# Completion Node Dissection of Sentinel Node Positive Melanoma

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# Outline

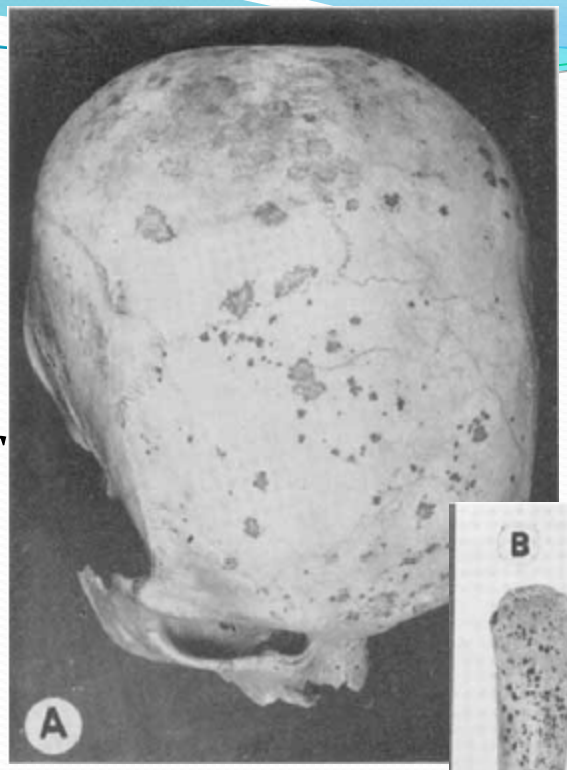
- Historical Perspective
- Changes In The Staging System
- Studies That Started The Talk
- Where We Go From Here

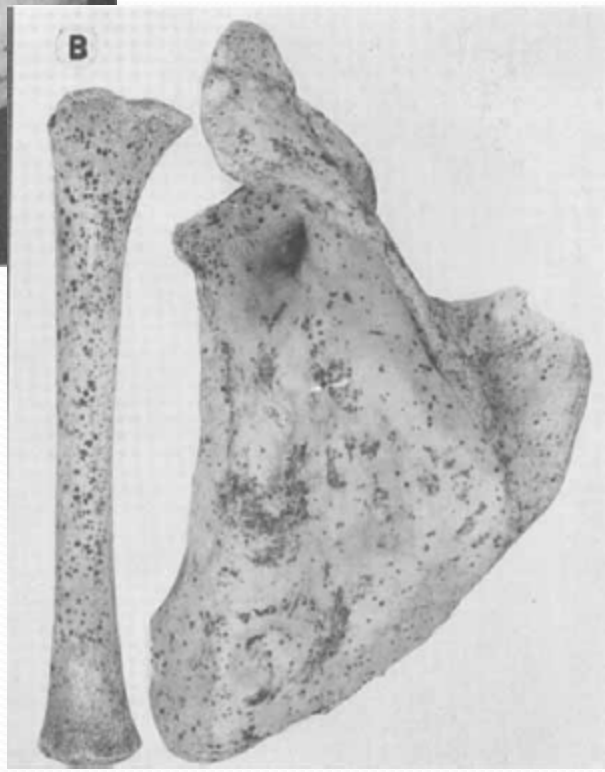
- Cutaneous melanoma has become an increasingly growing problem, with a rapid rise in incidence rates in the United States over the last several decades

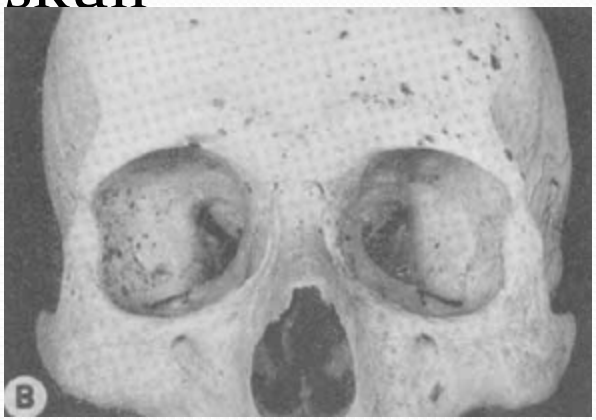
- Melanoma now accounts for 5% of all cancers diagnosed

- According to the American Cancer Society an estimated 62,190 new cases of melanoma were diagnosed in 2006, and approximately 7,910 patients will die of this disease

- Several mummies of pre-Colombian Incas of Peru, some estimated to be 2,400 years old, which show diffuse metastases to bones, particularly of the skull and extremities



# *Everything in excess is opposed to nature.* – Hippocrates

- John Hunter is reported to be the first to operate on metastatic melanoma in 1787
  - "Cancerous fungous excrescence"
  - The excised tumor was preserved in the Royal College of Surgeons of England
    - It was not until 1968 that microscopic examination of the specimen revealed it to be an example of metastatic melanoma

- René Laennec, a French physician, was the first to describe melanoma as a disease entity
- Presented during a lecture for the Faculté de Médecine de Paris in 1804 and then published as a bulletin in 1806

- As early as the mid-19th century, British surgeon William Norris recognized the importance of treatment margins in primary melanoma:
  - “Not only remove the disease, but cut away some of the healthy parts. I would, after excising the part, touch the wound with caustic so as not to leave an atom of the disease, if possible, and occasionally apply the same remedy to the skin in the vicinity”

- In the late 1800s, Herbert Snow initiated a surgical controversy by recommending elective removal of clinically normal regional lymph nodes in patients with cutaneous melanoma

- He believed that early removal of “infected” lymph nodes would prevent subsequent metastasis to distant sites and therefore improve patient outcomes

