ações em bolsa de valores das empresas supracitadas.

Conflito de interesses

Sou cirurgião oncológico!!

Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

REVIEW ARTICLE

The Role of Elective Lymph Node Dissection in Melanoma: Rationale, Results, and Controversies

By Charles M. Balch

J Clin Oncol 6:163-172. *© 1988 by American Society of Clinical Oncology.*

Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

Technical Details of Intraoperative Lymphatic Mapping for Early Stage Melanoma

Donald L. Morton, MD; Duan-Ren Wen, MD; Jan H. Wong, MD; James S. Economou, MD, PhD; Leslie A. Cagle, MD; F. Kristian Storm, MD; Leland J. Foshag, MD; Alistair J. Cochran, MD

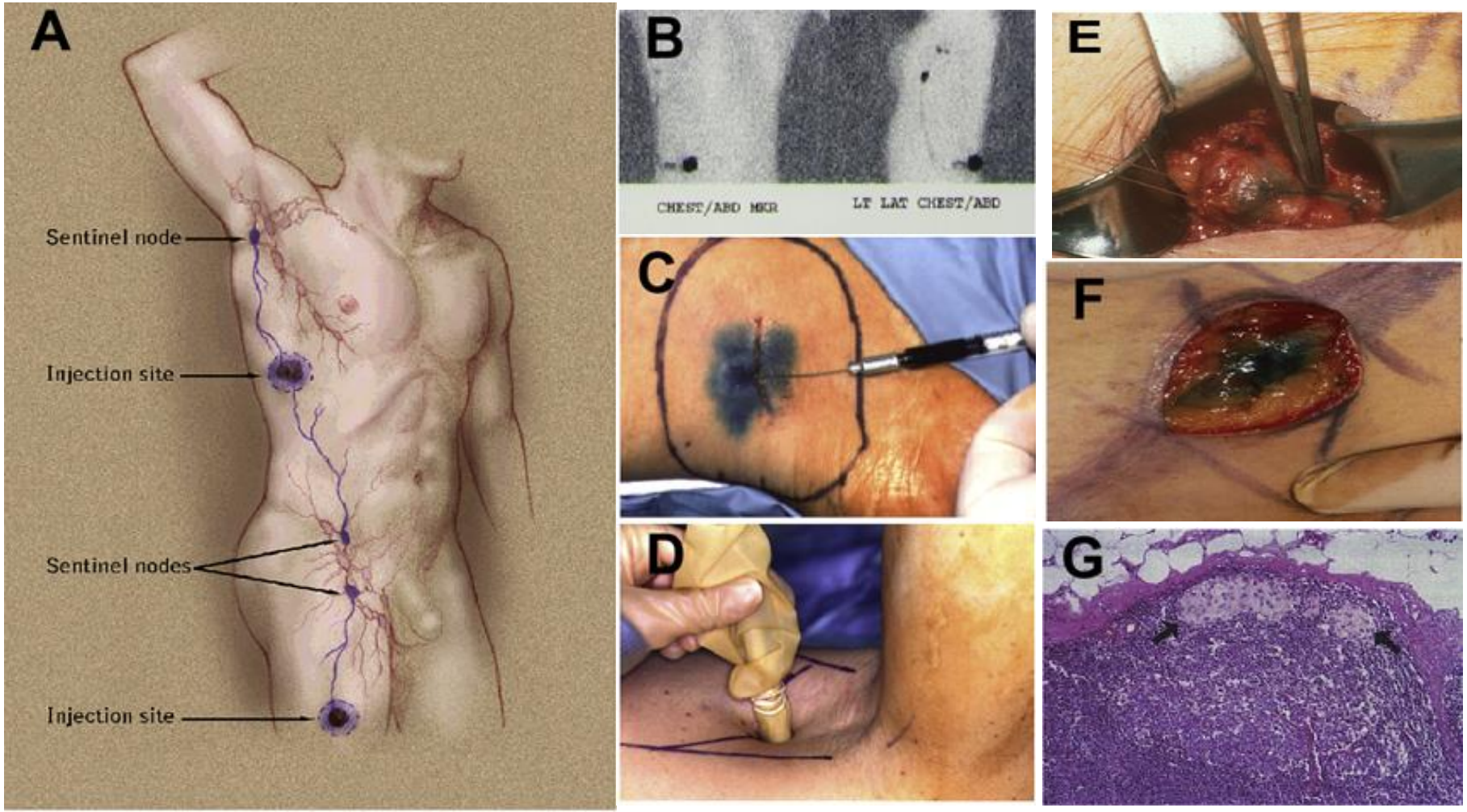
(*Arch Surg*. 1992;127:392-399)

Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

Doença linfonodal por LNS +

- Detecção de linfonodos adicionais comprometidos

Doença linfonodal clínica



Extraído e adaptado de Ross et al. *Surg Oncol Clin North Am*, 2011

Table 4. Rates of Positive Non-Sentinel Lymph Nodes

Study	Patients with CLND, n	Patients with Positive NSLN, n (%)
McMasters 2002 [302]	272	45 (16%)
Dewar 2004[291]	146	24 (16%)
Sabel 2005[278]	221	34 (15%)
Kettlewell 2006[303]	105	34 (32%)
Cascinelli 2006[172]	176	33 (19%)
Govindarajan 2007[279]	127	20 (16%)
Gershenwald 2008[288]	343	48 (16%)
Cadili 2010[77]	606	142 (24%)
Leung 2013[293]	329	79 (24%)
Wevers 2013[295]	130	30 (23%)
Pasquali 2014[304]	1,538	353 (23%)
Bertolli 2015[285]	146	23 (16%)
Rutkowski 2015[287]	473	132 (28%)
Kim 2015[79]	111	13 (12%)
Total	**4723**	**1010 (21%)**

CLND, complete lymph node dissection; NSLN, non-sentinel lymph node

Sentinel Node Tumor Burden According to the Rotterdam Criteria Is the Most Important Prognostic Factor for Survival in Melanoma Patients

A Multicenter Study in 388 Patients With Positive Sentinel Nodes

Alexander C. J. van Akkooi, MD,† Zbigniew I. Nowecki, MD, PhD,†‡ Christiane Voit, MD,†§ Gregor Schäfer-Hesterberg, MD,†§ Wanda Michej, MD,†‡ Johannes H. W. de Wilt, MD, PhD,*† Piotr Rutkowski, MD, PhD,†‡ Cornelis Verhoef, MD,*† and Alexander M. M. Eggermont, MD, PhD*†*

The Microanatomic Location of Metastatic Melanoma in Sentinel Lymph Nodes Predicts Nonsentinel Lymph Node Involvement

D.J. Dewar, B. Newell, M.A. Green, A.P. Topping, B.W.E.M. Powell, and M.G. Cook

Annals of Surgical Oncology, **11**(3):162S–168S
DOI: 10.1245/ASO.2004.12.920

Sentinel Lymphonodectomy and S-Classification: A Successful Strategy for Better Prediction and Improvement of Outcome of Melanoma

Hans Starz, MD, Katharina Siedlecki, MD, and Bernd-Rüdiger Balda, MD

References	Patient no. for research	Significant clinicopathological parameters	Discrimination AUC (95% CI)	Calibration brier score (95% CI)
Lee et al. (12)	191	Breslow thickness SLN tumor burden diameter	0.65 (0.60–0.70)	0.19 (0.18–0.20)
Sabel et al. (13)	221	Sex Breslow thickness Extranodal extension in SLN No. of positive SLNs	0.67 (0.63–0.74)	0.18 (0.16–0.20)
Gershenwald et al. (14)	343	SLN tumor burden diameter Breslow thickness No. of SLNs harvested	0.65 (0.60–0.70)	0.18 (0.17–0.20)
Murali et al. (15)	309	Sex Primary tumor regression No. of positive SLNs SLN tumor burden diameter SLN metastasis site	0.65 (0.60–0.70)	0.18 (0.17–0.19)
Kibrite et al. (16)	171	Breslow thickness SLN tumor burden diameter	0.65 (0.60–0.70)	0.19 (0.18–0.20)
Rossi et al. (17)	1220	Breslow thickness Primary tumor site SLN tumor burden diameter SLN metastasis site No. of SLNs harvested No. of positive SLNs	0.74 (0.70–0.79)	0.16 (0.15–0.17)
Bertolli et al. (18)	1213	Breslow thickness No. of positive SLNs SLN tumor burden diameter	0.86 (0.73–0.99)	0.085 (N.A.)

