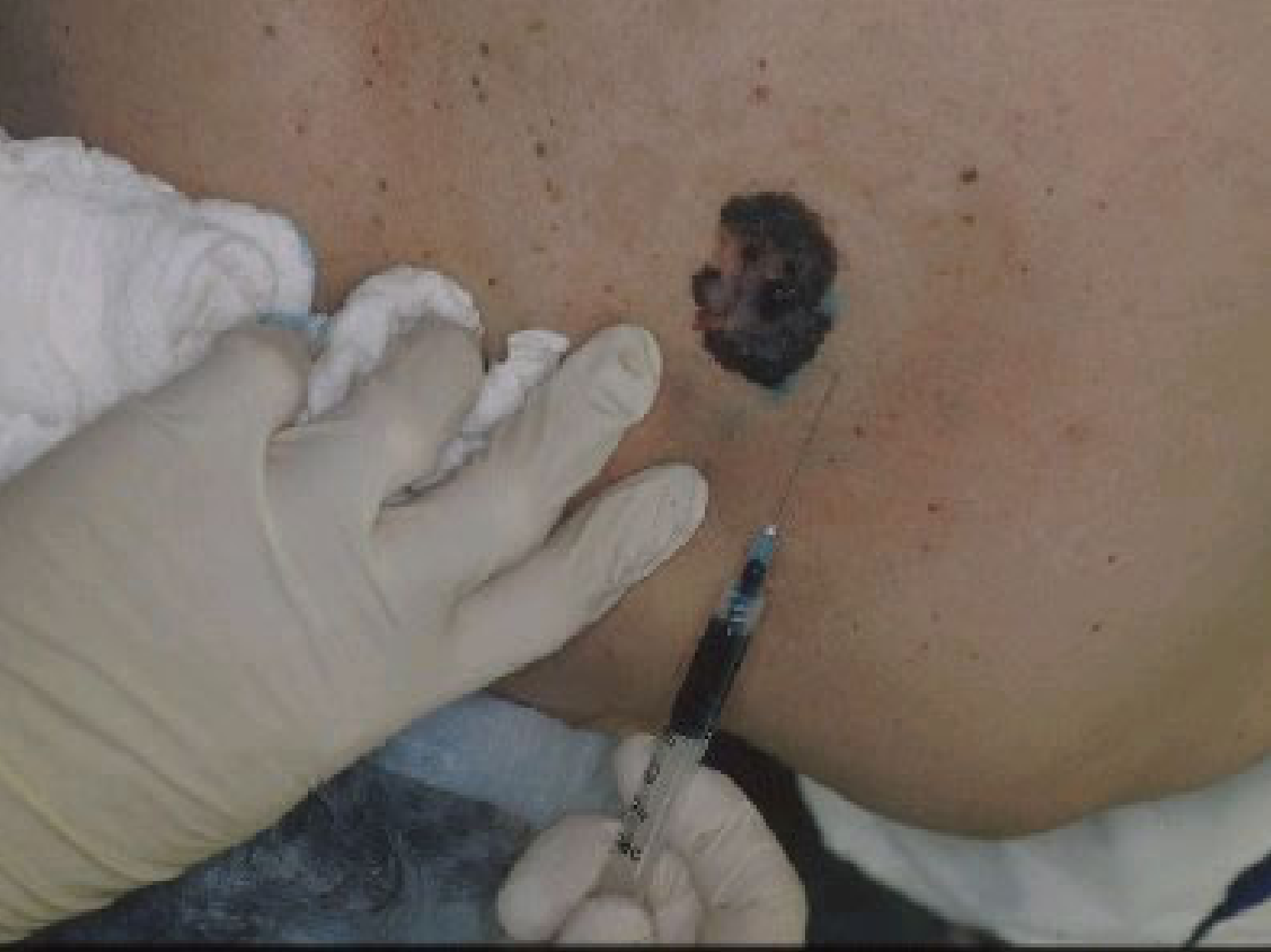
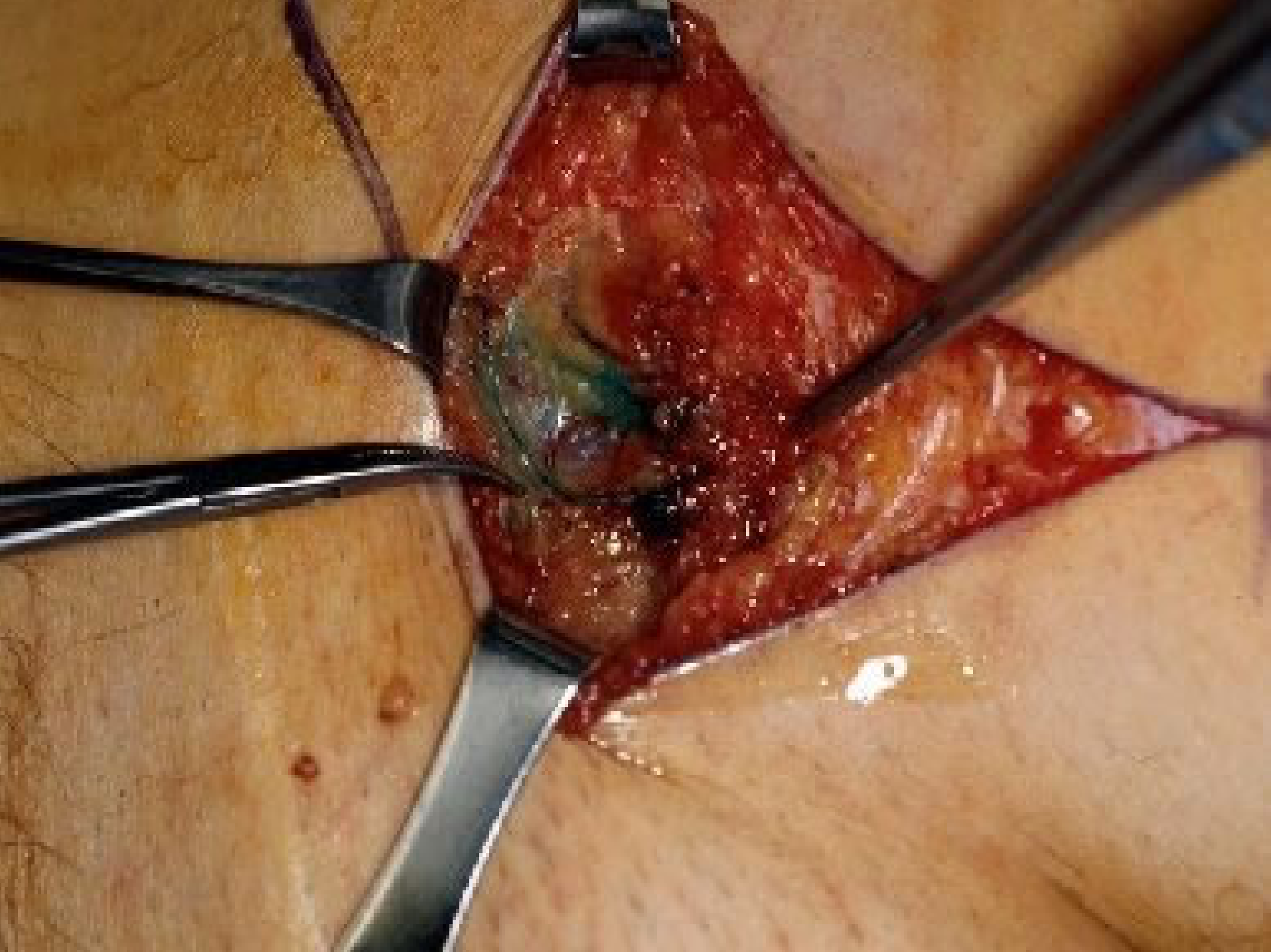
Gold Standard

