The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2018

Management of Head and Neck Melanomas

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Cutaneous Melanoma - A Rapid Rise

- Leading cause of death from skin cancer
- Death rate has doubled in the last 35 yrs – One American dying / hour
- Lifetime risk of developing melanoma:

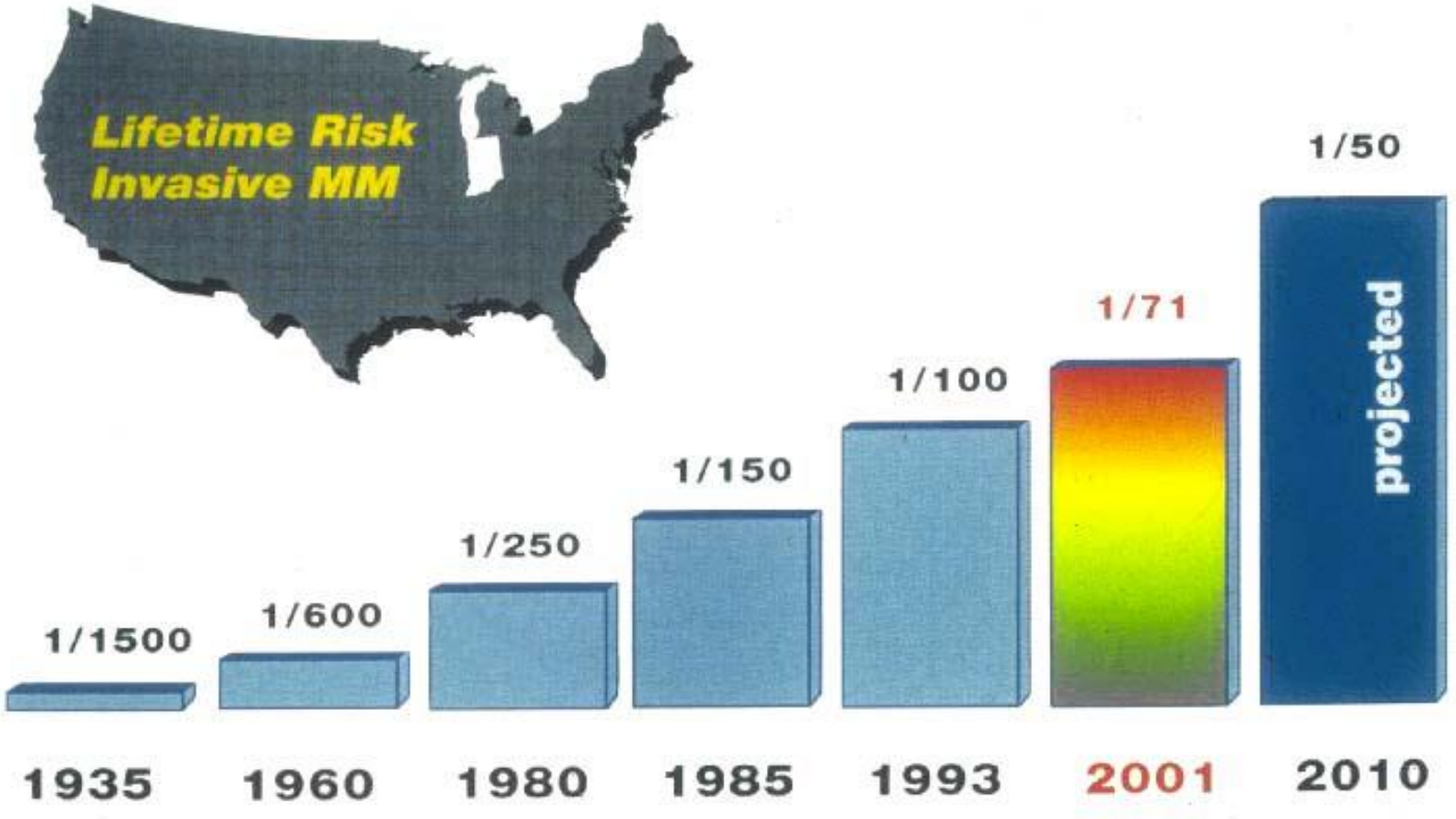
  1935 - 1:1500

  1980 - 1:250

  2000 - 1:75

  2010 - 1:50

- Increased detection – 68,130 in 2010
- Increased exposure to UV-B



Rigel et al, NYU Melanoma Cooperative Group, 2001

Risk Factors for Melanoma

Greatly Elevated Risk

changing mole

dysplastic nevi in familial melanoma

> 50 nevi ≥ 2 mm

Moderately Elevated Risk

one family member with melanoma

history of prior melanoma

sporadic dysplastic nevi

congenital nevus

Slightly Elevated Risk

immunosuppression

sun sensitivity

severe sunburns / sun exposure (UVB)

Growth Patterns of Melanoma

- Superficial Spreading Melanoma: 70%
  - flat with notched perimeter
  - radial growth → vertical growth
- Nodular Melanoma: 15-30%
  - raised, dome shaped
  - more aggressive, early vertical growth

Growth Patterns of Melanoma

- Lentigo Maligna Melanoma: 4-10%
  - often long history, large size
  - unlikely to metastasize
- Desmoplastic Melanoma: 1%
  - tendency to invade nerves
  - high rate of local recurrence
  - low rate of regional metastases

Biopsy Technique

- Always full thickness biopsy (never shave)
- Excisional biopsy for small lesions with narrow margin
- Punch or incisional biopsy for larger lesions at the thickest area

Immunohistochemistry

- Essential for poorly dif., amelanotic, spindle cell, or small cell melanomas
- S-100 protein
  - expressed by almost all melanomas
  - also expressed by sarcomas, nerve sheath tumors, some carcinomas
- HMB-45
  - more specific for melanoma
  - may not stain desmoplastic or spindle cell melanoma
- MEL-5, Melan-A, NKI/C3, neuron-specific enolase

Localized Stage I & II

T Classification

T1	< 1.0 mm	a: without ulceration *and*
T2	1.01 – 2.0 mm	mitosis < 1/mm^2
T3	2.01 – 4.0 mm	b: with ulceration *or*
T4	> 4.0 mm	mitosis ≥ 1/mm^2