Nakamura Y. *Front Med,* 2019

Ann Surg Oncol (2019) 26:395–405
https://doi.org/10.1245/s10434-018-7038-9

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

ORIGINAL ARTICLE – MELANOMA

Validation of a Nomogram for Non-sentinel Node Positivity in Melanoma Patients, and Its Clinical Implications: A Brazilian–Dutch Study

Eduardo Bertolli, MD, PhD[1,2], Viola Franke, MD[2], Vinicius Fernando Calsavara, PhD[3], Mariana Petaccia de Macedo, MD, PhD[4], Clovis Antonio Lopes Pinto, MD, PhD[4], Winan J. van Houdt, MD, PhD[2], Michel W. J. M. Wouters, MD, PhD[2], Joao Pedreira Duprat Neto, MD, PhD[1], and Alexander C. J. van Akkooi, MD, PhD[2]

A.C.Camargo Cancer Center

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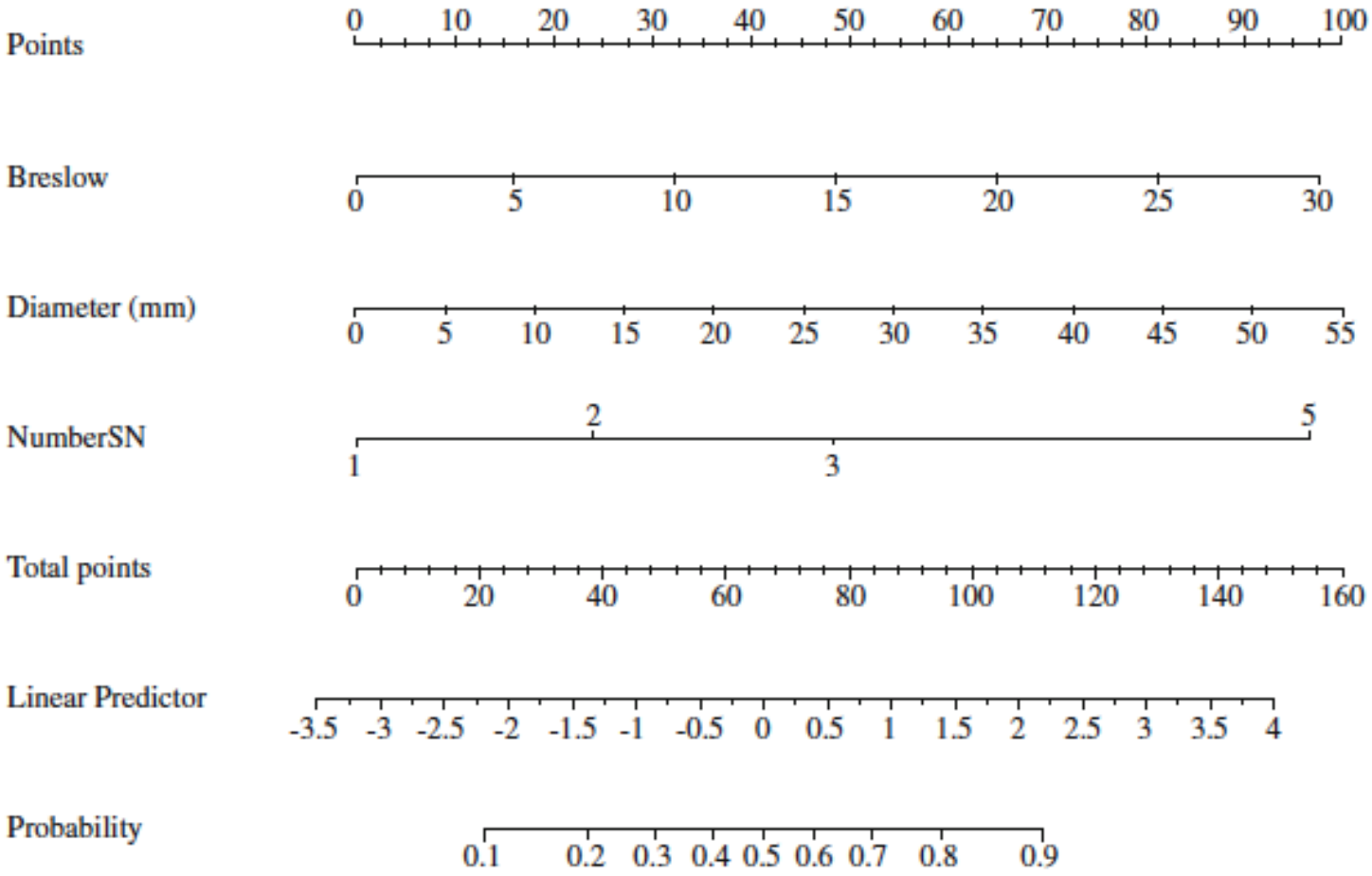
NEDERLANDS KANKER INSTITUUT



Bertolli et al. *Ann Surg Oncol,* 2019

https://accamargo.org.br/noticias/nomograma-preditor-de-comprometimento-adicional-de-linfonodos-em-pacientes-com-sentinela

Breslow (mm)

2.2

Maior diâmetro da metástase dos linfonodos sentinelas (mm)

0.5

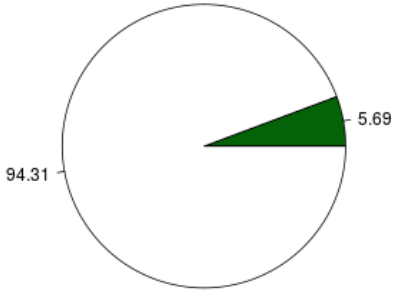
Número de linfonodos sentinelas positivos

1

Probabilidade de linfonodos adicionais comprometidos | Nomograma

Probabilidade de linfonodos adicionais comprometidos 5.69 %

Probabilidade de linfonodos adicionais comprometidos



Breslow (mm)

4.5

Maior diâmetro da metástase dos linfonodos sentinelas (mm)

1.5

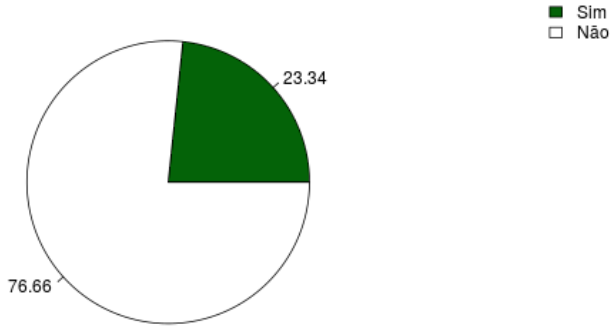
Número de linfonodos sentinelas positivos