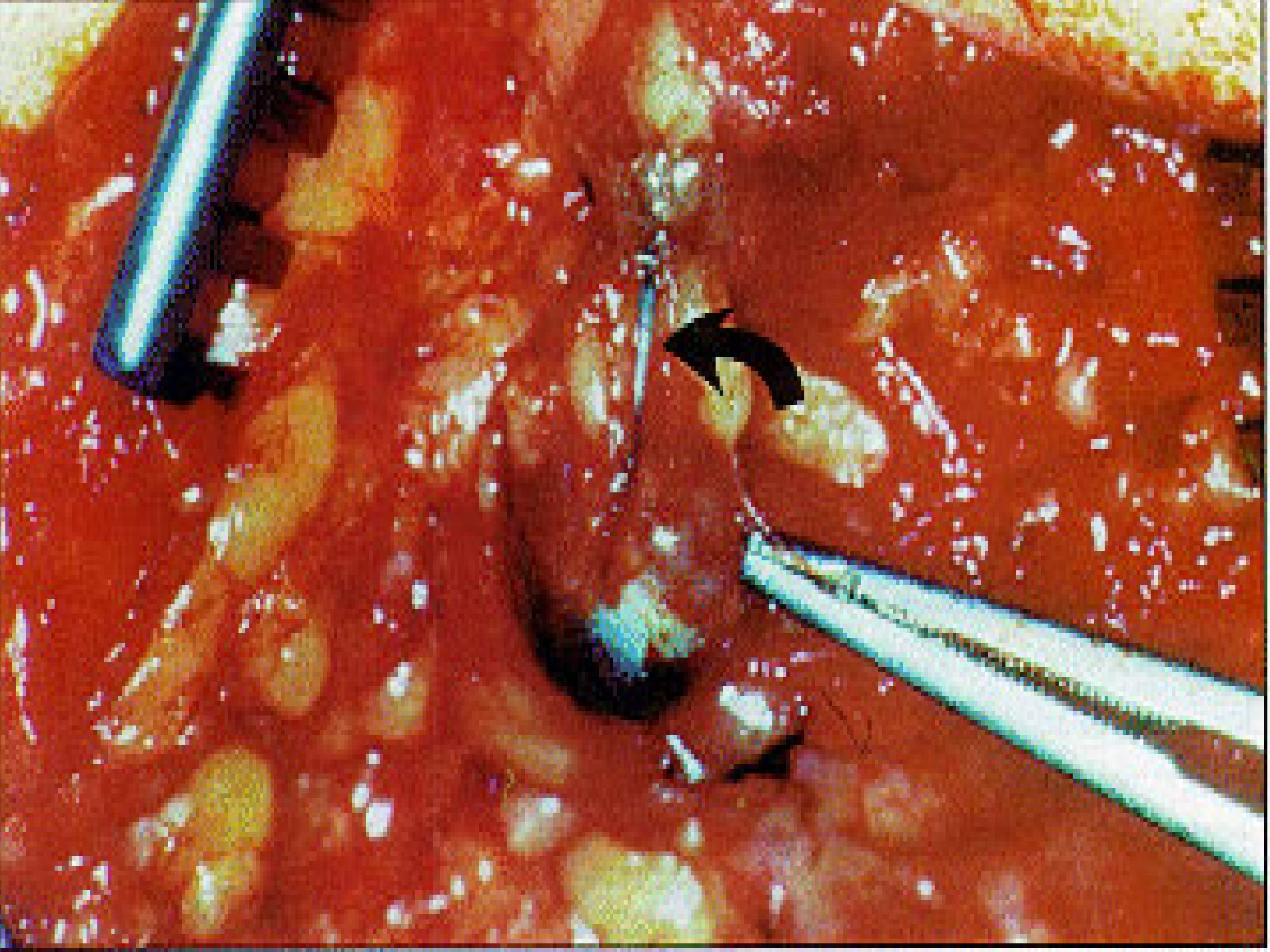
100% Guaranteed Customer Satisfaction

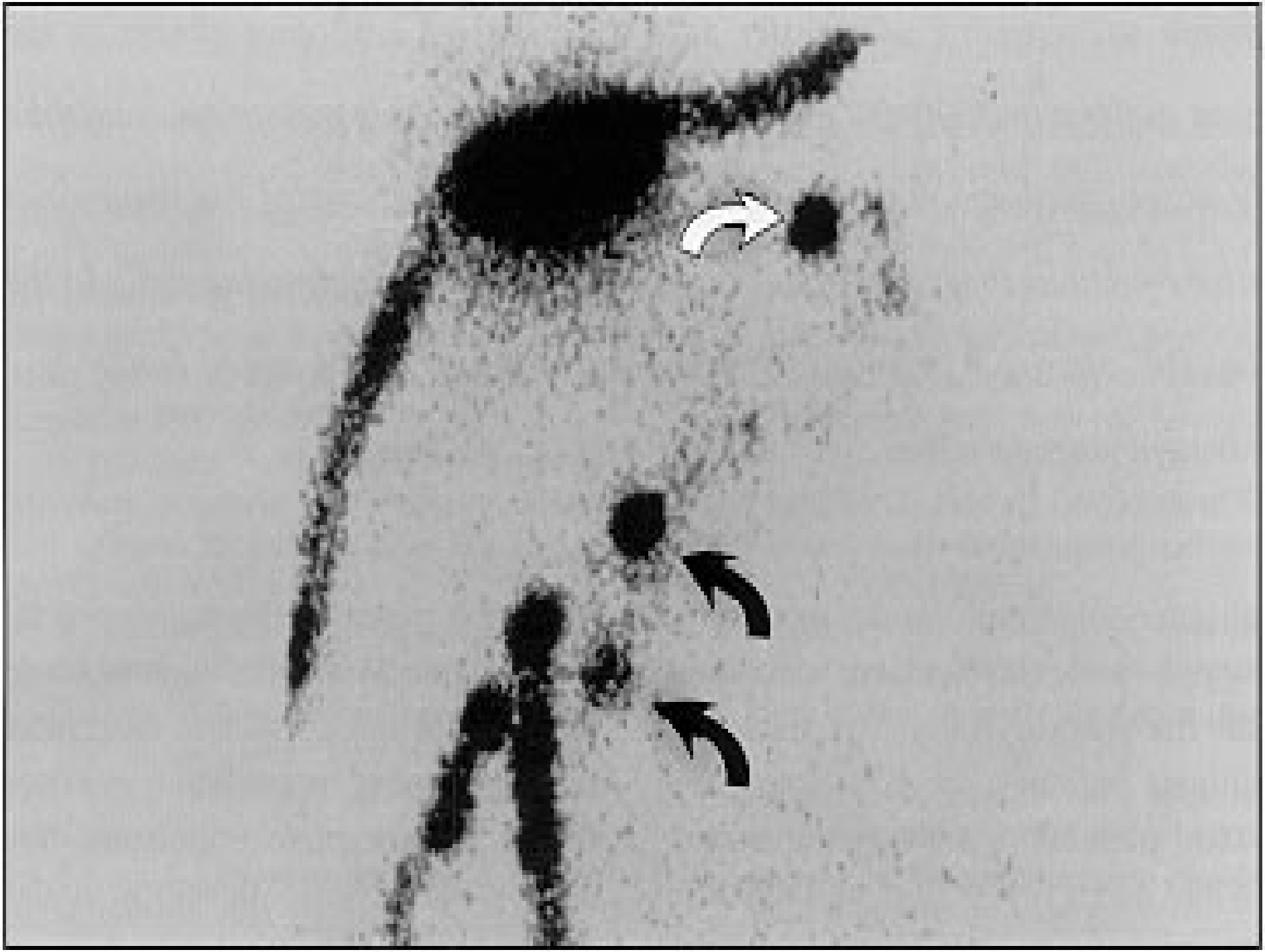
Melanoma Sentinel Lymph Node Biopsy- Is it the Gold Standard?