2 Prognostic Features of Outcome

1. Tumor Thickness (1.0, 2.0, 4.0 mm)

   - *Clark's level of invasion – no longer used; replaced by mitotic rate for thin T1 tumors*

2. Ulceration – Histologic Diagnosis; Upstages patient
3. Mitotic Rate

Regional Metastatic Stage III

Class	# Nodes	Tumor Burden
N1	1	a: Micromets b: Macromets
N2	2 - 3	a: Micromets b: Macromets c: In transit/satellite(s) without metastatic nodes
N3	4+ *or* Matted Nodes *or* in transit mets/satellites with metastatic nodes	

4 Major Prognostic Features of Outcome

- Number of Metastatic Nodes
- Micro vs. Macroscopic Disease Mets
- Ulceration
- Intralymphatic

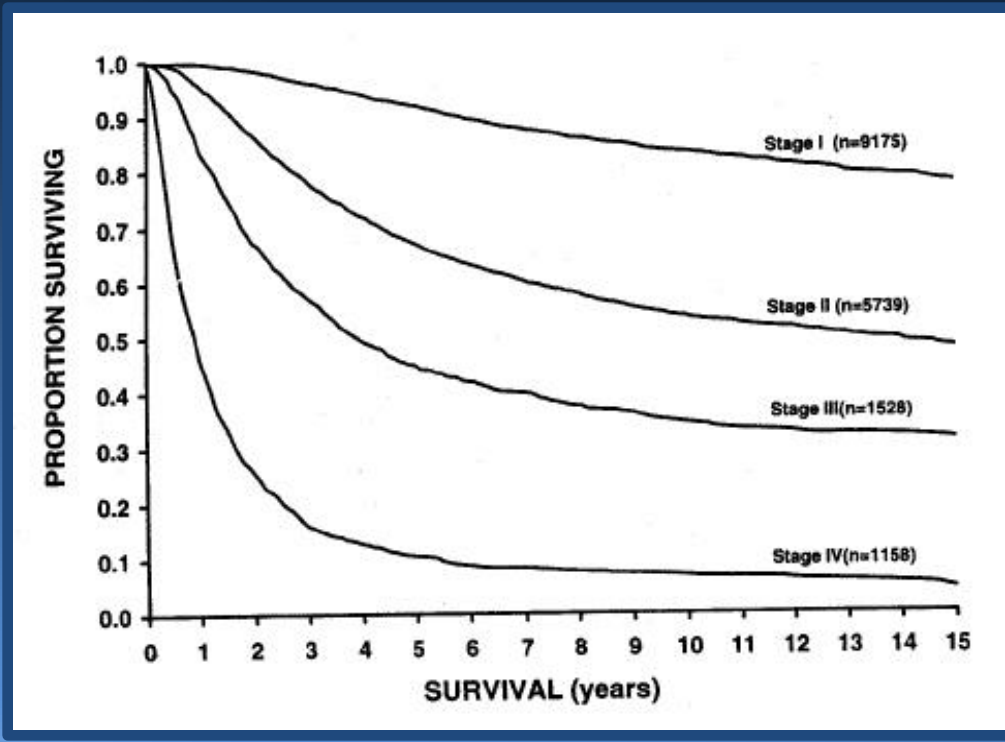
Summary of 2010 AJCC Staging System

1) Local Stage I/II Disease:
   - Tumor thickness (*** Clarks level NO LONGER used)
   - Ulceration
   - Mitiotic rate (< 1/mm^2; ≥ 1/mm^2) use for thin T1 melanomas
2) Regional Stage III Disease:
   - # of metastatic nodes
   - Tumor burden (micro vs macroscopic disease)
   - Ulceration
3) Metastatic Stage IV Disease:
   - Anatomic site
   - LDH

Changes to 2010 AJCC Staging system highlighted in yellow

Staging Summary

I:	T1, T2a	N0	M0
II:	T2b, T3-4	N0	M0
III:	Any T	N2-3	M0
IV:	Any T	Any N	M1



What is an Adequate Surgical Margin?

- 1988 – Veronesi – WHO Trial - 612 pts
- < 2 mm (trunk/extremity)
- Randomized to 1 cm vs. 3 cm resection margin
- No differences: disease free survival (81.6% vs 84.4%)
  overall survival
  regional nodal metastases
  distant metastases

Veronesi, *N Engl J Med*, 318:1159-62,1988

What is an Adequate Surgical Margin?

- 1993 - Balch – Intergroup Trial – 486 pts
- 1-4 mm thick (trunk/extremity)
- Randomized to 2 cm vs. 4 cm resection margin
- No differences:

	2 cm	4 cm
Local Recurrence	0.8%	1.7%
5-yr Overall Survival	79.5%	83.7%

Balch, *Ann Surg*, 218:262-269,1993

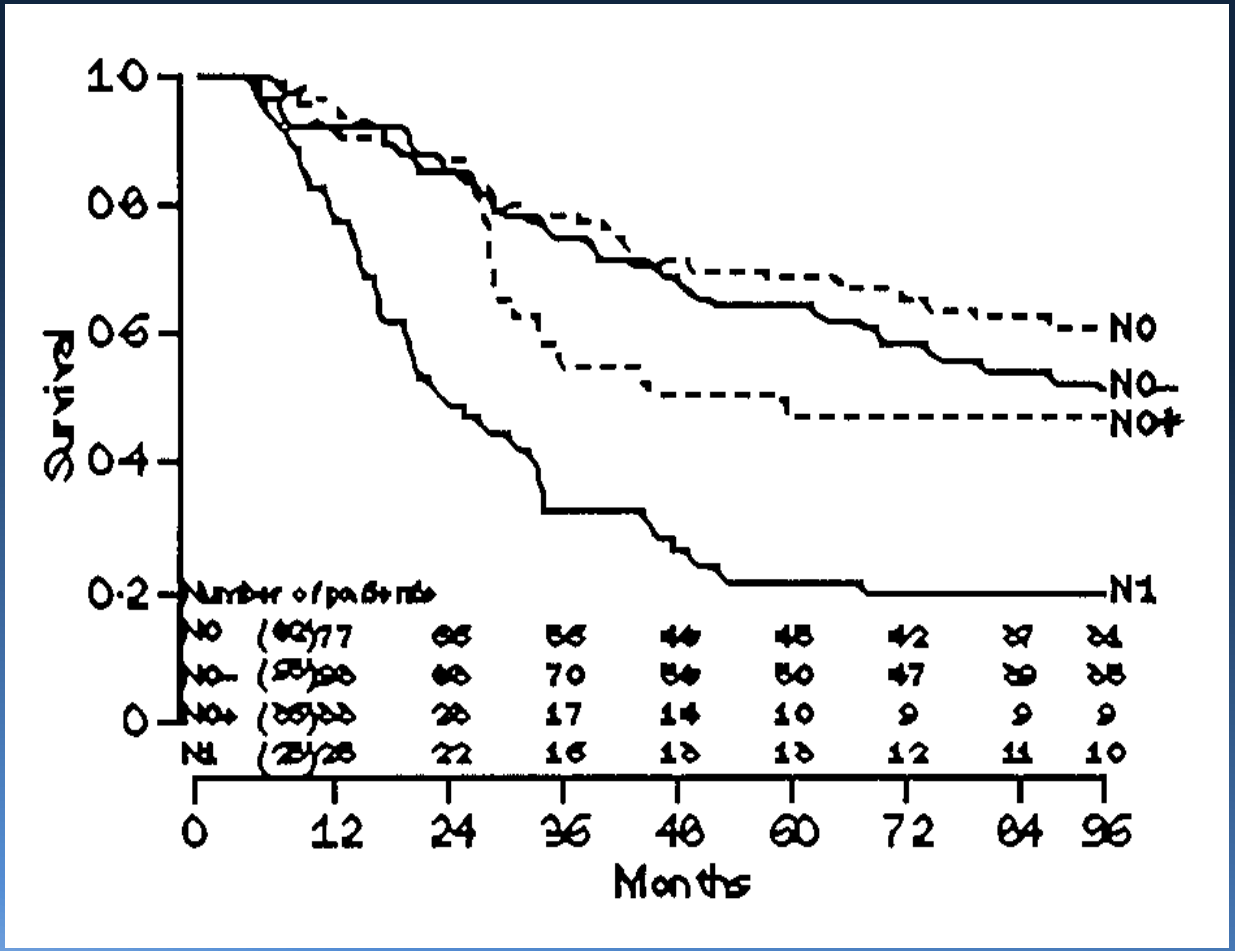
Summary - Margins for Excision

Thickness	Margin
≤ 1 mm	1 cm
1-4 mm	2 cm
> 4 mm	> 2 cm

Margins of excision of H&N melanoma limited:

- Cosmetic / functional considerations
- Intraoperative frozen sections vs. delayed closure after rush final pathology