2

Probabilidade de linfonodos adicionais comprometidos | Nomograma

Probabilidade de linfonodos adicionais comprometidos 23.34 %

Probabilidade de linfonodos adicionais comprometidos



Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

Doença linfonodal por LNS +

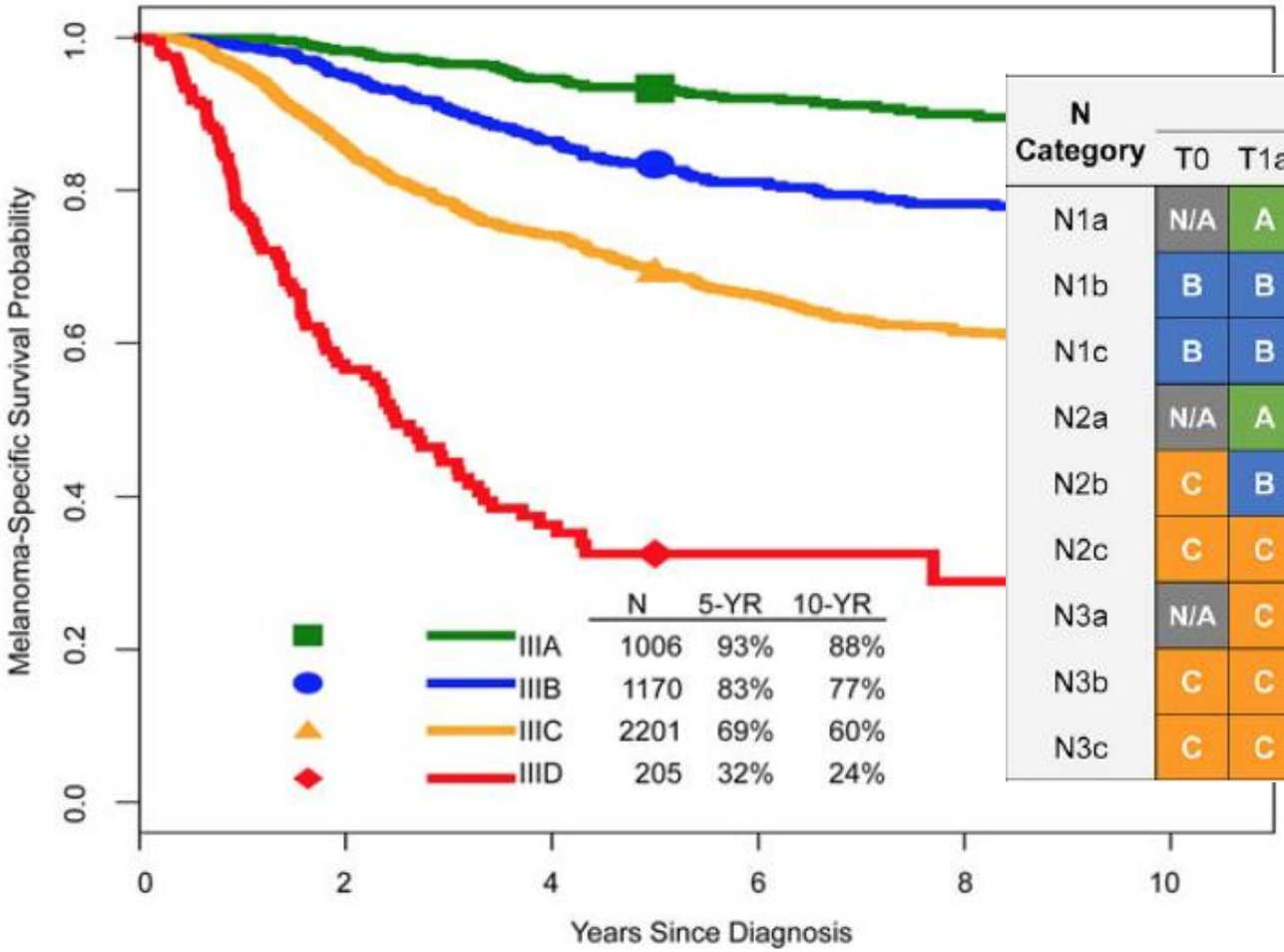
- Detecção de linfonodos adicionais comprometidos **+ / -**

- Melhorar estadiamento

Doença linfonodal clínica

N CATEGORY	EXTENT OF REGIONAL LYMPH NODE AND/OR LYMPHATIC METASTASIS: NO. OF TUMOR-INVOLVED REGIONAL LYMPH NODES	PRESENCE OF IN-TRANSIT, SATELLITE, AND/OR MICROSATELLITE METASTASES
NX	Regional nodes not assessed (eg, sentinel lymph node [SLN] biopsy not performed, regional nodes previously removed for another reason); Exception: pathological N category is not required for T1 melanomas, use clinical N information	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or 3 tumor-involved nodes or any number of in-transit, satellite, and/or micro-satellite metastases with one tumor-involved node	
N2a	Two or 3 clinically occult (ie, detected by SLN biopsy)	No
N2b	Two or 3, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (ie, detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Gershenwald et al. *CA J Clin* , 2017



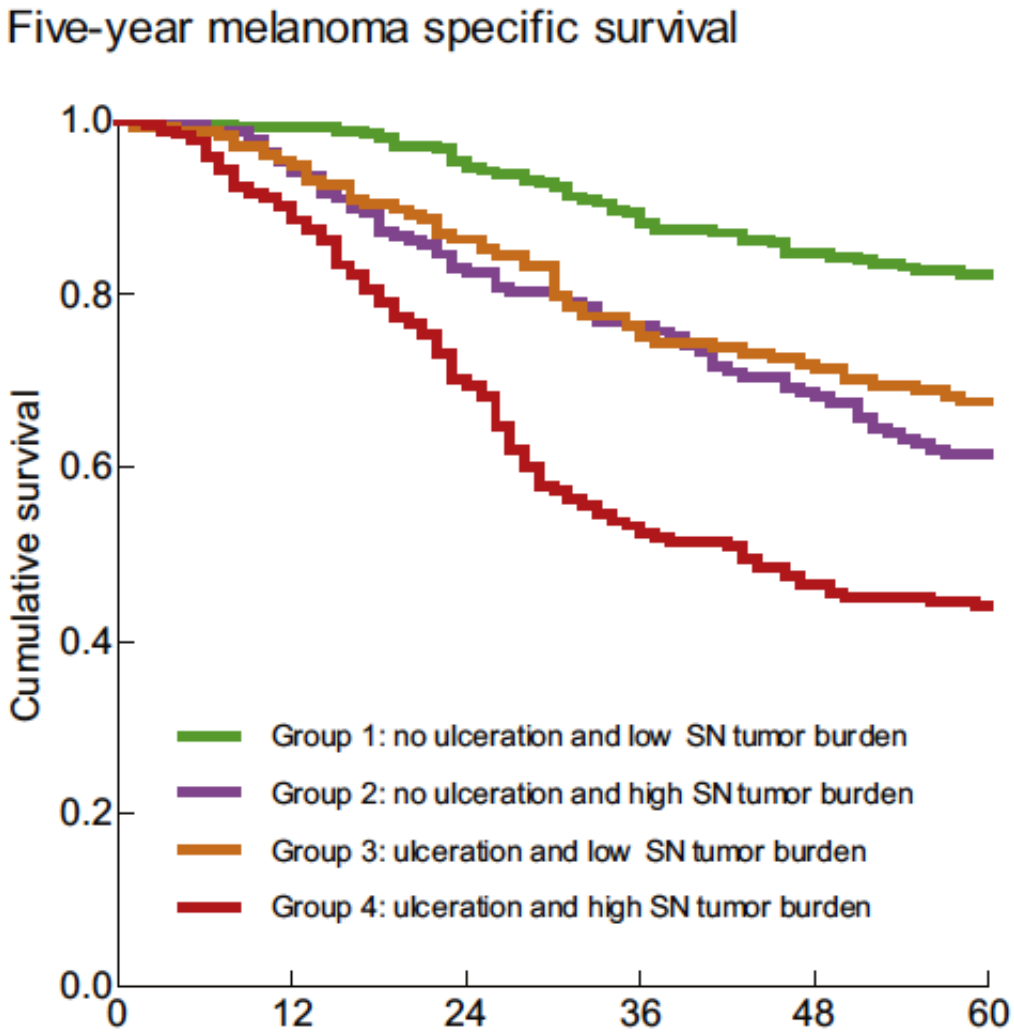
N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Gershenwald et al. *CA J Clin* , 2017

European Journal of Cancer 96 (2018) 25–33

Risk stratification of sentinel node–positive melanoma patients defines surgical management and adjuvant therapy treatment considerations

Daniëlle Verver [a,*], David van Klaveren [b], Alexander C.J. van Akkooi [c], Piotr Rutkowski [d], Barry W.E.M. Powell [e], Caroline Robert [f], Alessandro Testori [g], Barbara L. van Leeuwen [h], Astrid A.M. van der Veldt [i], Ulrich Keilholz [j], Alexander M.M. Eggermont [k], Cornelis Verhoef [a], Dirk J. Grünhagen [a]



"… it was demonstrated that adequate **stratification** of positive SN patients was possible based on **ulceration** and **SN tumor burden** category only, with at least similar predictive ability **compared with the model incorporating the AJCC stages**…"

Verver et al. *Eur J Cancer* , 2018

Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

Doença linfonodal por LNS +

- Detecção de linfonodos adicionais comprometidos **+ / -**
- Melhorar estadiamento **+ / -**
- Controle da doença loco – regional