Paul K. Shitabata, M.D.
Dermatopathologist
Pathology Inc.









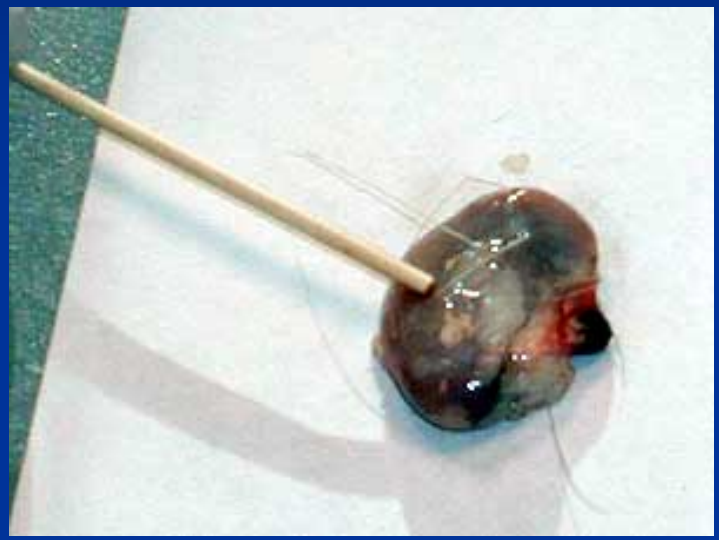
Technical details of intraoperative lymphatic mapping for early stage melanoma

Sites	% Metastases
SLN	18% (47/259)
Non-SLN	<1% (2/3079) FN<1%

Method of detection	% Detection n=40 spec.
H and E	21% (194/237)
IPOX	9%

Arch Surg. 1992 Apr;127(4):392-9
Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ.
John Wayne Institute for Cancer Treatment and Research, St John's Hospital and Health Center, Santa Monica, Calif 90404.

Preparation of Sentinel LN



- Bisect through longest meridian
- 10 full face sections-
  - 1, 3, 5, 10 for H and E
  - 2, 4, 6, for S100, HMB-45, Mart1
- 20% positive SN

Skip metastasis beyond the first node is rare

Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group

Group	LM with blue dye	LM with blue dye/radiocolloid
MSLT	95.2%	99.1%
JWCI	95.2%	99.1%

- 30-case learning phase
- Comparison group of JWCI patients
  - 551 pts. MSLT group
  - 584 pts. JWCI group
- Selection criteria:
  - Thickness > or =1 mm
  - Clark level > or =III, or
  - Thickness <1 mm with a Clark level > or =IV

Ann Surg. 1999 Oct;230(4):453-63
Morton DL, Thompson JF, Essner R, Elashoff R, Stern SL, Nieweg OE, Roses DF, Karakousis CP, Mozzillo N, Reintgen D, Wang HJ, Glass EC, Cochran AJ. John Wayne Cancer Institute, Santa Monica, CA 90404, USA.

Melanoma recurrence patterns after negative sentinel lymphadenectomy

Location of recurrence	3YR Survival after first recurrence
Regional basin	63.5% (13 pts)
Local or in-transit	48.7% (19 pts)
Distant	17.1% (37 pts)

- Median follow-up of 36.7 months, 69 (8.9%) of 773 patients with tumor-negative SNs had recurrent disease.
- 8.9% of patients with tumor-negative SNs will develop recurrence
- Low incidence (1.7%) of regional basin recurrence in patients with negative SNs

Arch Surg. 2005 Sep;140(9):865-71 **Zogakis TG**, **Essner R**, **Wang HJ**, **Turner RR**, **Takasumi YT**, **Gaffney RL**, **Lee JH**, **Morton DL**.
Roy E. Coats Research Laboratories, John Wayne Cancer Institute, Saint John's Health Center, Santa Monica, CA 90404, USA.

ELND failed to increase survival because it was applied to unselected patients

Single-institution experience in the management of patients with clinical stage I and II cutaneous melanoma: results of sentinel lymph node biopsy in 240 cases

Breslow thickness of 0.99 mm was the optimal cutpoint for predicting the SLNB result.

- Stage I and II (AJCC 2002)
- Positive SLN 20.8%
- 24 pts. (12.3%) developed a locoregional or distant recurrence at a median follow-up of 31 months.
  - Recurrences were more frequent with positive SLN.
  - Recurrences with positive SLN were more likely to have distant metastases

Dermatol Surg. 2005 Nov;31(11 Pt 1):1385-93. **Rex J**, **Paradelo C**, **Mangas C**, **Hilari JM**, **Fernandez-Figueras MT**, **Fraile M**, **Alastrue A**, **Ferrandiz C**. Department of Dermatology, Hospital Universitari Germans Trias i Pujol, Badalona, Universitat Autonoma de Barcelona, Badalona, Spain

Complete regional dissection in patients with positive SN would result in more effective cure by disrupting the metastatic cascade

Sentinel lymphadenectomy does not increase the incidence of in-transit metastases in primary melanoma

Procedure	% ITM
ENLD	6.56
WLE	3.36
SLN	3.64

- 4,412 patients who underwent WLE (n = 2,771), SLND (n = 1,016), or ELND (n = 625) for stage I/II melanoma (1971 through 2002)
- Incidence of ITM increased with:
  - Breslow depth, Clark level, and T stage.
  - No significant differences in ITM overall or as a first recurrence
  - Treatment groups matched by T stage, age, sex, Breslow depth, and primary location No relationship between SLND and ITM.

J Clin Oncol. 2005 Jul 20;23(21):4764-70
Kang JC, **Wanek LA**, **Essner R**, **Faries MB**, **Foshag LJ**, **Morton DL**.
Roy E. Coats Research Laboratories of the John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA

SLNB reduces the morbidity of ELND

Immediate dissection of nodes containing micrometastases improves prognosis…Does SNLB improve Survival?


Safe Landing

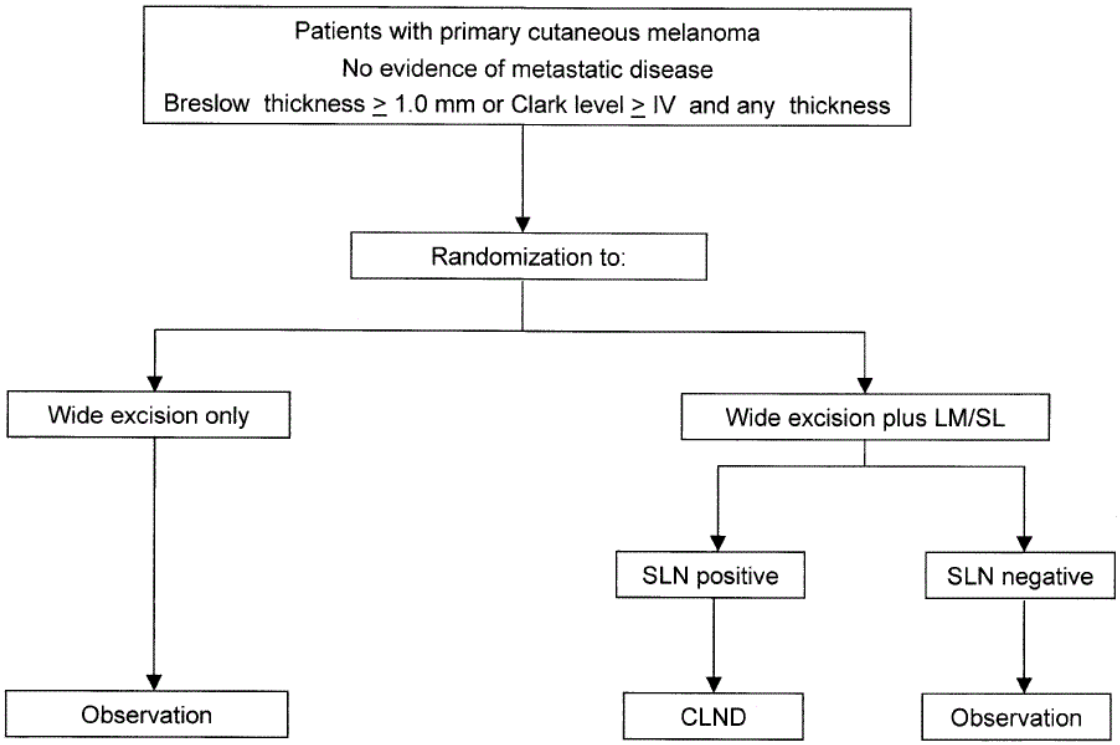


Fig 8. Multicenter Selective Lymphadenectomy Trial treatment algorithm. *CLND*, Complete lymph node dissection; *LM/SL*, lymphatic mapping and sentinel lymphadenectomy; *SLN*, sentinel lymph node.

Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial

- Clear survival benefit for immediate vs. delayed dissection of LN mets
  - 71% of those treated with LM/SNB and immediate lymph-node removal were alive at five years, compared with 53% of those in the "watch and wait" group.
  - "Watch and wait" group had more cancerous lymph nodes on average (3.4) than those in the LM/SNB group (1.6)
- 10.1% complication rate for LM/SNB vs. 37.2%
- LM/SNB were 26% less likely to have a recurrence of melanoma after five years than those treated with the "watch and wait" approach
- 2001 pts
- Clinically localized intermediate thickness primary melanoma
- Randomize to WE with CLND if mets develop or WE plus LM/SNB with immediate complete dissection if SN+
- 20% had SLN+
- One cancerous node were 2.6 times more likely to die of melanoma within five years

Ann Surg. 2005 Sep;242(3):302-11 **Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, Mozzillo N, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Reintgen DS, Coventry BJ, Wang HJ; Multicenter Selective Lymphadenectomy Trial Group**. John Wayne Cancer Institute, Santa Monica, CA

SLNB is a derivative of an ineffective therapy

TRIAL	DESIGN	OUTCOME
Intergroup Melanoma Trial	Melanoma 1-4 mm ELND	ELND with slightly better survival at 10 yrs
WHO #1*	Extremity melanoma No lymphoscintigraphy	ELND no difference in survival
WHO #14*	Trunk melanoma	ELND with slightly better survival at 10 yrs


THE TRUTH IS OUT THERE

THE SMALLEST SPECIMEN YET.

Lymphatic mapping identifies the first node receiving lymphatic drainage from a given skin area in over 95% of cases

Role of lymphoscintigraphy for selective sentinel lymphadenectomy

Primary Site	LN Basins
Base of scalp	Base of the neck up Occipital or upper cervical areas Neck base
Upper limb	Above axilla
Post. Body wall	Para-aortic Paravertebral Retroperitoneal
Hand and arm	Epitrochlear region
Foot and leg	Popliteal

- SNs outside the axilla, which occur in about 50% of patients
  - Internal mammary chain
  - Supraclavicular region
  - Interpectoral region
  - Intramammary interval nodes

Cancer Treat Res. 2005;127:15-38
Uren RF, Howman-Giles RB, Chung D, Thompson JF. Nuclear Medicine and Diagnostic Ultrasound, RPAH Medical Centre and Discipline of Medicine, The University of Sydney, Sydney, NSW, Australia.

Proportion of melanoma-positive sentinel nodes is higher in patients with thicker tumors

Factors predictive of tumor-positive nonsentinel lymph nodes after tumor-positive sentinel lymph node dissection for melanoma

Risk Factors	Probability % of SN+
0	12.3%
1	30.9%
2	41.9%

- 1,599 patients
- 19.5% underwent CLND for tumor-positive SN.
- Forty-six (24%) patients had tumor-positive NSN
- Risk Factors
  - Breslow > or = 3 mm
  - SN tumor size > or = 2 mm

J Clin Oncol. 2004 Sep 15;22(18):**Lee JH, Essner R, Torisu-Itakura H, Wanek L, Wang H, Morton DL.**
John Wayne Cancer Institute, Santa Monica, CA 90404, USA.

Presence of histologically and/or histochemically detectable tumor cells in the lymphatic basin is a more informative predictor of early relapse than Breslow thickness

Sentinel node biopsy provides more accurate staging than elective lymph node dissection in patients with cutaneous melanoma

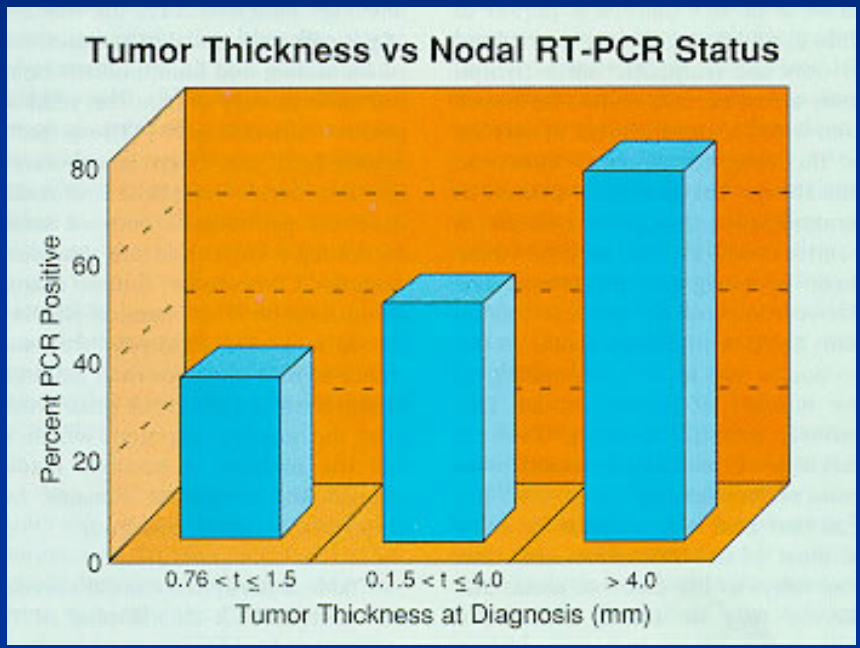
- Sentinel node biopsy identified more nodal micrometastases than ELND but did not influence survival*
- Preop LS with more detailed pathologic examination of the appropriate lymph nodes

- SNB (n = 672) or ELND (n = 793).

- Patient factors that influenced nodal positivity included:
  - Age
  - Breslow thickness
  - Ulceration
  - Head or neck primary
  - Operation type (SNB or ELND)

Ann Surg Oncol. 2004 Sep;11(9):829-36.
Doubrovsky A, De Wilt JH, Scolyer RA, McCarthy WH, Thompson JF
Sydney Melanoma Unit, Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia.

Sensitivity



- If an extremely sensitive test could detect any tumor cells, it may lead to a higher proportion of positive findings but with a much lower prognostic value

Quantification of melanoma micrometastases in sentinel lymph nodes using real-time RT-PCR

Assay	% Positive
Histology + mRNA of one or both markers	17%
Histology – positive RT-PCR	28%

- 139 patients with 235 SLN were assessed for Melan-A and tyrosinase expression by real-time quantitative RT-PCR
- Tumor recurrences were demonstrated (median 29 months)
  - Eight patients (35%) with histopathologically positive SLN
  - Four patients (10%) with submicroscopic tumor cells detected exclusively by real-time RT-PCR
  - *None of the patients negative by both methods*
- RT-PCR for the detection of minimal residual melanoma in SLN improves the prediction of disease-free survival

J Invest Dermatol. 2005 Mar;124(3):**Giese T**, **Engstner M**, **Mansmann U**, **Hartschuh W**, **Arden B**.
Institute of Immunology, University of Heidelberg, Heidelberg, Germany.