Nodal Dissection Enhances Survival for Pts with Microscopic Mets



Cascinelli, *Lancet*, 351:793-96,1998

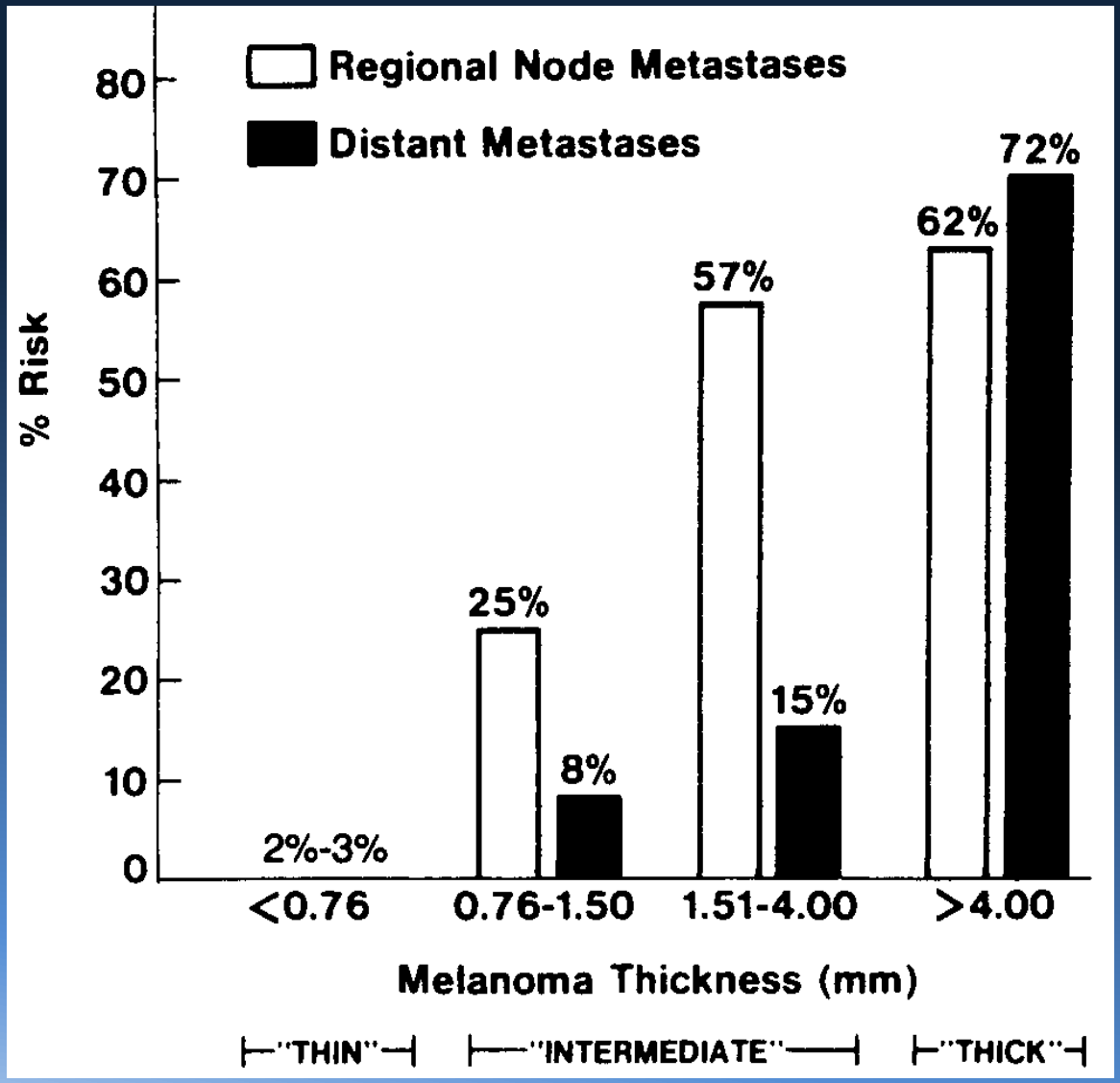
Sentinel Lymph Node - Principles

1. SLN is the first node in a lymphatic basin into which the primary melanoma drains.

2. SLN reflects the presence or absence of metastases in the remainder of the nodal basin.

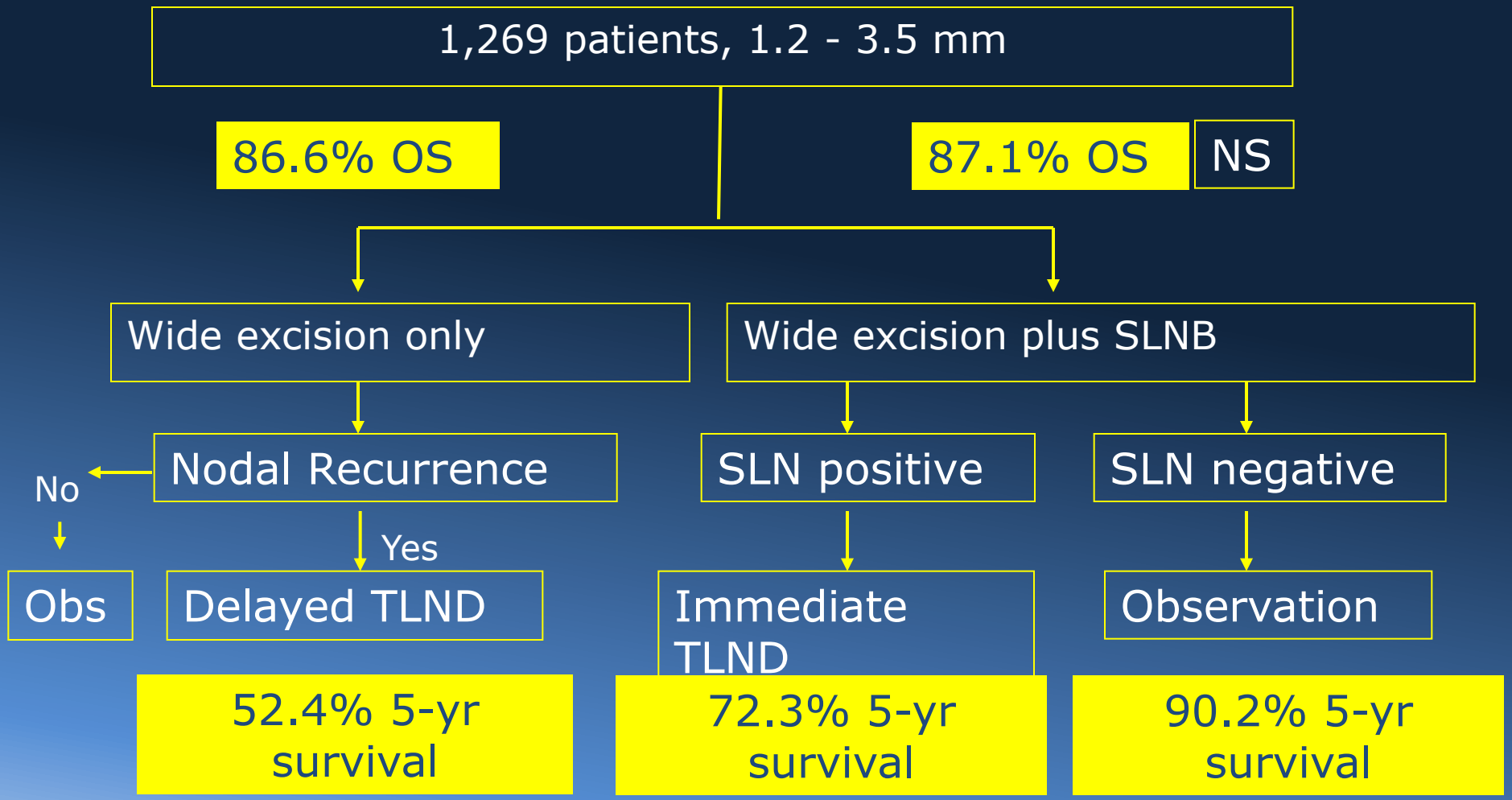
3. Patients with microscopic metastases in the SLN may benefit from complete nodal dissection.*

SLNB for Intermediate Thickness



Does SLNB and selective node dissection offer a survival benefit?

MSLT-1: Results



MSLT-1: SLN Take Home Point

"Staging of intermediate thickness (1.2 to 3.5 mm) primary melanomas according to the results of sentinel node biopsy provides important prognostic information

&

identifies pts with nodal metastases whose survival can be prolonged by immediate lymphadenectomy."