Doença linfonodal clínica

The NEW ENGLAND JOURNAL of MEDICINE

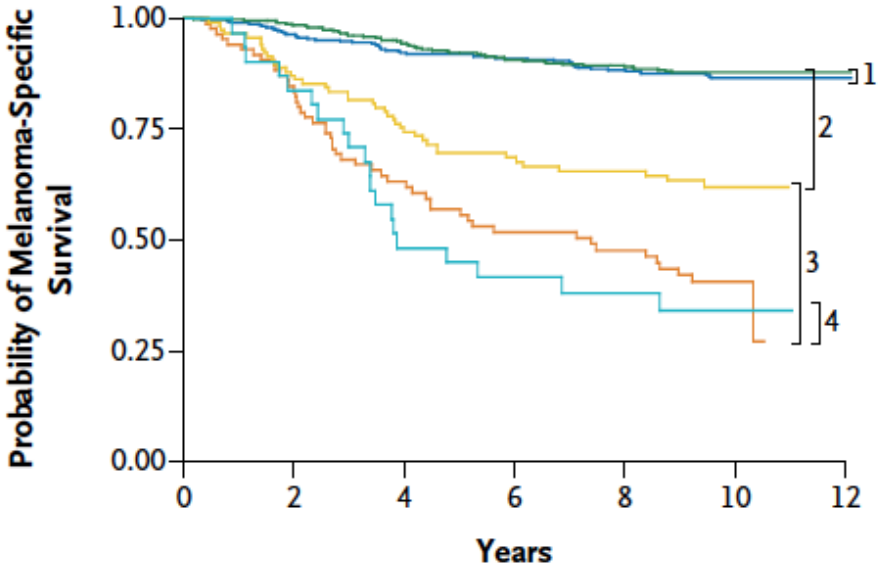
ESTABLISHED IN 1812 FEBRUARY 13, 2014 VOL. 370 NO. 7

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*

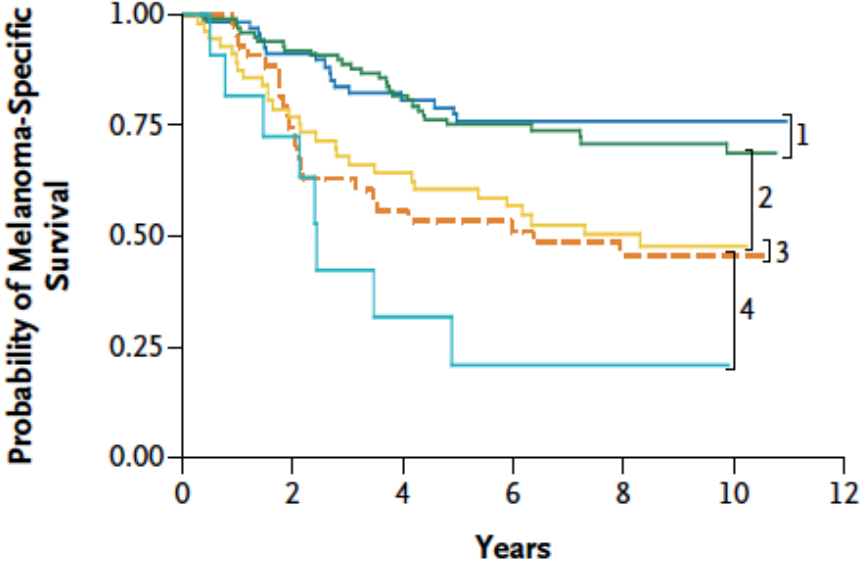
Melanoma-Specific Survival, Intermediate-Thickness Melanomas

	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



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	—



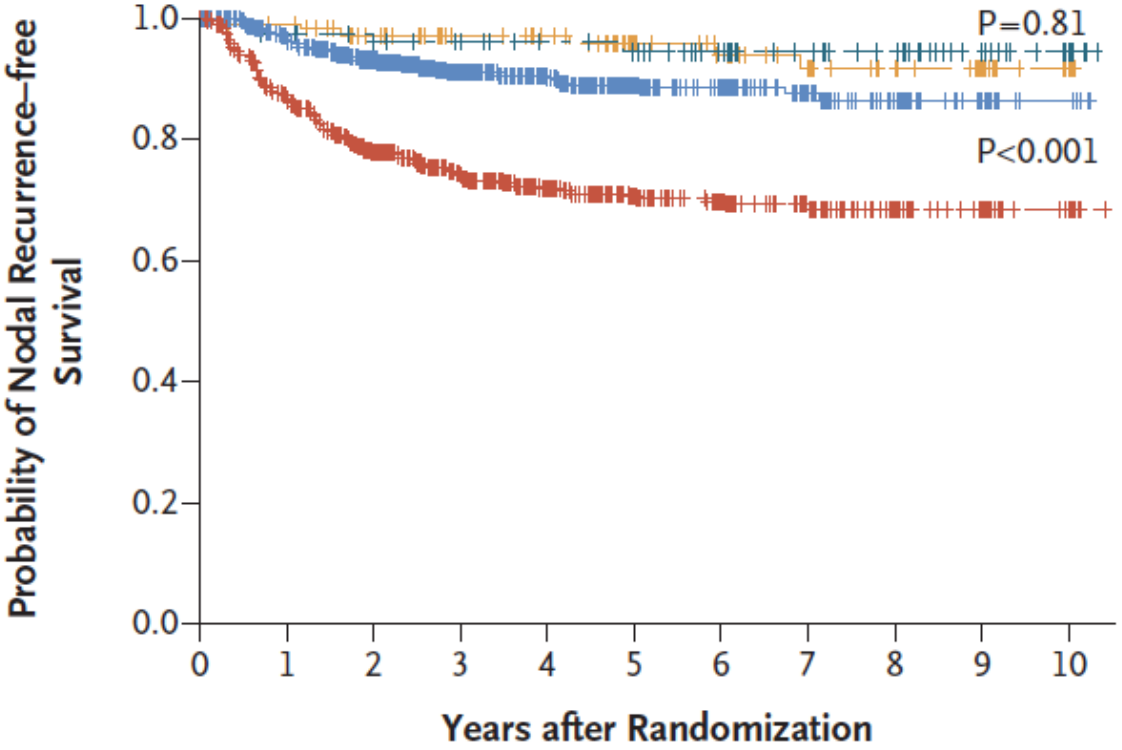
Morton et al. *NEJM,* 2014

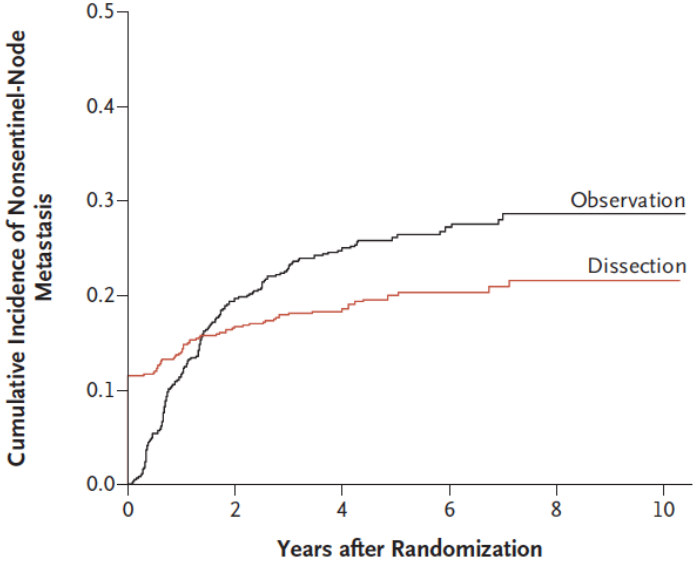
The NEW ENGLAND JOURNAL of MEDICINE

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

Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

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





Faries et al. *NEJM,* 2017

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)*

Summary

Background Complete lymph node dissection is recommended in patients with positive sentinel lymph node biopsy

Lancet Oncol 2016

original report

Final Analysis of DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node

Ulrike Leiter, MD[1]; Rudolf Stadler, MD, PhD[2]; Cornelia Mauch, MD, PhD[3]; Werner Hohenberger, MD[4]; Norbert H. Brockmeyer, MD[2]; Carola Berking, MD[5]; Cord Sunderkötter, MD[6,7]; Martin Kaatz, MD[8,9]; Kerstin Schatton, MD[10]; Percy Lehmann, MD[11]; Thomas Vogt, MD[12]; Jens Ulrich, MD[13]; Rudolf Herbst, MD[14]; Wolfgang Gehring, MD[15]; Jan-Christoph Simon, MD[16]; Ulrike Keim, PhD[1]; Danielle Verver, MD[17]; Peter Martus, PhD[1]; and Claus Garbe, MD[1]; on behalf of the German Dermatologic Cooperative Oncology Group

TABLE 1. Follow-Up Time, Recurrences, and Cause of Death in the Intention-to-Treat Population

Variable	Observation (n = 233)	CLND (n = 240)	Total (N = 473)
Median follow-up time, months (IQR)	74.0 (55-96)	66.0 (50-97)	72.0 (67-77)
Recurrences, No. (%)			
Total	80 (34.3)	86 (35.8)	166 (35.1)
Regional LN without distant recurrence	16 (6.9)	7 (2.9)	23 (4.9)
Regional LN and distant recurrence	22 (9.4)	19 (7.9)	41 (8.7)
Distant without regional recurrence	30 (12.9)	43 (17.9)	73 (15.4)
Other	12 (5.2)	17 (7.1)	29 (6.1)
Cause of death, No. (%)			
MM	57 (24.5)	59 (24.6)	116 (24.5)
Other malignancy	1 (0.42)	0 (0.00)	1 (0.2)
Other disease	9 (3.9)	7 (2.0)	16 (3.4)