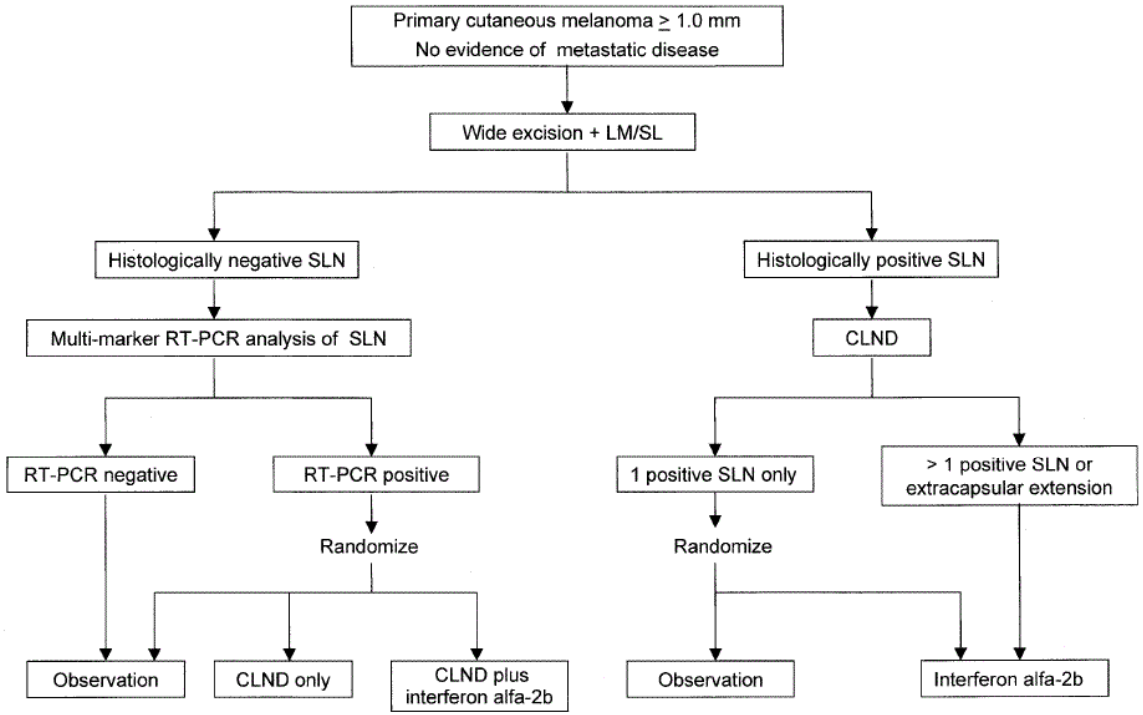


Fig 9. Sunbelt Melanoma Trial treatment algorithm. *CLND*, Complete lymph node dissection; *LM/SL*, lymphatic mapping and sentinel lymphadenectomy; *RT-PCR*, reverse transcriptase polymerase chain reaction; *SLN*, sentinel lymph node.

…The only drawback of SNLB is the side effects of mini-invasive surgery…

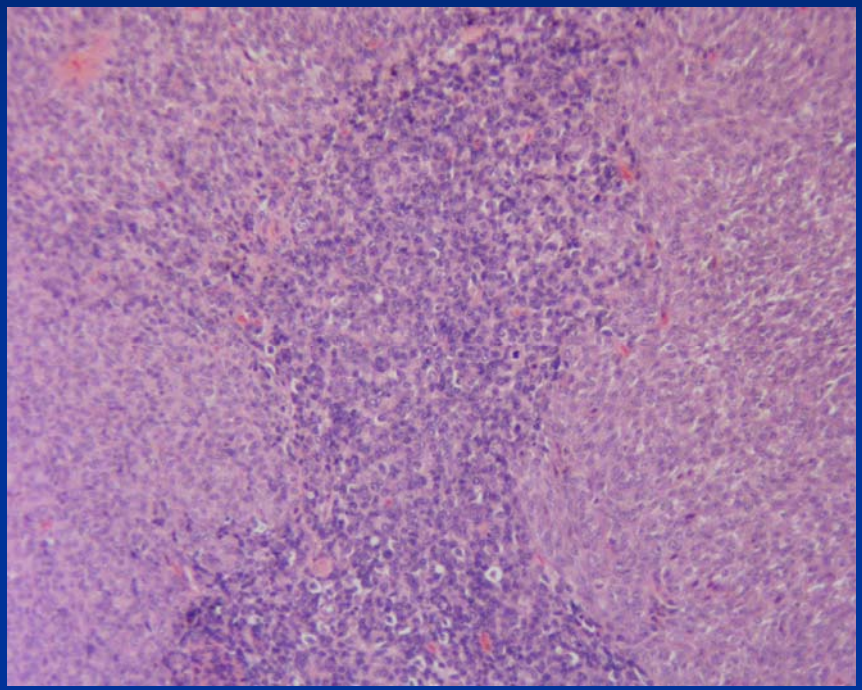
Sentinel-lymph-node biopsy (SLNB) for melanoma is not complication-free

- Neck SLNB-highest rate of identification failure
- Prognostic factors of morbidity
  - Patient age
  - Basin location
  - Number of excised nodes

- Three hundred and nine lymphatic basins of 250 patients
- Overall complication rate was 20%.
- Sensory morbidity was significantly associated with axillary SLNB ($p=0.04$) and was more prevalent in younger patients.

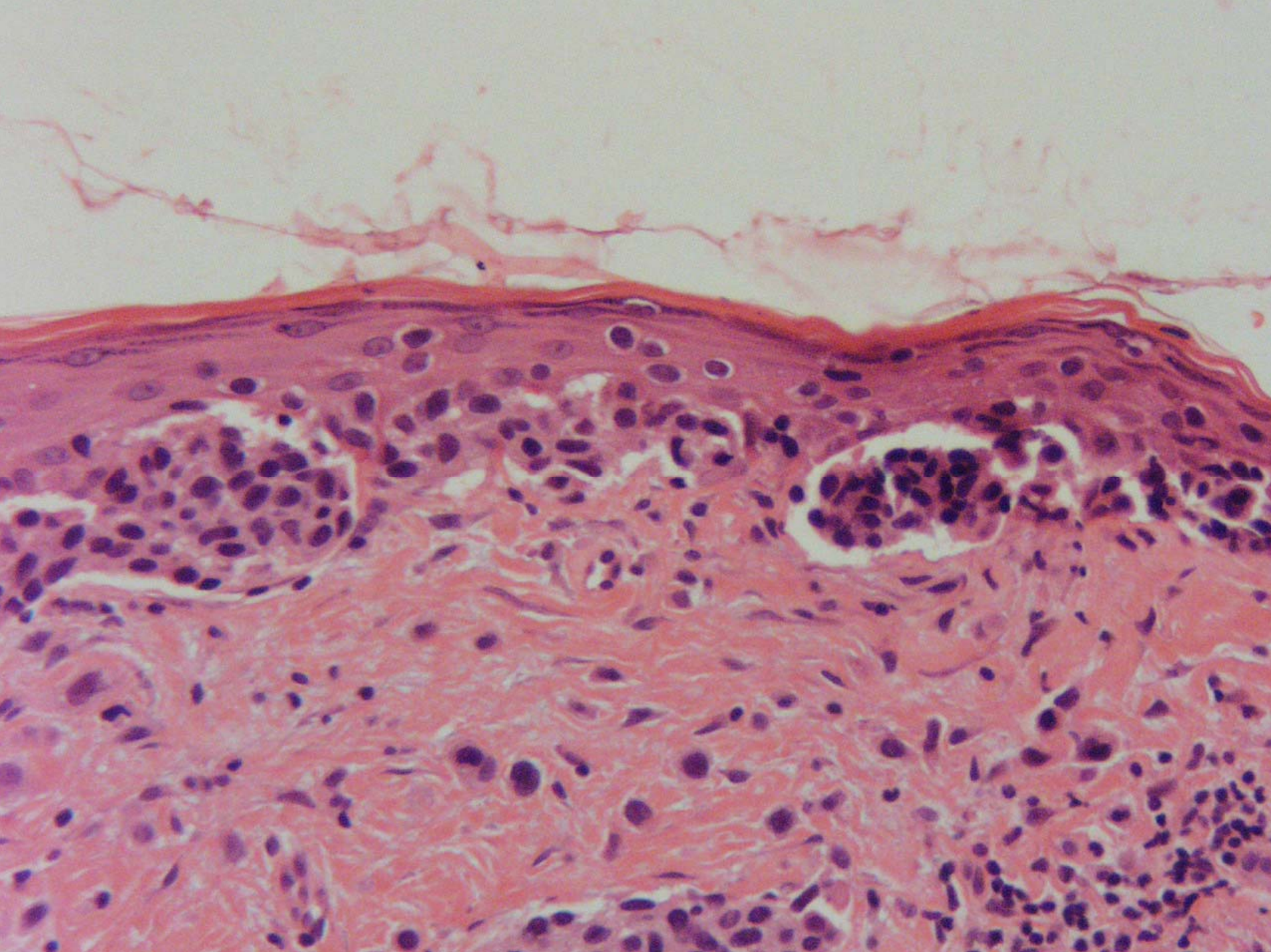
Eur J Surg Oncol. 2004 Oct;30(8):851-6
Wasserberg N, **Tulchinsky H, Schachter J**, **Feinmesser M**, **Gutman H**. Department of Surgery B, Rabin Medical Center, Beilinson Campus, Petah Tiqwa 49100 and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Immune System Alterations