Morton DL et al. NEJM 355:1307, 2006

SLN Biopsy in the Head and Neck

Study	N	% Pts SLN Found	% Pts SLN Positive	% False Negative SLN	Mean F/U
Patel* 2002	56	93%	8%	2%	20 mo
Eicher 2002	43	98%	21%	0%	Immed. ND
Wagner 2000	70	99%	17%	2%	11 mo
Bostick 1997	117	92-96%	13%	0%	46 mo

*Patel SG, *Arch Otolaryngol Head Neck Surg.*, 128:285-291,2002

Specific issues of SNB in Head & Neck

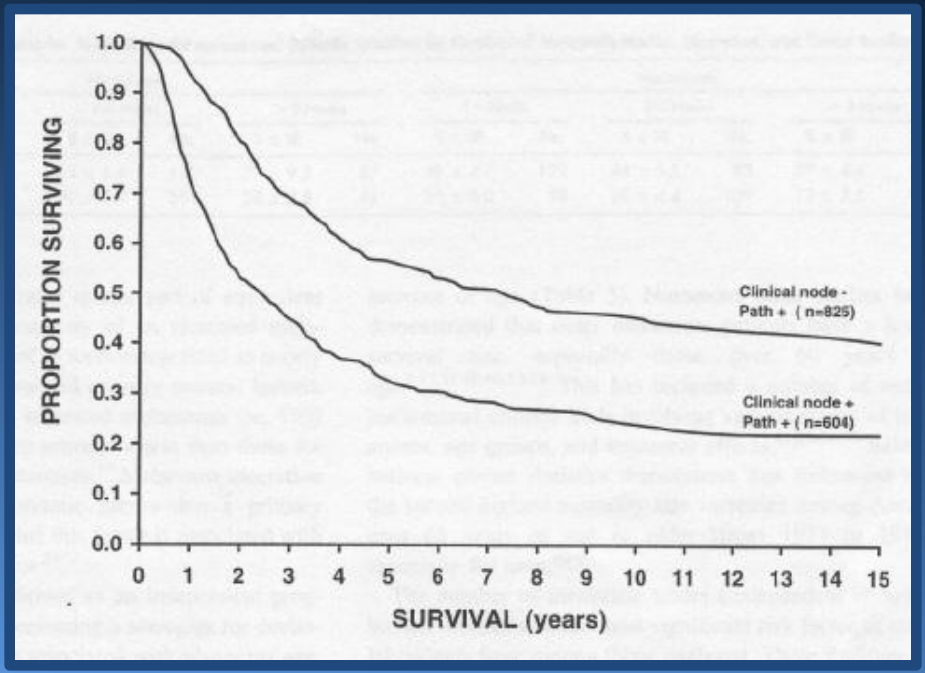
1. Blue dye not very useful
2. Multiple nodes
3. Parotid nodes / technical issues
4. Role of completion neck dissection

Sentinel Lymph Node Biopsy (SLNB)

- Minimally invasive procedure to identify patients harboring occult nodal disease
  - Identifies patients who warrant therapeutic neck dissection & adjuvant therapy
  - Spares 80% of patients without regional disease the morbidity of a neck dissection and parotidectomy

Importance of SLNB:

Survival benefit for Stage III pts diagnosed with occult nodal metastasis compared to palpable nodal metastasis.



Balch CM, et al. *J Clin Oncol.* 2001; 19: 3635.

Importance of SLNB:

WHO considers SLNB standard of care. (*Oncology.* 1999; 13: 288.)

Identification of a homogeneously staged patient population for entry into clinical trials. (McMasters, et al. *J Clin Oncol.* 2001; 19: 2851.)

Sentinel Lymph Node Mapping

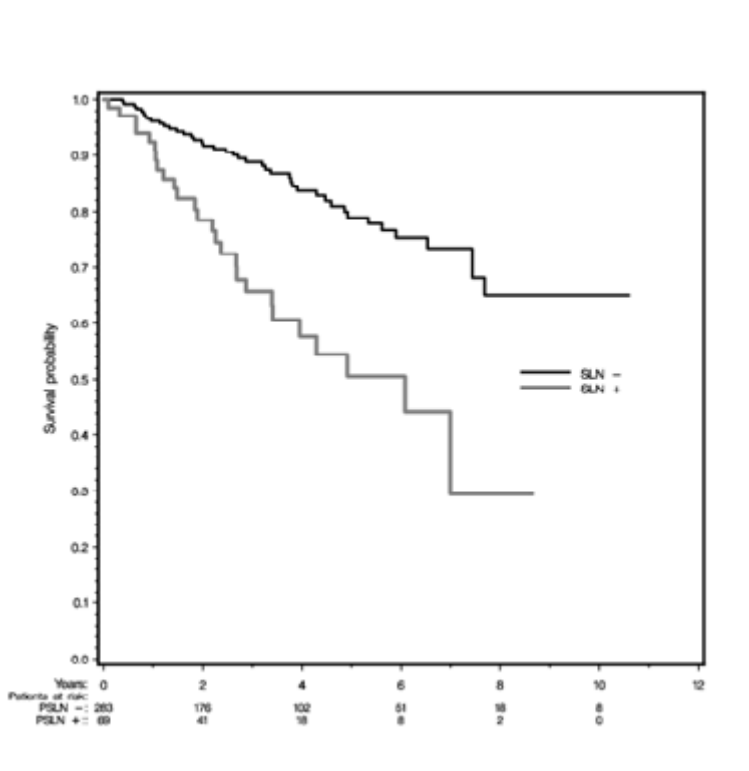
- Positive SLN biopsy
  - Therapeutic Neck Dissection
  - Superficial Parotidectomy
    - Temple; forehead; cheek; anterior scalp
  - Counseling for adjuvant interferon α-2b & radiation