# DIFFERENCES FROM 2002 TNM SYSTEM

•Mitotic rate, defined as mitoses/mm2, has been incorporated as a primary prognostic factor in defining the tumor (T) stage

•The Clark level of invasion, which was used in conjunction with tumor thickness in the sixth version of the TNM system, is not a statistically significant prognostic factor on multivariate analysis and is no longer utilized

•Immunohistochemical detection of melanoma in regional lymph nodes is now acceptable evidence of disease involvement, rather than just hematoxylin and eosin

•There is no minimum tumor burden to define positive regional lymph node involvement. Previously tumor deposits <0.2 mm in diameter were not considered clinically significant

•Isolated metastases arising in lymph nodes, skin, or subcutaneous tissue, without an identifiable primary, are classified as stage III rather than stage IV

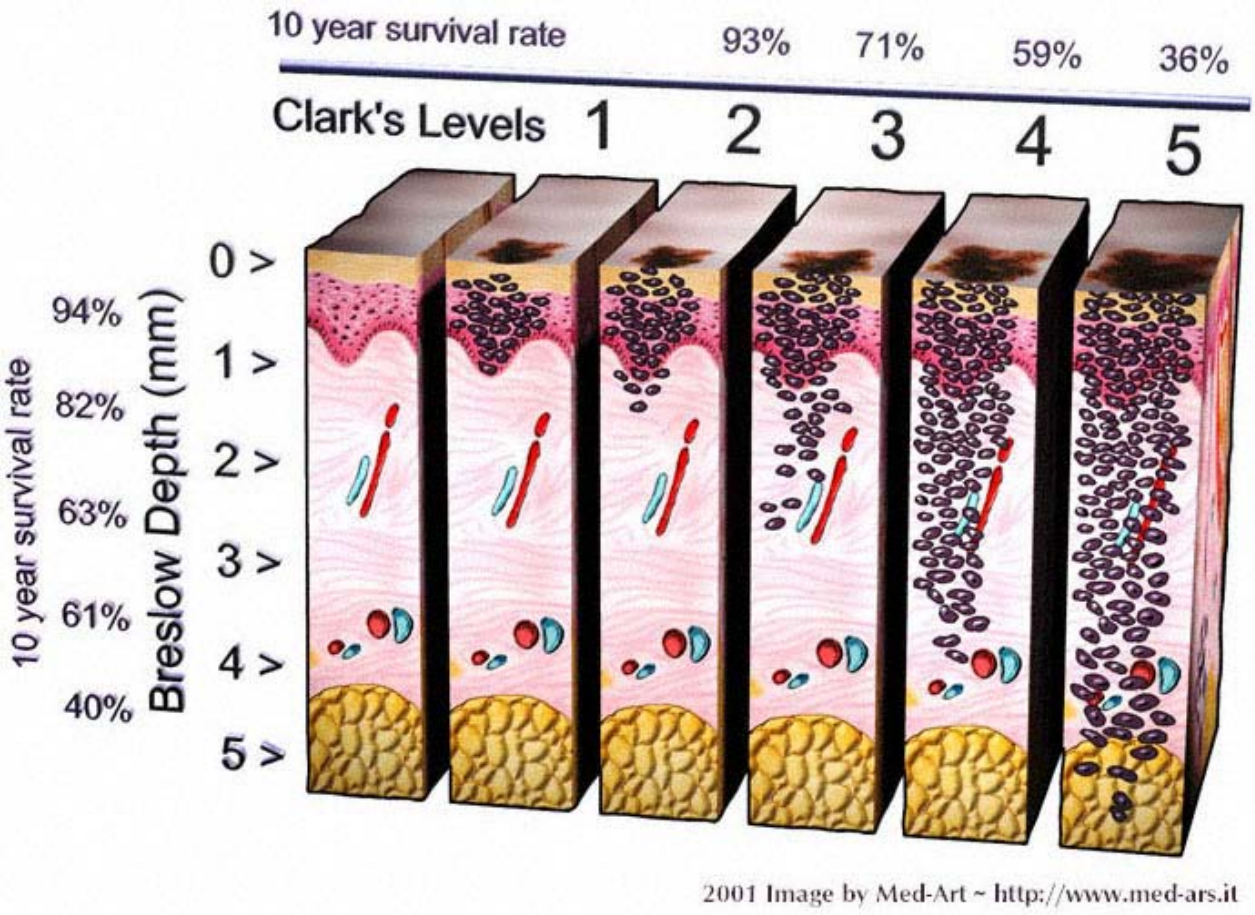
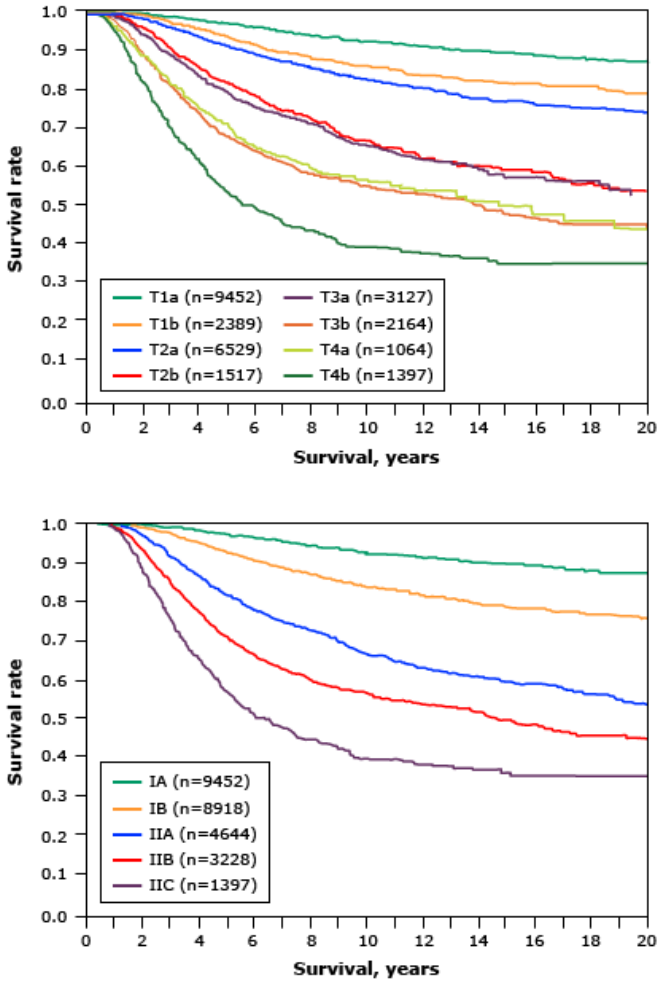