- Resecting SN may remove the critical first defense
- Nodal mets may occur years after resection implying active nodal immune response
- Few tumor cells may provide a natural vaccine

Should All Patients with Melanoma undergo SNLB?



Sentinel lymph node biopsy for the T1 (thin) melanoma: is it necessary?

- LN mets in 2/24 pts (8.3%) in whom the thickness of the melanoma was 0.9 mm and 1 mm.
- Both patients have died of metastatic melanoma
- No recurrence has been demonstrated in the remaining 22 patients at the 2 to 5-year follow-up.
- Superficial spreading or nodular melanoma larger than 0.9 mm should include sentinel lymph node biopsy regardless of other associated histological factors.

- Retrospective analysis of 34 patients with T1 melanoma was completed over a 3-year period.
- Selection criteria:
  - Breslow thickness of less than or equal to 1 mm
  - Clark level of III or IV tumor ulceration, or tumor regression
- Mean tumor thickness for all patients:
  - 0.69 mm (range, 0.3-1.0 mm)
  - 0.61 mm for the Clark level III patients (N = 15)
  - 0.72 mm for the Clark level IV patients (N = 9).
  - Tumor ulceration-1 patient
  - Regression-2 patients

Ann Plast Surg. 2003 Jun;50(6):601-6 **Nahabedian MY**, **Tufaro AP, Manson PN** Division of Plastic and Reconstructive Surgery, Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA.

Sentinel node biopsy for thin melanomas: which patients should be considered?

Clark Level*	Pts. n=409	SLN+
II or III	252 (62%)	11 (4%)
IV	157 (38%)	9 (6%)

- Cutaneous melanomas less than 1.00 mm in Breslow thickness
- Pts with melanomas between 0.75 and 1.00 mm are appropriate candidates

Cancer Control. 2005 Oct;12(4):230-5 **Pole CA**, **Messina JL**, **Riker AI**, **Glass LF**, **Nelson C**, **Cruse CW**, **Johnson TM**, **Sondak VK**
Cutaneous Oncology Division, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA.

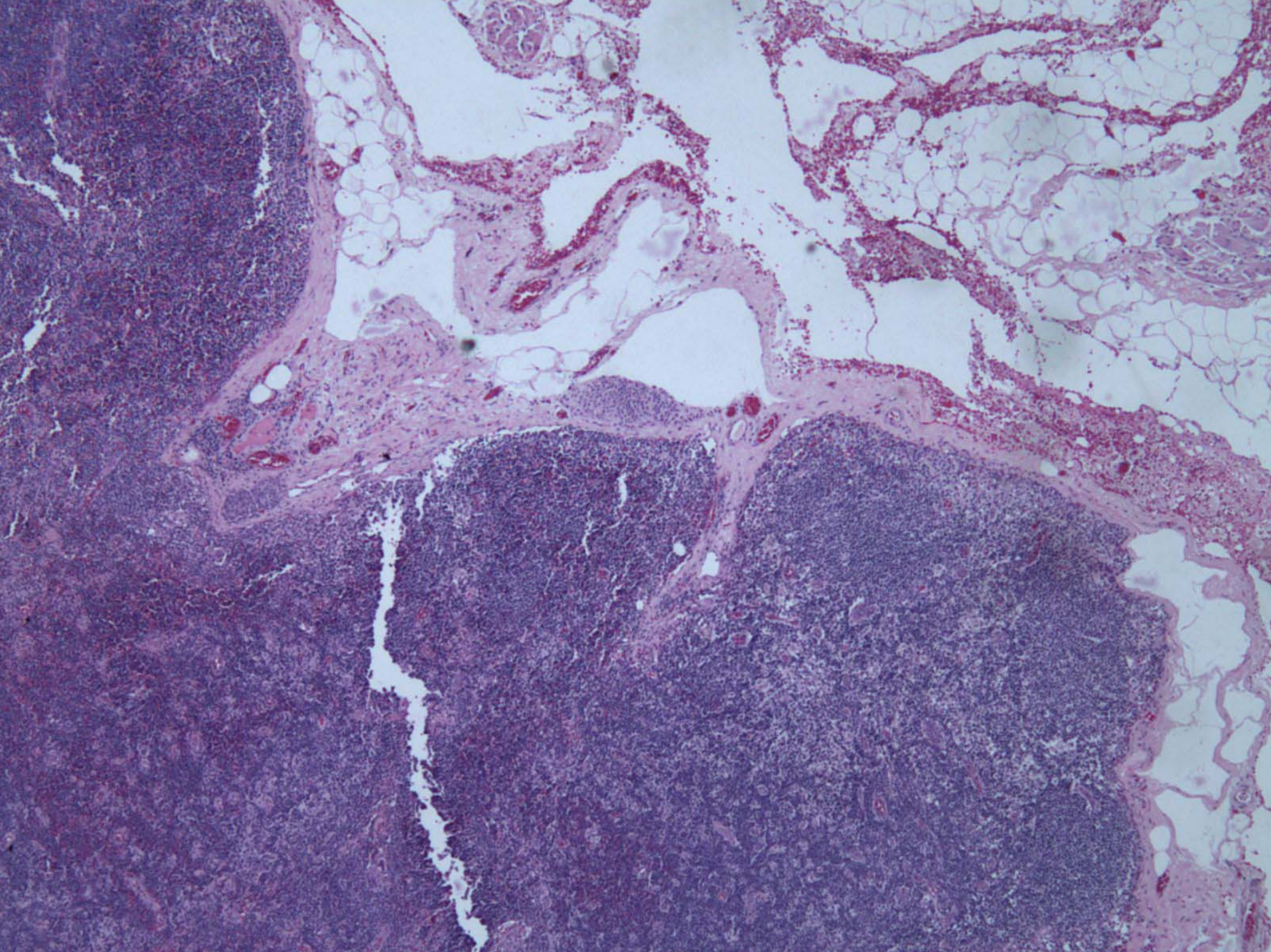
No indication for performing sentinel node biopsy I melanoma patients with a Breslow thickness of less than 0.9 mm.