- Negative SLN biopsy
  - Followed clinically

NCCN V.4.2011

Standard of Care

Survival Estimates by SLN Status



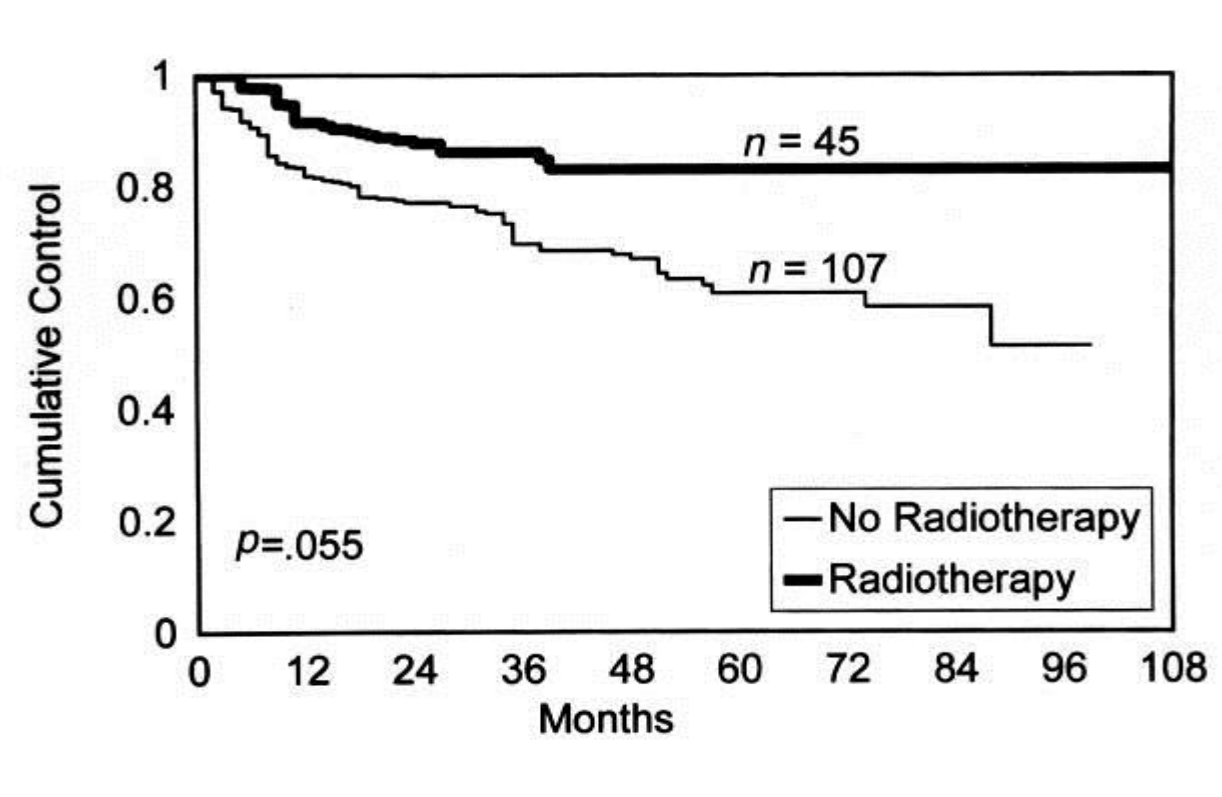
- SLN

+ SLN

Conclusions

- Sentinel lymph node biopsy is a safe and effective tool to characterize the regional nodal basin in patients with cutaneous melanoma of the head and neck.
- Status of the sentinel lymph node is highly predictive of overall and disease-free survival
- Patients with a negative sentinel lymph node must be watched closely for recurrent disease.

Adjuvant hypofractionated radiotherapy improves regional control



N=152 non-randomised node positive patients

Irradiated: 67% had > 1 +ve node, 48% had ECS

Non-irradiated: 43% had > 1 +ve node, 19% had ECS

(Head and Neck 1997)

Adjuvant Therapy For Regional Disease: Radiation Therapy

Adjuvant Tx: for intermediate thickness lesions

- Multiple positive nodes
- ECS

Primary Tx:

- Elderly, non-surgical candidate
- Large LMM lesions

Note that melanomas are radioresistant

Failure of Systemic Therapy

- Dacarbazine - alkylating agent
  - Response: 10-20%
  - N/V, neutropenia, thrombocytopenia
- Carmustine, Cisplatin, Taxol not better
- Combination therapy is not better
- High dose IL-2
- No survival benefit

Interferon-α2b

- 1996 – Kirkwood - ECOG 1684 trial - 280 pts
- thick (> 4 mm) or regionally metastatic (N1)
- IFN-α2b vs. observation
  - 20 MU/m^2/d IV for 5d/wk x 4 wks
  - 10 MU/m^2 SC for 3x/wk x 12 mo
- median overall survival prolonged (3.8 vs 2.8 yrs)
- 5-yr RFS survival increased (37% vs 26%)

Kirkwood JM, *J Clin Oncol.*, 14:7-17,1996

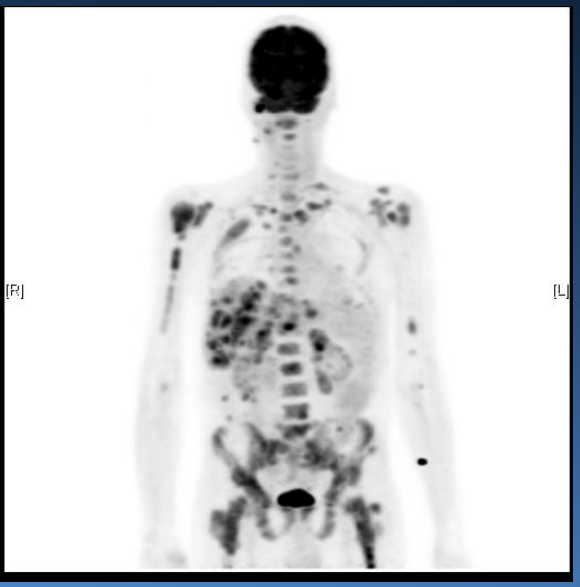
Interferon-α2b: Controversy

- Significant Toxicities
  - Fevers, chills, flu-like symptoms, fatigue, myelosuppression, hepatic & neurotoxicity
  - 78% had grade 3 or worse toxicity
  - 50% required treatment delay or dose ↓
  - 23% of pts discontinued treatment

- 2000 - Kirkwood - ECOG 1690 trial - 642 pts
  - No benefit of low dose interferon
  - RFS improved for high dose, but not overall survival