10 year survival rate
93%
71%
59%
36%
Clark's Levels 1 2 3 4 5
10 year survival rate
94%
82%
63%
61%
40%
Breslow Depth (mm)
0 >
1 >
2 >
3 >
4 >
5 >
2001 Image by Med-Art ~ http://www.med-ars.it

**TABLE I. Revised Stage Groupings for Cutaneous Melanoma Proposed by the American Joint Committee on Cancer**

| Stage | TNM classification | Definition | 5-year survival rate (% ±SE) |
|---|---|---|---|
| IA | T1a N0 M0 | ≤1 mm; no ulceration (Clark level II/III) | 95.3 ± 0.4 |
| IB | T1b N0 M0 | ≤1 mm with ulceration or Clark level IV/V | 90.9 ± 1.0 |
| | T2a N0 M0 | 1.01–2 mm; no ulceration | 89.0 ± 0.7 |
| IIA | T2b N0 M0 | 1.01–2 mm with ulceration | 77.4 ± 1.7 |
| | T3a N0 M0 | 2.01–4 mm; no ulceration | 78.7 ± 1.2 |
| IIB | T3b N0 M0 | 2.01–4 mm with ulceration | 63.0 ± 1.5 |
| | T4a N0 M0 | >4 mm; no ulceration | 67.4 ± 2.4 |
| IIC | T4b N0 M0 | >4 mm with ulceration | 45.1 ± 1.9 |
| IIIA | Anyt N1a M0 | 1 micro node; no ulceration | 69.5 ± 3.7 |
| | Anyt N2a M0 | 2–3 micro nodes; no ulceration | 63.3 ± 5.6 |
| IIIB | Anyt N1a M0 | 1 micro node with ulceration | 52.8 ± 4.1 |
| | Anyt N2a M0 | 2–3 micro nodes with ulceration | 49.6 ± 5.7 |
| | Anyt N1b M0 | 1 macro node; no ulceration | 59.0 ± 4.8 |
| | Anyt N2b M0 | 2–3 macro nodes; no ulceration | 46.3 ± 5.5 |
| IIIC | Anyt N1b M0 | 1 macro node with ulceration | 29.0 ± 5.1 |
| | Anyt N2b M0 | 2–3 macro nodes with ulceration | 24.0 ± 4.4 |
| | Anyt N3 M0 | ≥4 nodes, matted, or nodes + in-transit metastasis | 26.7 ± 2.5 |
| IV | Anyt anyN M1a | Distant skin, subcutaneous, or nodal metastasis | 18.8 ± 3.0 |
| | Anyt anyN M1b | Lung metastasis | 6.7 ± 2.0 |
| | Anyt anyN M1c | All visceral mets or elevated LDH with metastasis | 9.5 ± 1.1 |

TNM, Tumor, node, metastases; SE, Standard error; LDH, Lactate dehydrogenase. Adapted with permission from Balch et al. [5]

## Melanoma - Impact of T stage on prognosis




Twenty-year survival rates comparing the different T categories (top) and the stage groupings (bottom) for stages I and II melanoma.