Leiter et al. *JCO,* 2019

Foto: Arquivo pessoal do autor

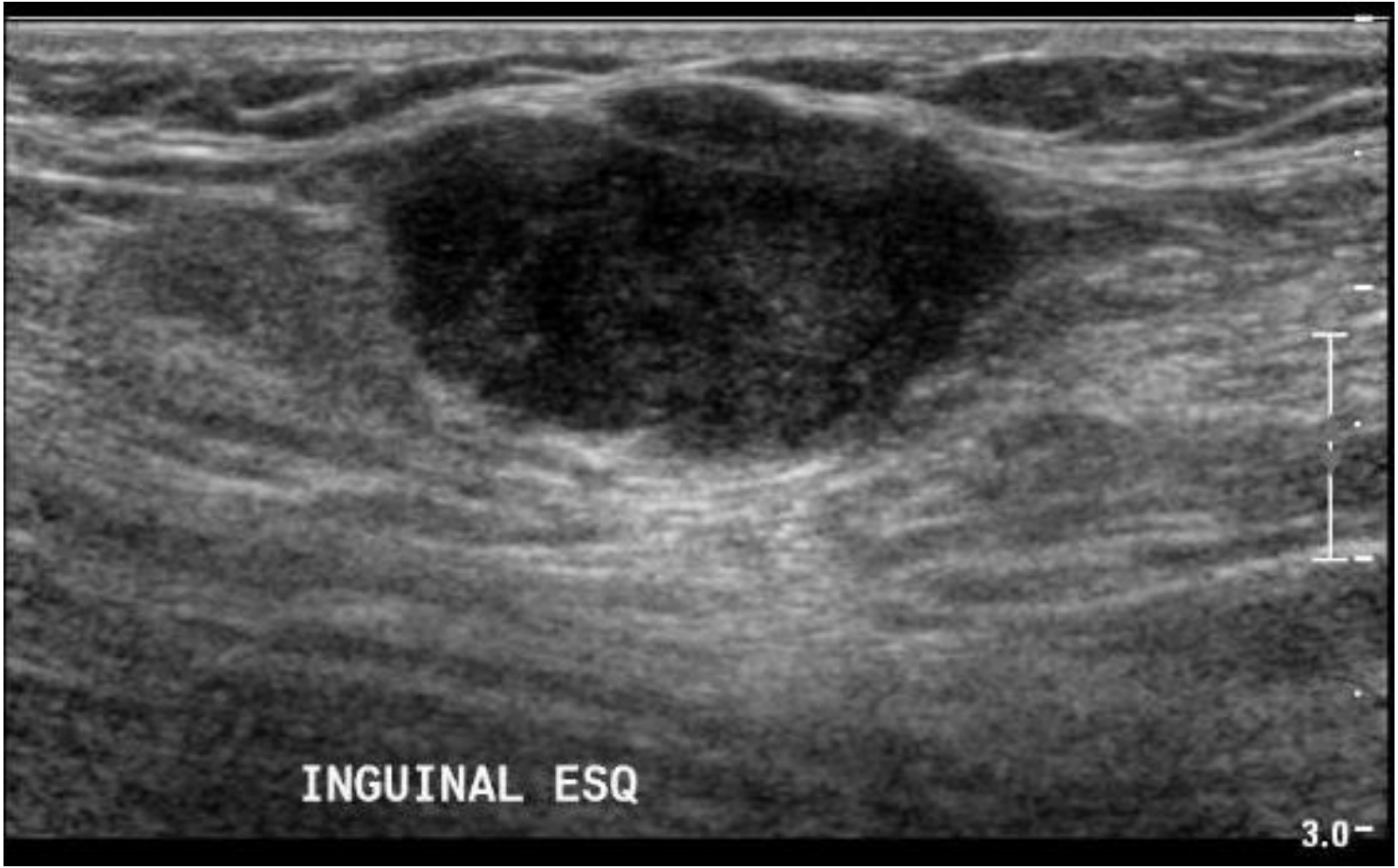
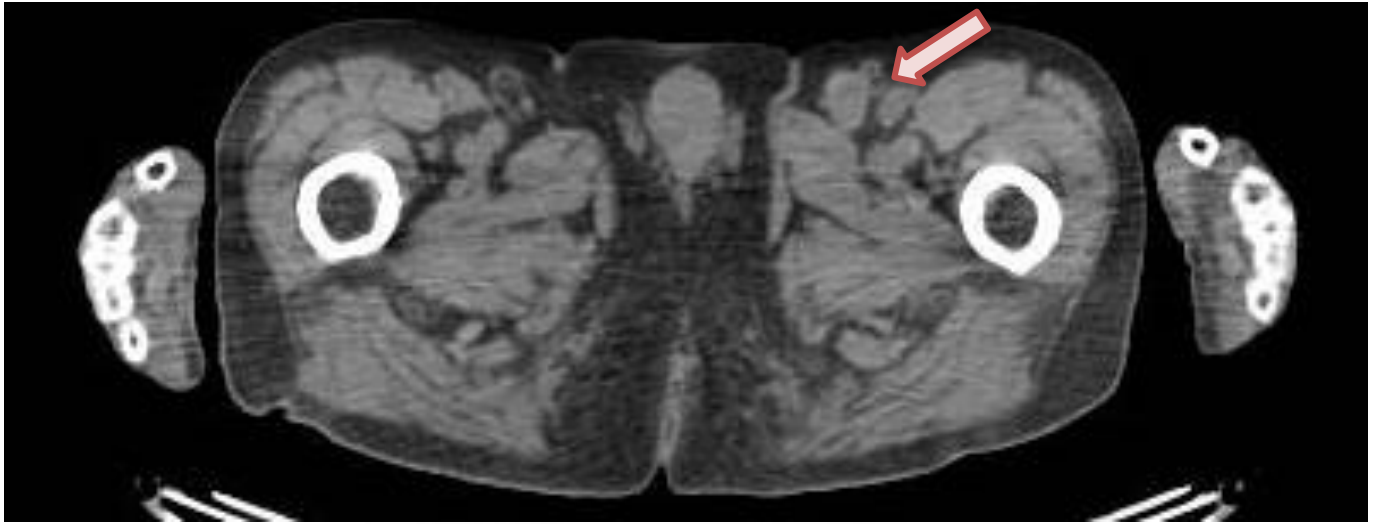