MSKCC Active Clinical Trials

- Ph II: Temozolamide + IFN-α2b
- Ph II: IL-12 + IFN-α2b
- Ph I/II: Temozolomide + Thalidamide
- Ph I/II: High Dose Tylenol + Carmustine
- Ph I: Dendritic Cell therapy
- Ph I: Gp75 DNA Vaccine
- Ipilimumab (MSK)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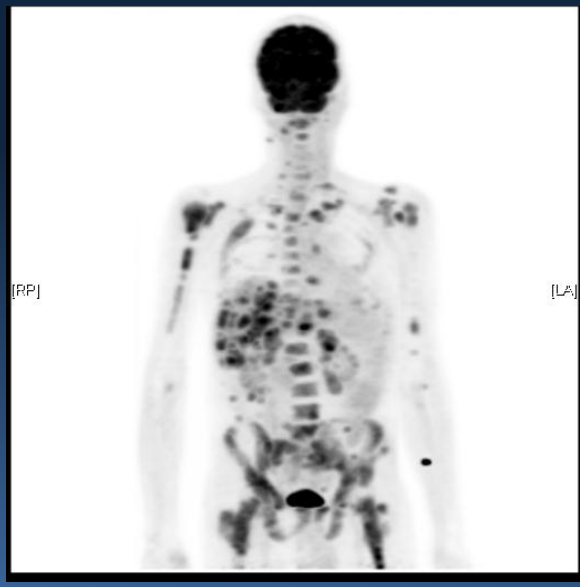