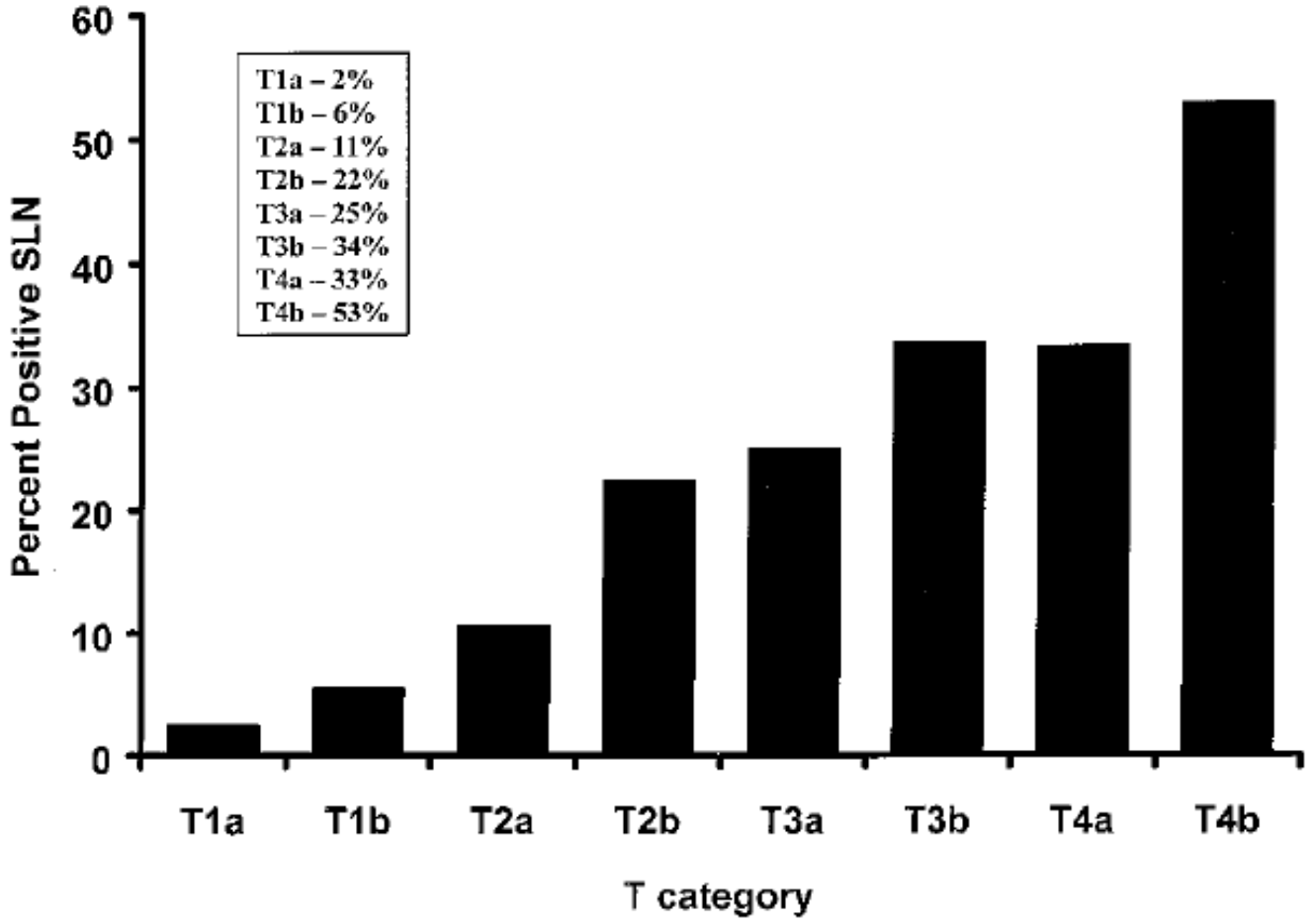
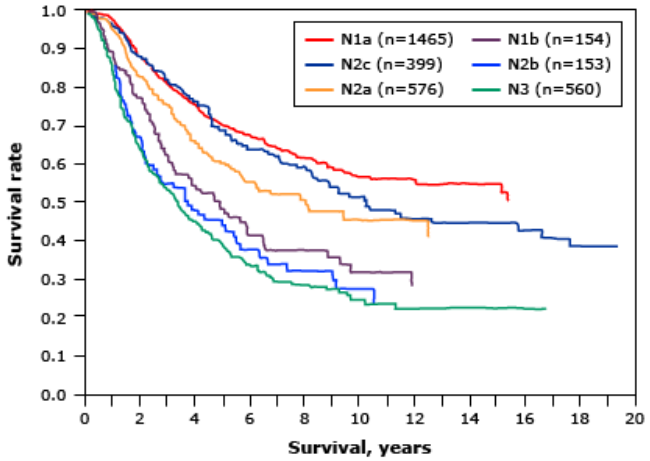


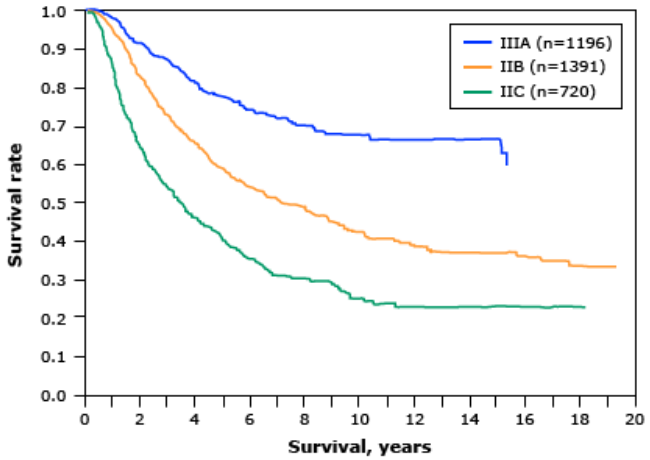

**FIG. 1.** Incidence of a positive sentinel lymph node (SLN) by American Joint Committee on Cancer T category (n = 1375). The inset shows the percentage of patients with a positive SLN within each category.

- For patients with nodal disease limited to micrometastases, the most important factor affecting prognosis was the number of nodes involved
    - Five-year survival rates with one, two, or three positive lymph nodes were 71, 65, and 61 percent, respectively
    - Other factors independently affecting prognosis: age, anatomic site, thickness, ulceration, and mitotic rate

- For patients with macrometastases in the regional nodes, the number of nodes was significantly associated with prognosis
    - Five-year survival rates one, two, or three positive lymph nodes were 50, 43, and 40 percent, respectively
    - The characteristics of the primary tumor were not independently associated with prognosis

## Melanoma - Impact of nodal involvement on prognosis




Twenty-year survival rates comparing the different N categories (top) and the stage groupings (bottom) for stage III melanoma.

- The number of tumor-positive lymph nodes is the single most important prognostic factor in AJCC stage III melanoma
  - CLND allows accurate assessment of the regional extent of disease and is the only effective therapeutic option for local control and potential cure

*Annals of Surgical Oncology*, 9(2):137–141
Published by Lippincott Williams & Wilkins © 2002 The Society of Surgical Oncology, Inc.