Foto: Arquivo pessoal do autor



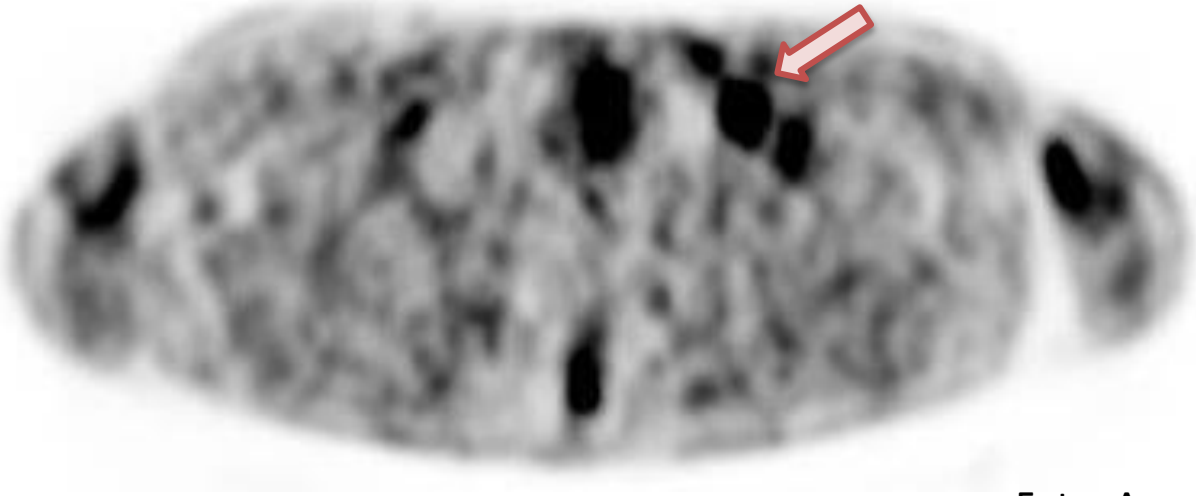


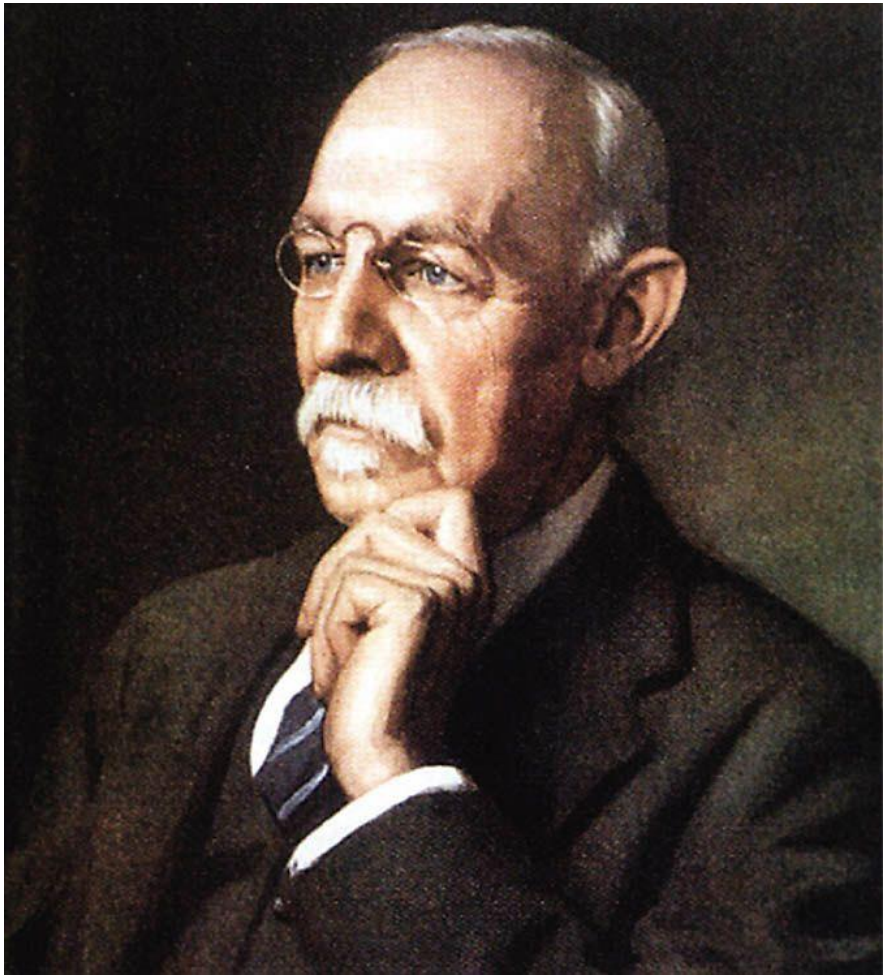
Foto: Arquivo pessoal do autor

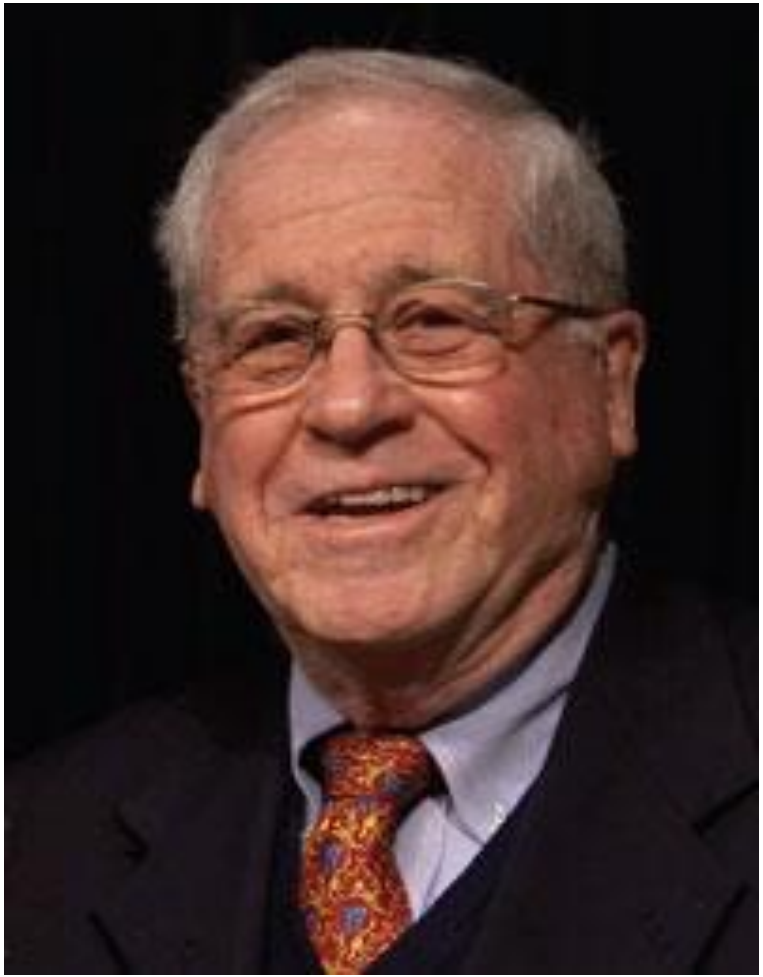
Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

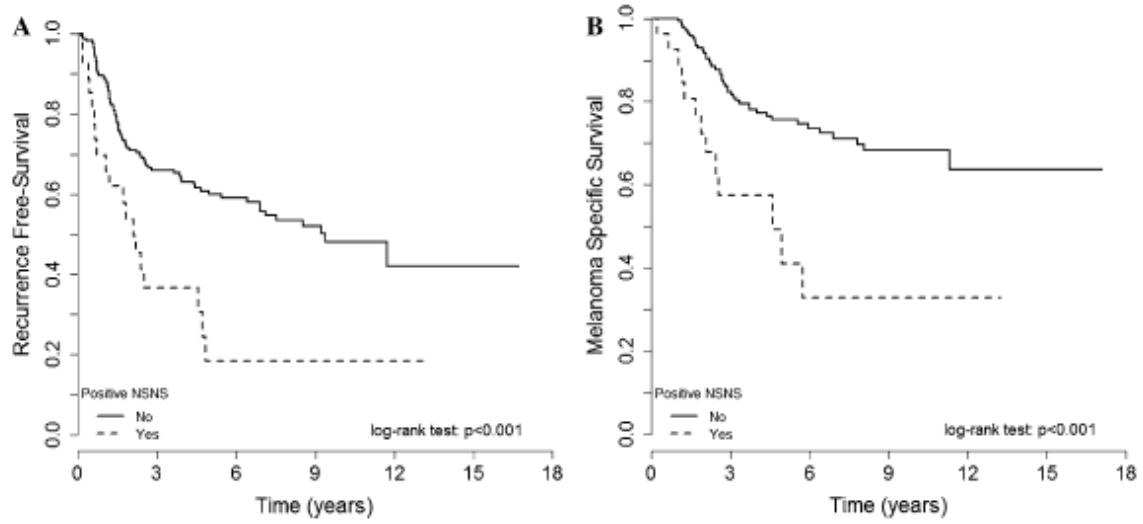
Doença linfonodal por LNS +

- Detecção de linfonodos adicionais comprometidos **+ / -**
- Melhorar estadiamento **+ / -**
- Controle da doença loco - regional **+ + +**
- Controle da doença a distância