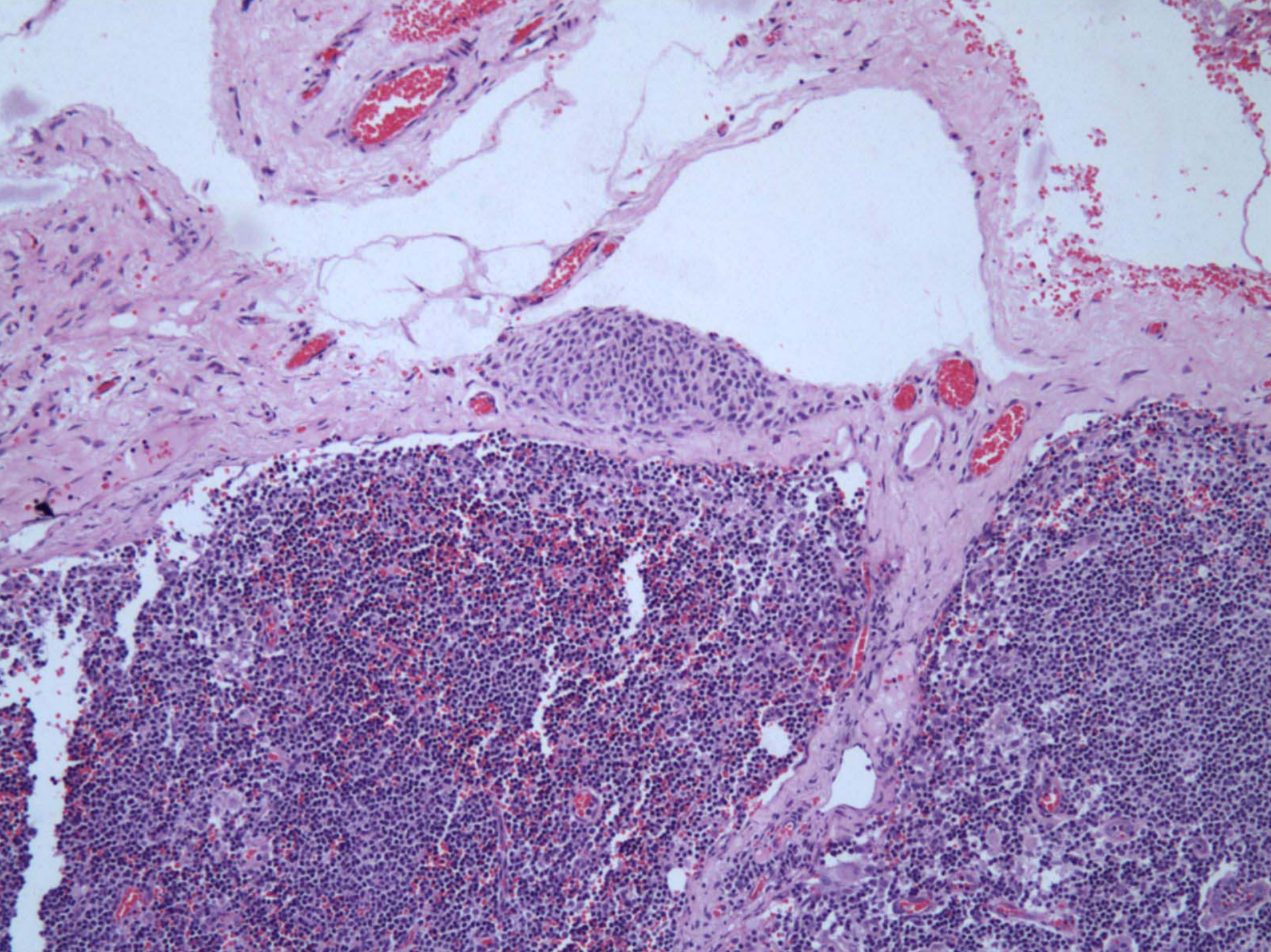
Melanomas thinner than 0.90 mm, no positive SN was found (95% confidence interval 0-5%).

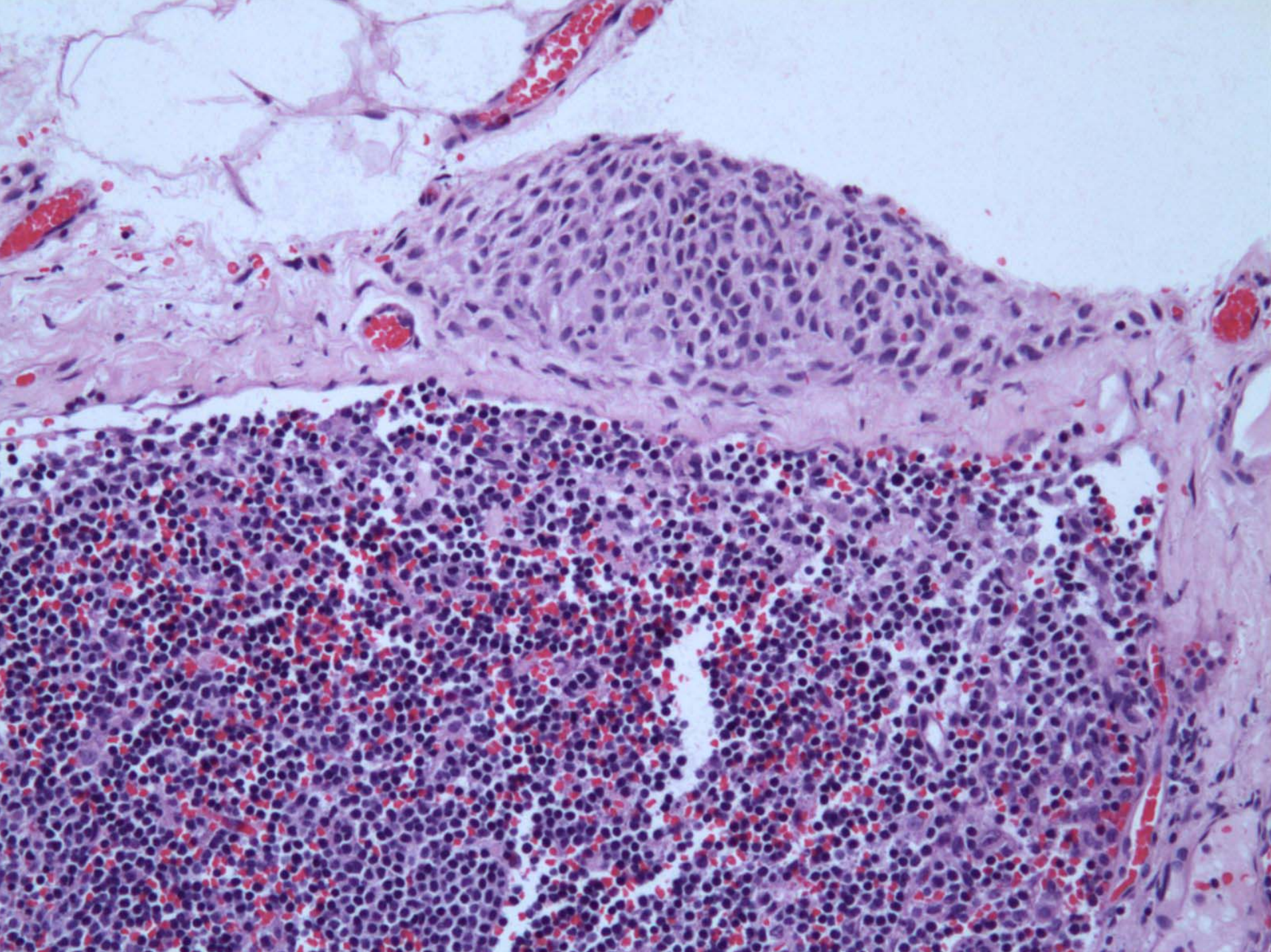
- 348 patients stages I or II cutaneous melanoma with a Breslow thickness > or = 0.5 mm
- 75 patients (22%), with a median follow-up of 31 months.