# Frequency of Nonsentinel Lymph Node Metastasis in Melanoma

Kelly M. McMasters, MD, PhD, Sandra L. Wong, MD, Michael J. Edwards, MD,
Celia Chao, MD, Merrick I. Ross, MD, R. Dirk Noyes, MD, Vicki Viar, RN, MSN,
Patricia B. Cerrito, PhD, and Douglas S. Reintgen, MD, for the Sunbelt Melanoma Trial Group

- This analysis included 274 patients with at least one positive SLN who underwent CLND of 282 involved regional nodal basins
- Of the 282 SLN-positive nodal basins, 45 (16%) were found to have positive NSNs in the CLND specimen
- When a positive SLN is identified on either H&E staining or IHC, “CLND should be performed routinely”

# Clinico-pathologic features of primary melanoma and sentinel lymph node predictive for non-sentinel lymph node involvement and overall survival in melanoma patients: A single centre observational cohort study

P. Quaglino [a,*,1], S. Ribero [c,1], S. Osella-Abate [a], L. Macrì [b], M. Grassi [c], V. Caliendo [c], S. Asioli [b], A. Sapino [b], G. Macripò [c], P. Savoia [a], M.G. Bernengo [a]

- The highest percentages of NSLN involvement were found in patients with Breslow thickness >4 mm (52%), ulceration (53.6%), and macro-metastatic pattern (70%)

- On the other hand, NSLN involvement after a positive SLN was found in 11.5% of patients with thin primary (between 1 and 2 mm)

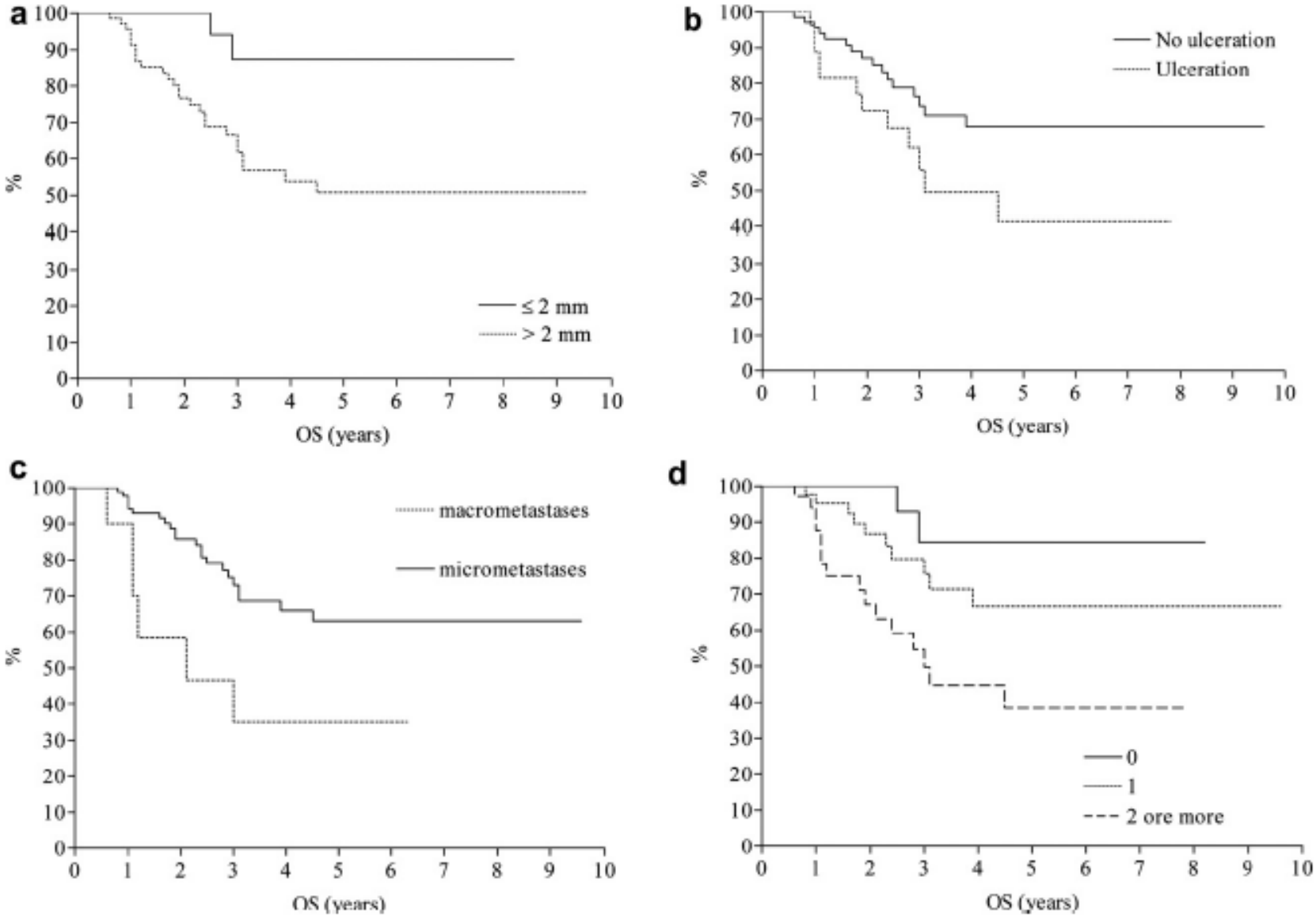



**Figure 1.** Overall Survival (OS) according to prognostic indicators: a) Breslow thickness > 2 mm ($p = 0.0069$); b) ulceration ($p = 0.0495$) c) SLN micro-/macro-metastatic pattern ($p = 0.0190$); d) number of adverse prognostic indicators (0,1,2 or more; $p < 0.001$).