Doença linfonodal clínica







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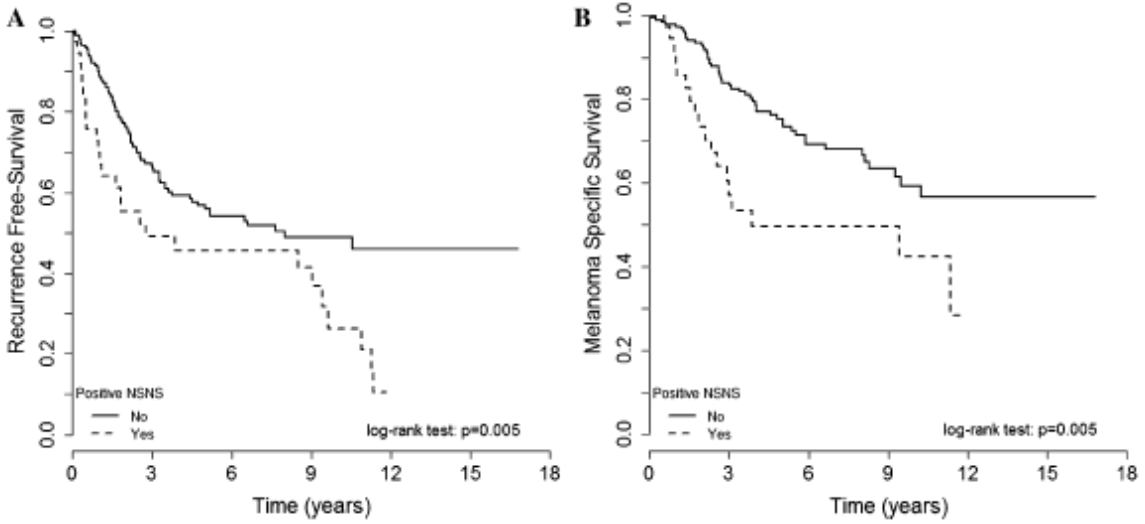

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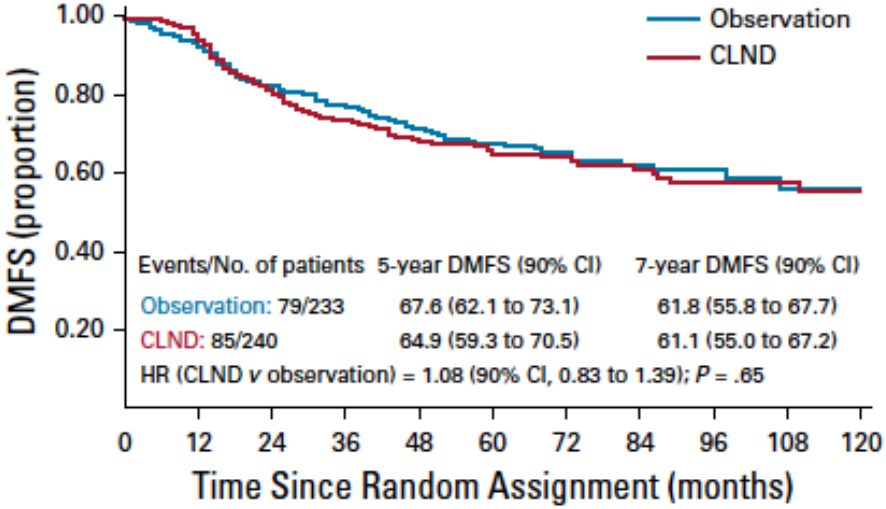
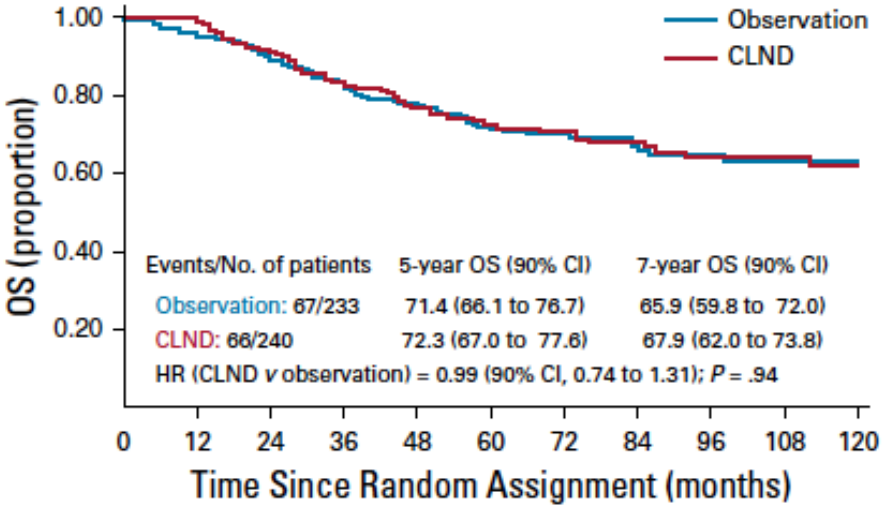
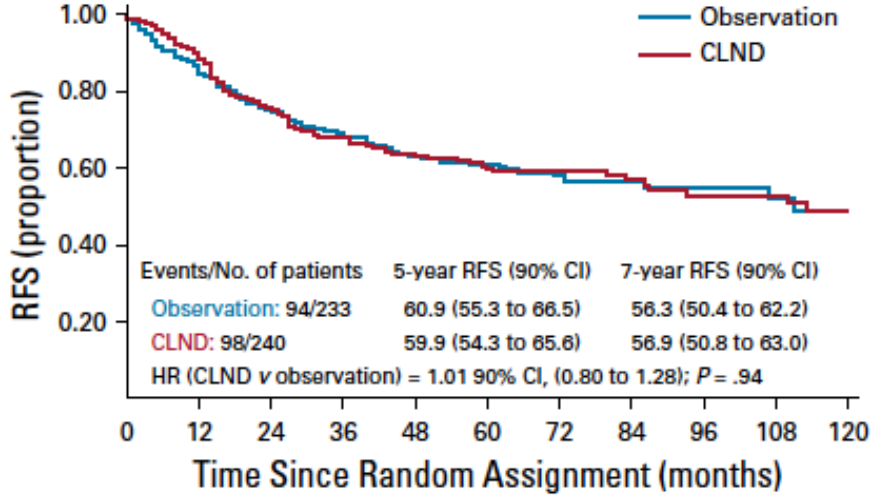
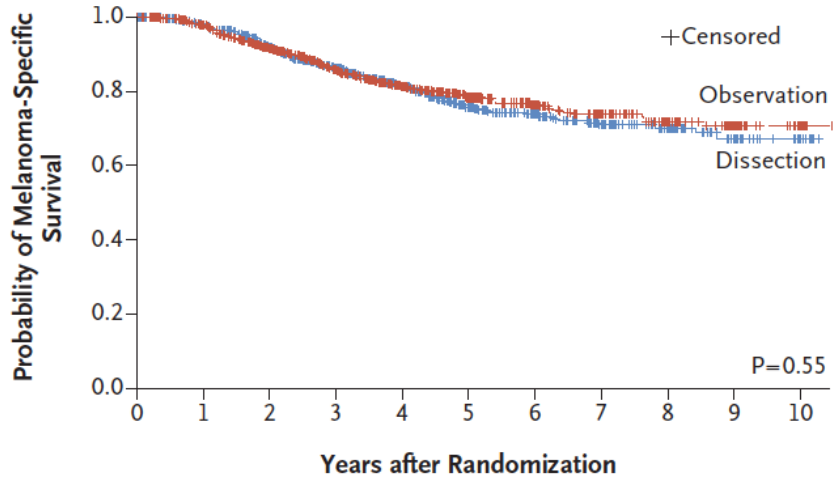
Bertolli et al. *Ann Surg Oncol,* 2019









Faries et al. *NEJM,* 2017; Leiter et al. *JCO,* 2019

Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

Doença linfonodal por LNS +

- Detecção de linfonodos adicionais comprometidos **+ / -**
- Melhorar estadiamento **+ / -**
- Controle da doença loco - regional **+ + +**
- Controle da doença a distância **- - -**

Doença linfonodal clínica

The NEW ENGLAND JOURNAL of MEDICINE

The Enigma of Regional Lymph Nodes in Melanoma

Daniel Coit, M.D.

Se esse agregado de dados for insuficiente para extinguir o entusiasmo pela dissecção linfonodal imediata, então não está claro o que mais é necessário.

Esses resultados devem ser vistos como uma mudança na prática.

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Management of Sentinel-Node Metastasis in Melanoma

N ENGL J MED 378;1 NEJM.ORG JANUARY 4, 2018

OPTION 1

Recommend Completion Lymph-Node Dissection

Charles M. Balch, M.D.,
and Merrick I. Ross, M.D.

OPTION 2

Recommend Observation of the Nodes with Ultrasonography

Caroline Robert, M.D., Ph.D.