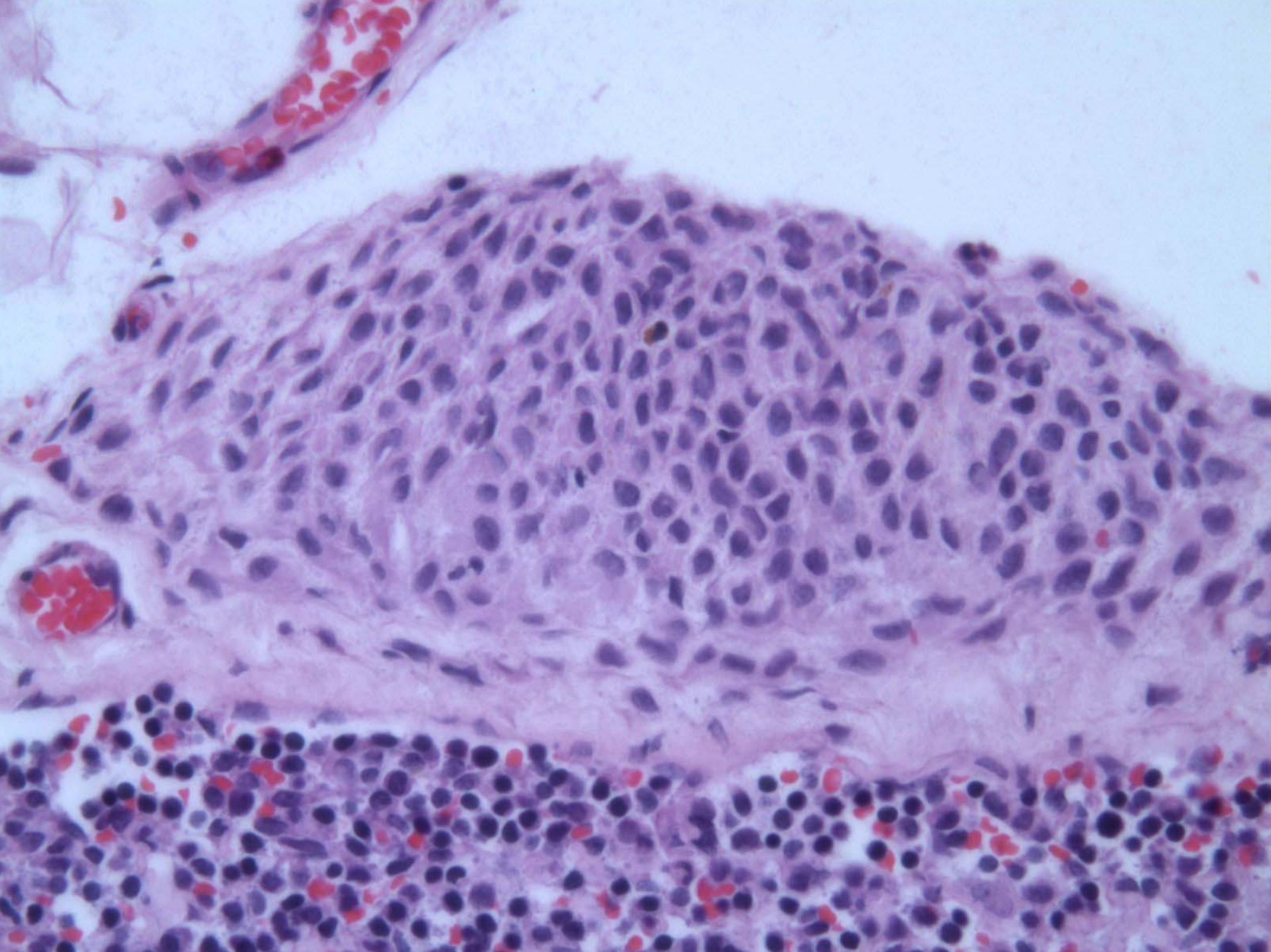
Melanoma Res. 2001 Jun;11(3):303-7 **Stations Muller MG**, **van Leeuwen PA**, **van Diest PJ**, **Vuylsteke RJ**, **Pijpers R**, **Meijer S**
Department of Surgical Oncology, Vrije Universiteit Medical Centre, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.

False Positives and False Negatives









Nodal Nevus Cells

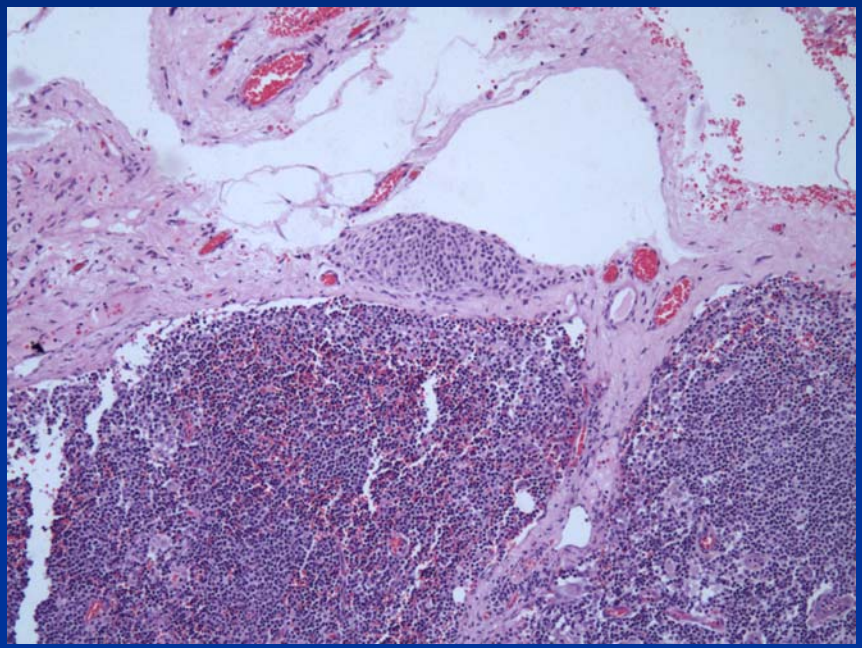
HMB-45, S-100, NK1/C3, and MART-1 in metastatic melanoma

Stain	Cases	%	Diffuse Staining Pattern % Tumor
S100	123/126	98	56
HMB45	95/125	76	34
NKI-C3	117/125	93	48
MART-1	103/126	82	83

- S-100 and NK1/C3 were the most sensitive stains for detecting metastatic melanoma; however, they both also stain other nontumor cells in lymph nodes.
- MART-1 did not stain histiocytes and exhibited a more frequently intense and diffuse staining pattern than NK1/C3.
- HMB-45 was less sensitive and demonstrated less diffuse staining than MART-1.

Zubovits J, Buzney E, Yu L, Duncan LM. Hum Pathol. 2004 Feb;35(2):217-23.

Size of the Micrometastases



- <1mm subcapsular deposits, no survival different from cases without mets (N0)
- Current AJCC staging is </=0.2 mm

Ann Surg Oncol 2004;11(Suppl 3);162-168.
Starz H, etal.

Gold Standard

100% Guaranteed Customer Satisfaction

References

- Dessureault S, etal. Ann Surg Oncol 2001;8:766-770.
- Kirkwood JM, etal. JCO 1996;14:7-17.
- Kirkwood JM, etal. ASCO 1999 (Abstract)
- Kirkwood JM, etal. JCO 2001;19:2370-2380.
- Wick MR and Patterson JW. Am J Surg Pathol 2005;29:412-415.
- Holt JB, etal. Am J Clin Pathol 2004:121:58-63.