- “The presence of at least one of these adverse factors identify patients in whom CLND is mandatory”

- “On the other hand, the finding of no adverse indicators identify patients who could be spared from CLND in the presence of significant co-morbidities or elderly age”

**TABLE 2.** Studies Describing Sentinel Node Characteristics Predictive of Additional Lymph Node Disease*

| Histopathologic Characteristics | Authors and Publication Yr | N | Predictive Factor or Cut-Off Point† | Additional Lymph Node Disease (%) |
|---|---|---|---|---|
| Depth of tumor invasion measured from capsule | Starz et al, 2004 | 45 | Invasion depth ≤1.0 mm | 11–13 |
| | Fink et al, 2005 | 26 | Invasion depth ≤1.0 mm | 0 |
| | Rossi et al, 2008 | 96 | Invasion depth ≤1.5 mm | Not mentioned |
| Largest diameter of tumor lesion | Lee et al, 2004 | 64 | Diameter ≤0.2 mm | 12 |
| | Van Akkooi et al, 2006 | 74 | Diameter <0.1 mm | 0 |
| | Pearlman et al, 2006 | 80 | Diameter ≤0.2 mm | 6 |
| | Govindarajan et al, 2007 | 127 | Diameter ≤0.2 mm | 0 |
| | Guggenheim et al, 2008 | 107 | Diameter ≤0.2 mm | 16 |
| Metastatic area | Cochran et al, 2004 | 90 | ≤4.3% ± 13.2%‡ | 0 |
| | Vuylsteke et al, 2005 | 71 | Area ≤0.3 $mm^2$ | 0 |
| | Frankel et al, 2008 | 64 | <1% surface area of tumor cells | 9 |
| Location of tumor deposit within node | Dewar et al, 2004 | 146 | Dewar A: subcapsular metastasis | 0 |
| No. positive sentinel nodes | Salti et al, 2003 | 56 | ≤2 involved nodes | Not mentioned |
| | Glumac et al, 2008 | 74 | <2 involved nodes | 0 |
| Multiple factors | Scolyer et al, 2004 | 140 | Invasion depth ≤2 mm, area ≤10 $mm^2$, and no perinodal involvement | 0 |
| | Sabel et al, 2005 | 221 | ≤3 involved nodes, and no extranodal extension | 2 |
| | Debarbieux et al, 2007 | 98 | No extracapsular invasion, and the lowest diameter of the largest metastasis | Not mentioned |

*The incidence of additional lymph node disease is given for the cut-off point, as suggested by the authors.

†Primary tumor characteristics predictive of additional lymph node disease are not mentioned.

‡Cochran et al determined the area of the node occupied by tumor using a computer-assisted image analysis program and expressed this as a percentage of the total surface of the cut surface of the sentinel node.

N indicate number of patients.

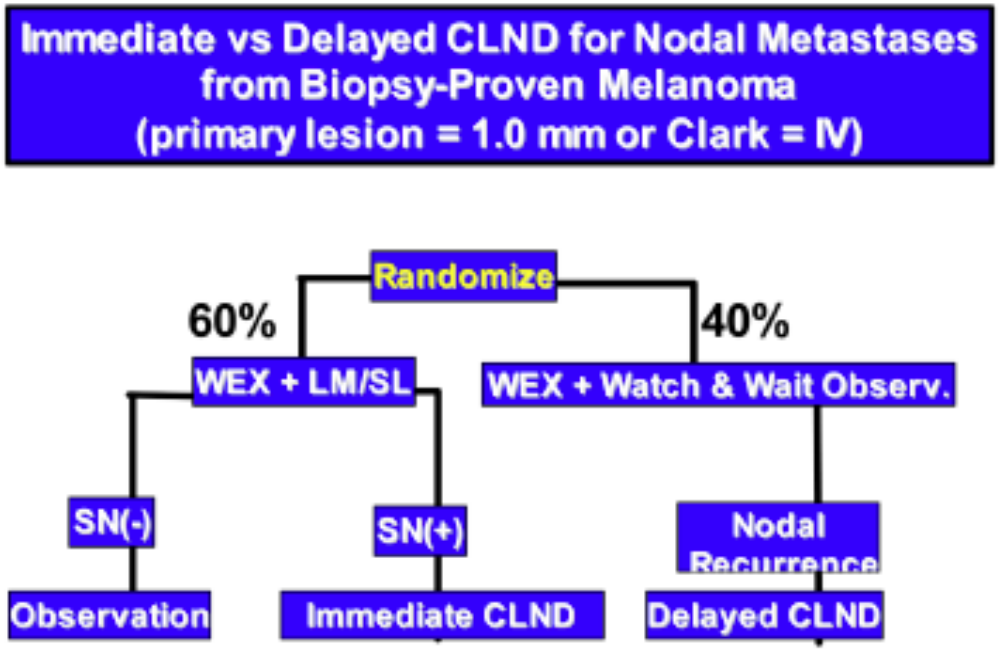
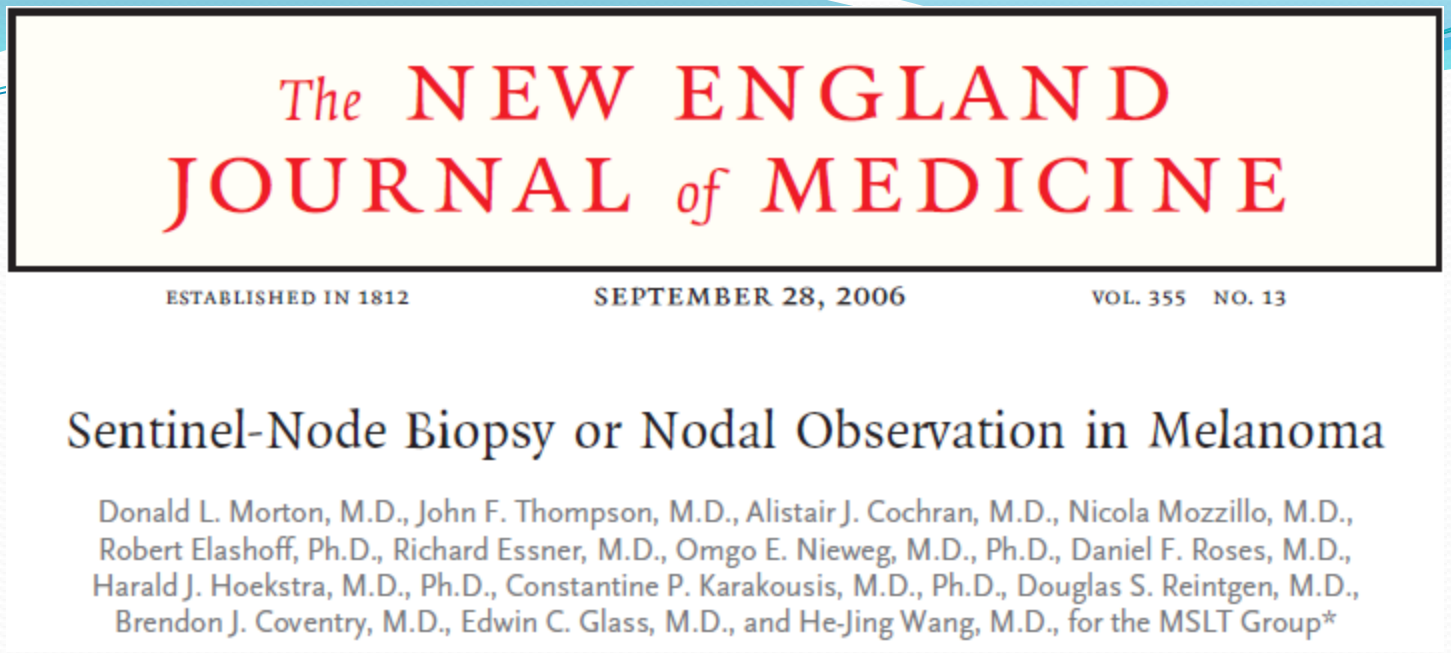