Ann Surg Oncol
https://doi.org/10.1245/s10434-018-6812-z

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

CrossMark

CONTINUING EDUCATION– MELANOMA

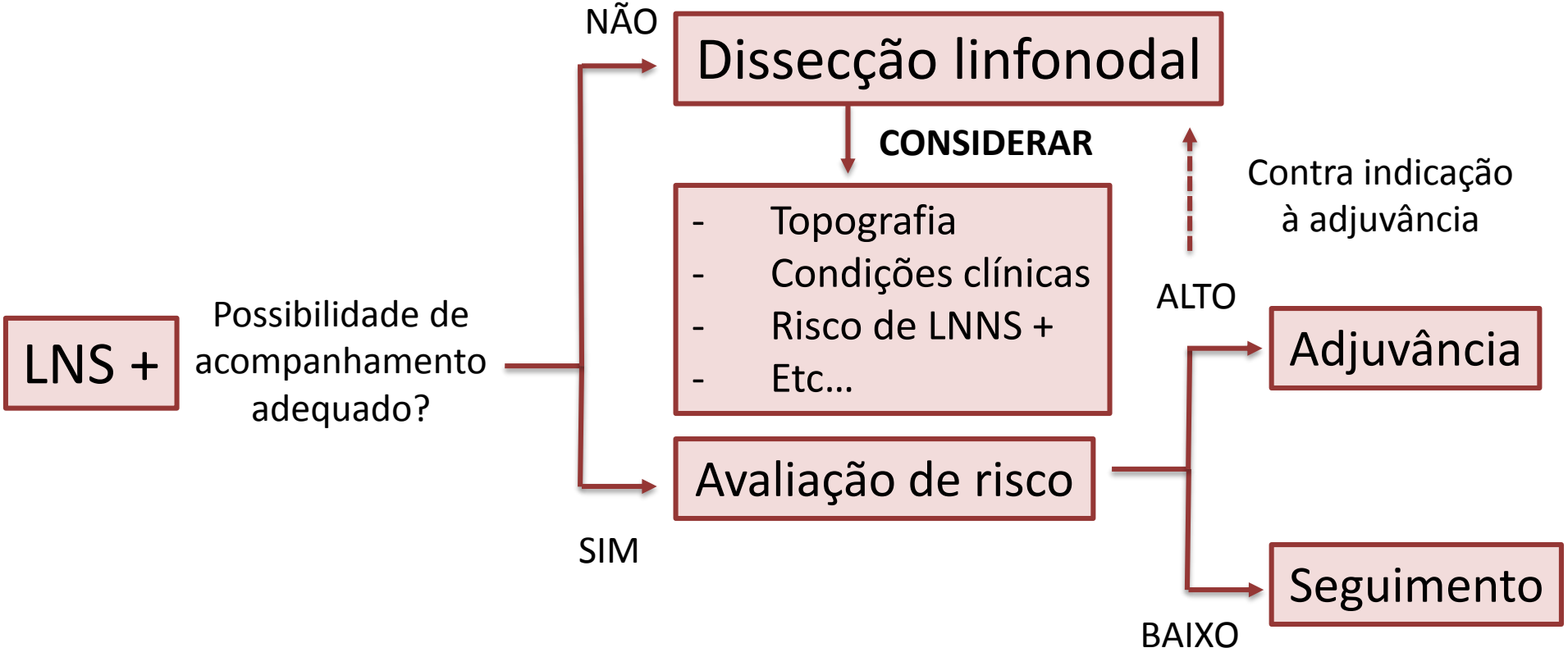
The Role of Completion Lymph Node Dissection for Sentinel Lymph Node-Positive Melanoma

Tina J. Hieken, MD[1], John M. Kane III, MD[2], and Sandra L. Wong, MD[3]

[1]Department of Surgery, Mayo Clinic, Rochester, MN; [2]Department of Surgical Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, NY; [3]Department of Surgery, Geisel School of Medicine at Dartmouth, Hanover, NH

“Data on long term outcomes are yet not available"

Sugestão de algoritmo



Slide do autor

Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

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- Melhorar estadiamento **+ / -**
- Controle da doença loco - regional **+ + +**
- Controle da doença a distância **- - -**

Doença linfonodal clínica

CLINICAL/ PATHOLOGIC STAGE	WORKUP[s]	PRIMARY TREATMENT	ADJUVANT TREATMENT	
Stage III (clinically positive node[s]) →	• Core biopsy or FNA preferred if feasible. If needle biopsy is not possible, incisional or excisional biopsy is acceptable • Imaging[j] for baseline staging and to evaluate specific signs or symptoms →	Wide excision of primary tumor[n] (category 1) + complete therapeutic lymph node dissection[cc] →	Locoregional option: • Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, gross and/or histologic extracapsular extension[dd,ee] (category 2B) and/or Systemic options:[v] • Preferred regimens ‣ Nivolumab[x] (category 1) ‣ Pembrolizumab[x] (category 1) ‣ Dabrafenib/trametinib for patients with *BRAF* V600-activating mutation (category 1) or Observation[v]	→ See Follow-up (ME-10)

Lancet Oncol. 2018 Jan 17. pii: S1470-2045(18)30016-0. doi: 10.1016/S1470-2045(18)30016-0. [Epub ahead of print]

Neoadjuvant therapy in melanoma: the next step?

Ascierto PA[1], Eggermont AMM[2].

Author information

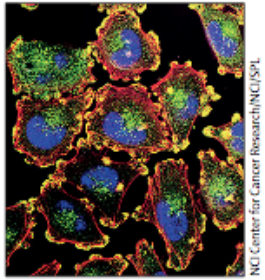
PMID: 29361473 DOI: 10.1016/S1470-2045(18)30016-0

Comment

Neoadjuvant therapy in melanoma: the next step?

Active drugs for the treatment of advanced melanoma are now available, including combinations of BRAF plus MEK inhibitors for *BRAF*-mutant melanoma and immune-checkpoint blockers for all melanomas regardless of *BRAF* status, especially regimens based on PD-1.[1] What works in the advanced setting is also effective in the adjuvant setting, especially the combination of dabrafenib and trametinib in patients with stage III *BRAF*-mutant melanoma[2] and nivolumab for all melanoma types in patients with stage IIIB or IIIC–IV disease.[3] Additionally, ipilimumab was shown to prolong overall survival compared with placebo in patients with stage III melanoma in a trial published in 2016.[4] With this radical change in adjuvant treatment strategy, neoadjuvant

Amaria and colleagues' trial was stopped early for ethical reasons, which led to only 21 patients being enrolled in total, of whom just 13 in the experimental group received neoadjuvant therapy. Additionally, only one of the seven patients in the standard of care group received adjuvant therapy (with the other six receiving observation alone), which is concerning and might have magnified the differences between the groups. No between-group differences in overall survival were recorded, although this result was probably due to the small number of patients and the effect of post-progression treatments. Additionally, median overall survival was not reached in either group. Toxicity is an important consideration in such trials, and four (36%)



NCI Center for Cancer Research/NCI/SPL

Lancet Oncol 2018

Published Online
January 17, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30016-0

See Online/Articles
http://dx.doi.org/10.1016/S1470-2045(18)30015-9

Modern melanoma NST trials

Trial	Regimen	N		RFS (mo)	med FU (mo)
Amaria Lancet Oncol 2018	Dab/Tram			19.7	18.6
Long Lancet Oncol 2019*	Dab/Tram		9	23.0	27.0
Blank Nat Med 2018	Ipi+		33	NR	32
Amaria Nat Med 2018		1	25 45	NR NR	20
Huang Nat Med 2019		30	19	NR	18
Rozeman Lancet Onc		86	57^	NR	8.3

* In press

^arm B = I1N3

Papel da neoadjuvância na recorrência loco-regional

ANTONIO CARLOS BUZAID

Palestrante

11:30 - 11:55

PRESENTED AT: 2019 ASCO ANNUAL MEETING

PRESENTED BY: Alexander M Menzies, MIA

Presented By Alexander Menzies at 2019 ASCO Annual Meeting

Em que situações clínicas a dissecção linfonodal **AINDA** é necessária?

- Quando o número de linfonodos comprometidos (e o estadiamento pela AJCC) for critério de inclusão em trials

… o que vai se tornar cada vez mais raro

- Quando houver necessidade de controle local

- Na doença linfonodal clínica

… provavelmente por pouco tempo

Reunião Científica
SAVE THE DATE
GBM
ITINERANTE
Reunião Científica
14 de dezembro de 2019
São Paulo - SP
TEMA:
O QUE MUDOU NOS ÚLTIMOS ANOS?
VISANA

VII SIMPÓSIO INTERNACIONAL DE Melanoma

HOTEL PULLMAN VILA OLÍMPIA

29 E 30 DE NOVEMBRO 2019

Muito obrigado!

Thank you very much!

Grazie mille!

Merci beaucoup!

Hartelijk bedankt!

Vielen Dank!

¡Muchas gracias!

ebertolli@hotmail.com