**Figure 4.**
In the first Multicenter Selective Lymphadenectomy Trial (MSLT-I), patients with biopsy-proven melanoma were randomly assigned to receive wide excision alone or wide excision and sentinel node biopsy, in a ratio of 6:4. (LM/SLN, lymphatic mapping/selective lymphadenectomy; SLN, sentinel node; CLND, completion lymph node dissection).



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Sentinel-Node Biopsy or Nodal Observation in Melanoma

Donald L. Morton, M.D., John F. Thompson, M.D., Alistair J. Cochran, M.D., Nicola Mozzillo, M.D., Robert Elashoff, Ph.D., Richard Essner, M.D., Omgo E. Nieweg, M.D., Ph.D., Daniel F. Roses, M.D., Harald J. Hoekstra, M.D., Ph.D., Constantine P. Karakousis, M.D., Ph.D., Douglas S. Reintgen, M.D., Brendon J. Coventry, M.D., Edwin C. Glass, M.D., and He-Jing Wang, M.D., for the MSLT Group*

- 1269 patients: sentinel- node biopsy provided important prognostic information for the staging of intermediate thickness – 1.2 to 3.5 mm
  - Survival could be prolonged be immediate lymphadenectomy
    - The 5-year survival rate was higher among those who underwent immediate lymphadenectomy than among those in whom lymphadenectomy was delayed (72.3±4.6% vs. 52.4±5.9%)

# Impact of MSLT-I

- Early CLND was performed in 225 patients, and in the wide excision-alone arm 132 have undergone delayed CLND
  - The two groups were similar for primary tumor features, body mass index, basin location and demographics except age, which was higher for delayed CLND
- The number of nodes evaluated and the number of positive nodes was greater for delayed CLND
- Lymphedema was significantly higher in the delayed CLND group (20.4% vs. 12.4%, p=0.04)
- Length of inpatient hospitalization was longer for delayed CLND

- A retrospective analysis of 760/2313 patients with stage III melanoma who underwent lymphadenectomy for node-positive melanoma
  - Conditional disease-specific survival (the survival probability after a given length of survival) improved from 78 to 90 percent from year 0 to year 5 for patients with stage IIIa melanoma, and from 54 to 79 percent and 39 to 78 percent for those with stage IIIb and IIIc disease

# Completion Node Dissection in Patients with Sentinel Node–Positive Melanoma of the Head and Neck

Valerie A. Smith[1], Joan E. Cunningham, PhD[2], and Eric J. Lentsch, MD[3]

Otolaryngology–
Head and Neck Surgery
XX(X) 1–9

DOI: 10.1177/0194599811432672
http://otojournal.org
SAGE

- Compared with SLNB alone, CLND does not seem to be associated with improved survival however there was CLND was an associated improved disease-specific survival at 5 years for a subgroup of patients
  - Age <60 years with nonulcerated tumors 2 mm

- “CLND is considered the standard of care in melanoma patients found to have SLN metastasis”
- “Additional disease in the CLND specimen can dramatically impact survival”

# PROS

- A CLND helps to accurately determine the stage of the melanoma, which assists with recommendations for adjuvant treatment
- The number of nodes containing melanoma cells is a predictor of survival for patients who have stage III disease, and only a CLND can provide this information
- Some studies show that 20% of patients who undergo a CLND immediately after finding out they have a positive sentinel lymph node experience improved survival. This is especially true for patients who had intermediate-thickness tumors on their skin (1.2 to 3.5 mm)
- By stopping the spread of melanoma at the lymph nodes, a CLND optimizes the chance for a cure

# CONS

- Complications of a CLND occur in up to 67% of patients, especially in those over 60. These include:
  - Seroma
  - Infection
  - Lymphedema
  - Numbness, tingling, or pain in the surgical area
  - Sloughing of skin over the area

# MSLT-II

- Ongoing phase III trial comparing immediate completion lymph node dissection with a strategy of observation and completion lymph node dissection if there is evidence of regional lymph node recurrence
- This trial is limited to patients with a primary melanoma that has a Breslow thickness of 1.20 mm or greater and Clark Level III or is a Clark Level IV or V regardless of Breslow thickness
- Results for the primary endpoint, melanoma-specific survival, are not anticipated until 2022

Primary Outcome Measures:

- Melanoma-specific survival

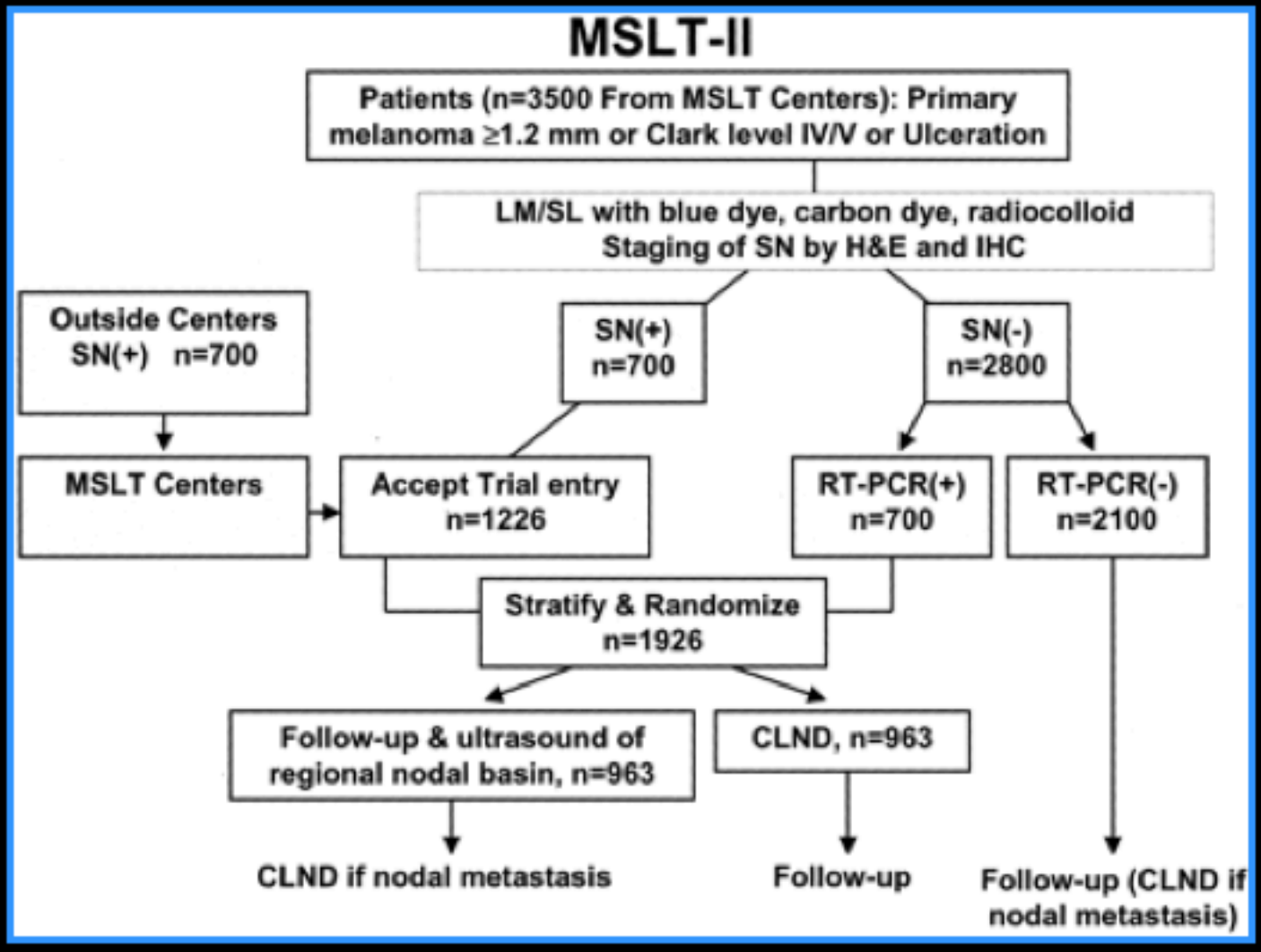
- This is defined as the time between the date of a subject's randomization (or date of CLND for those randomized to the CLND arm) and the date of death due to melanoma. Subjects are followed until death or 10yrs

Secondary Outcome Measures:

- Disease-free survival over 10 years of follow up

- Recurrence during 10 years of follow up

# Multicenter Selective Lymphadenectomy Trial-II



# Conclusion

- Early CLND, guided by SLN biopsy is the cornerstone of treatment for patients with intermediate thickness melanoma

- Benefits of this treatment paradigm include:
  - Unequaled prognostic value of regional nodal status
  - Ability to select patients for adjuvant therapy or clinical trials
  - Improved disease-free survival
  - For those with regional micrometastases at presentation, improved melanoma-specific survival

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