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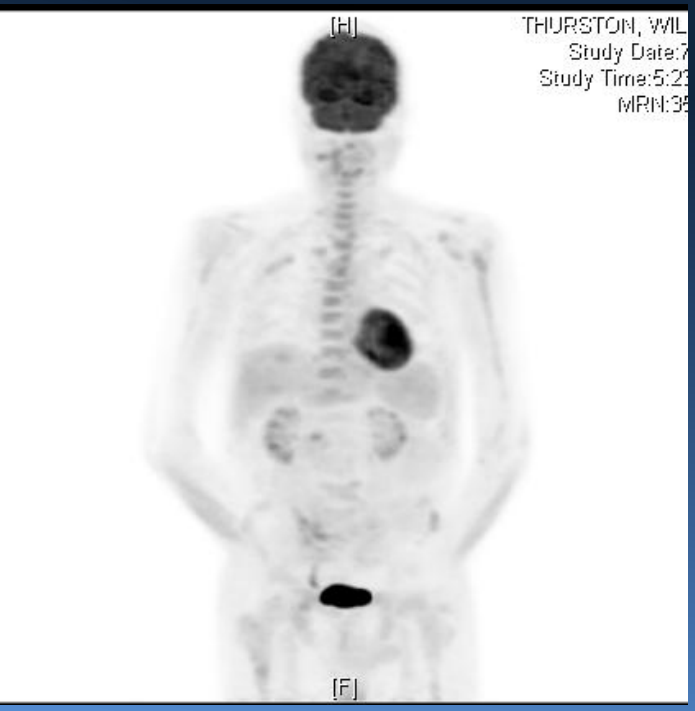
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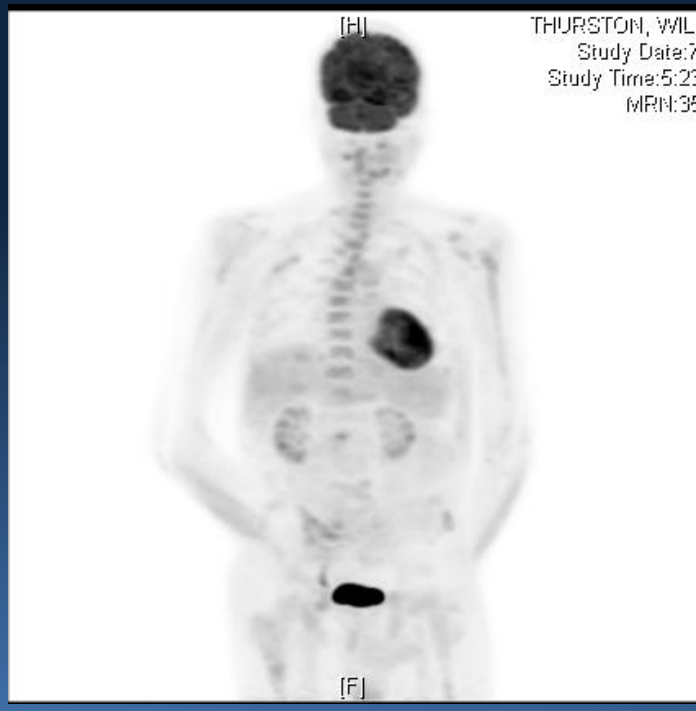
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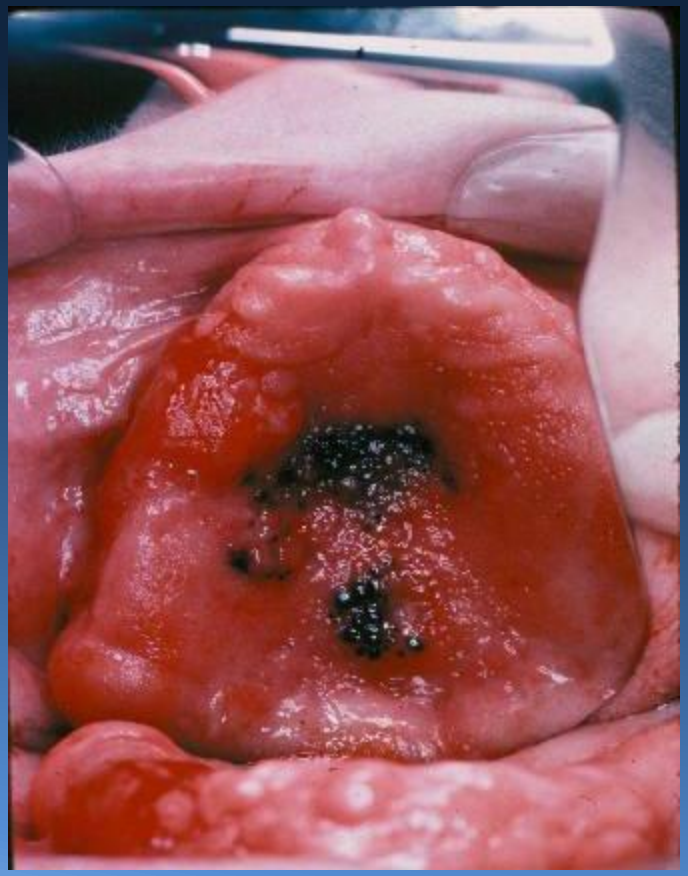
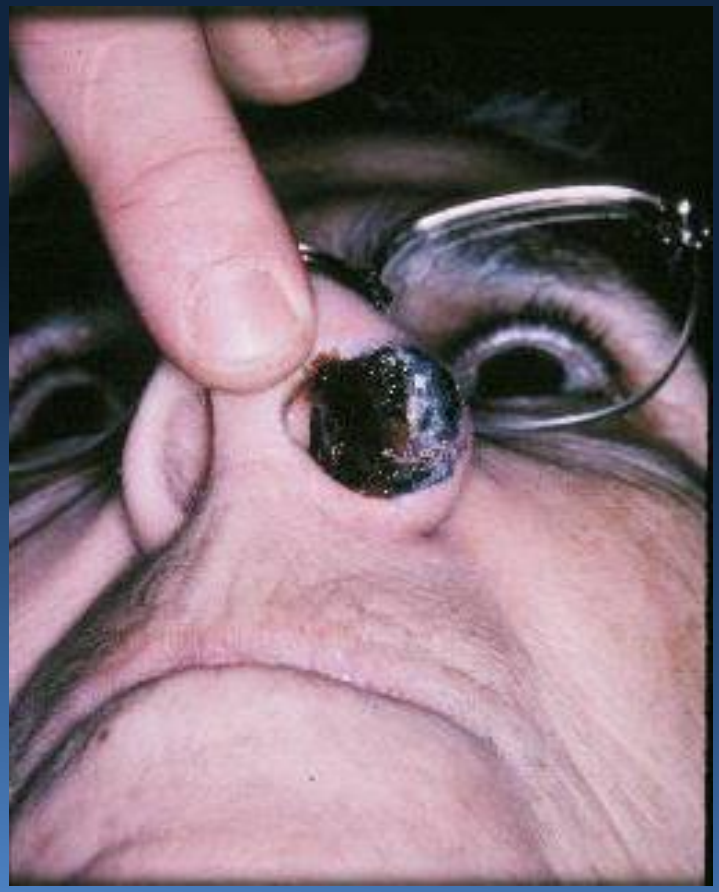
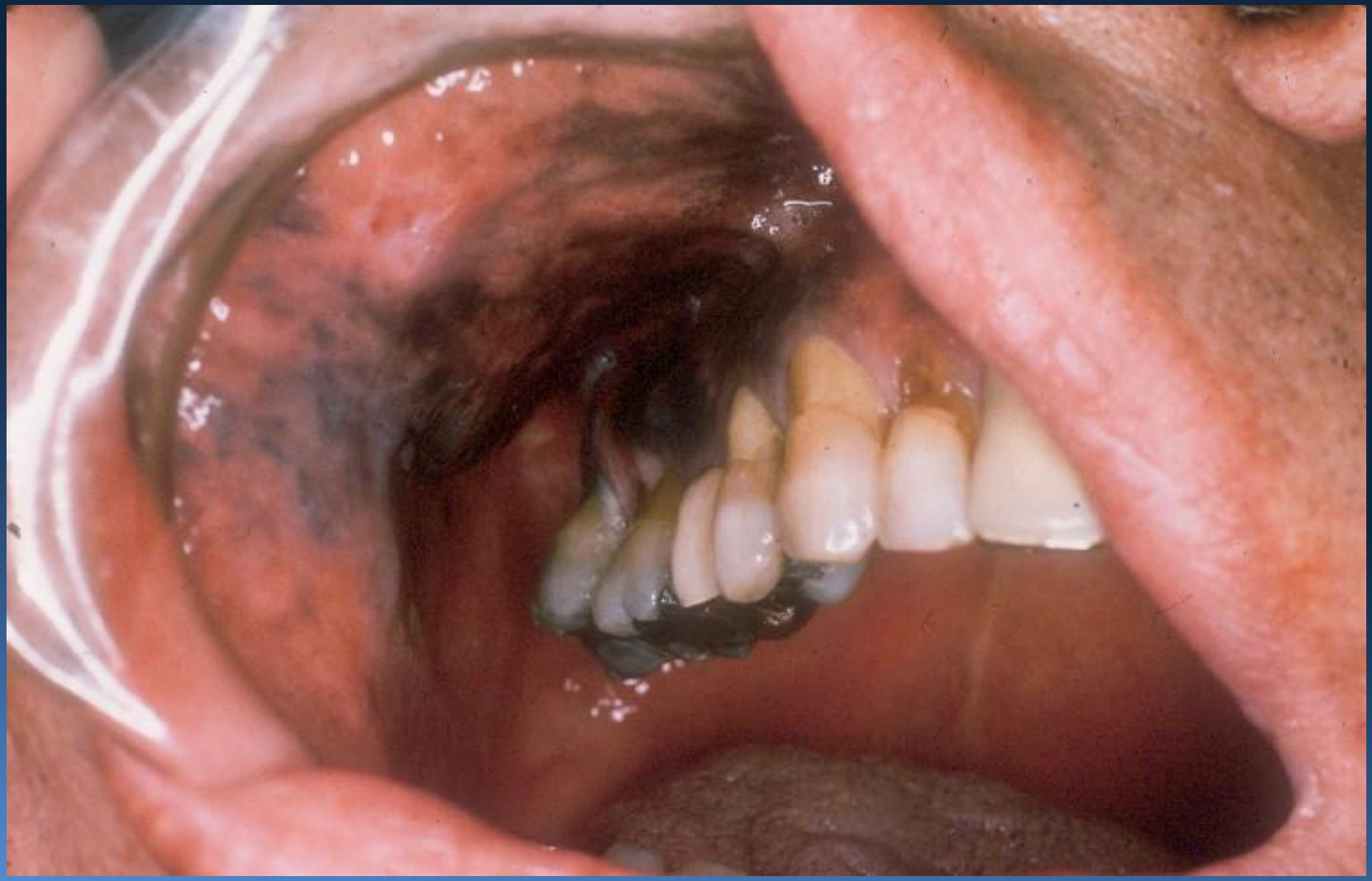
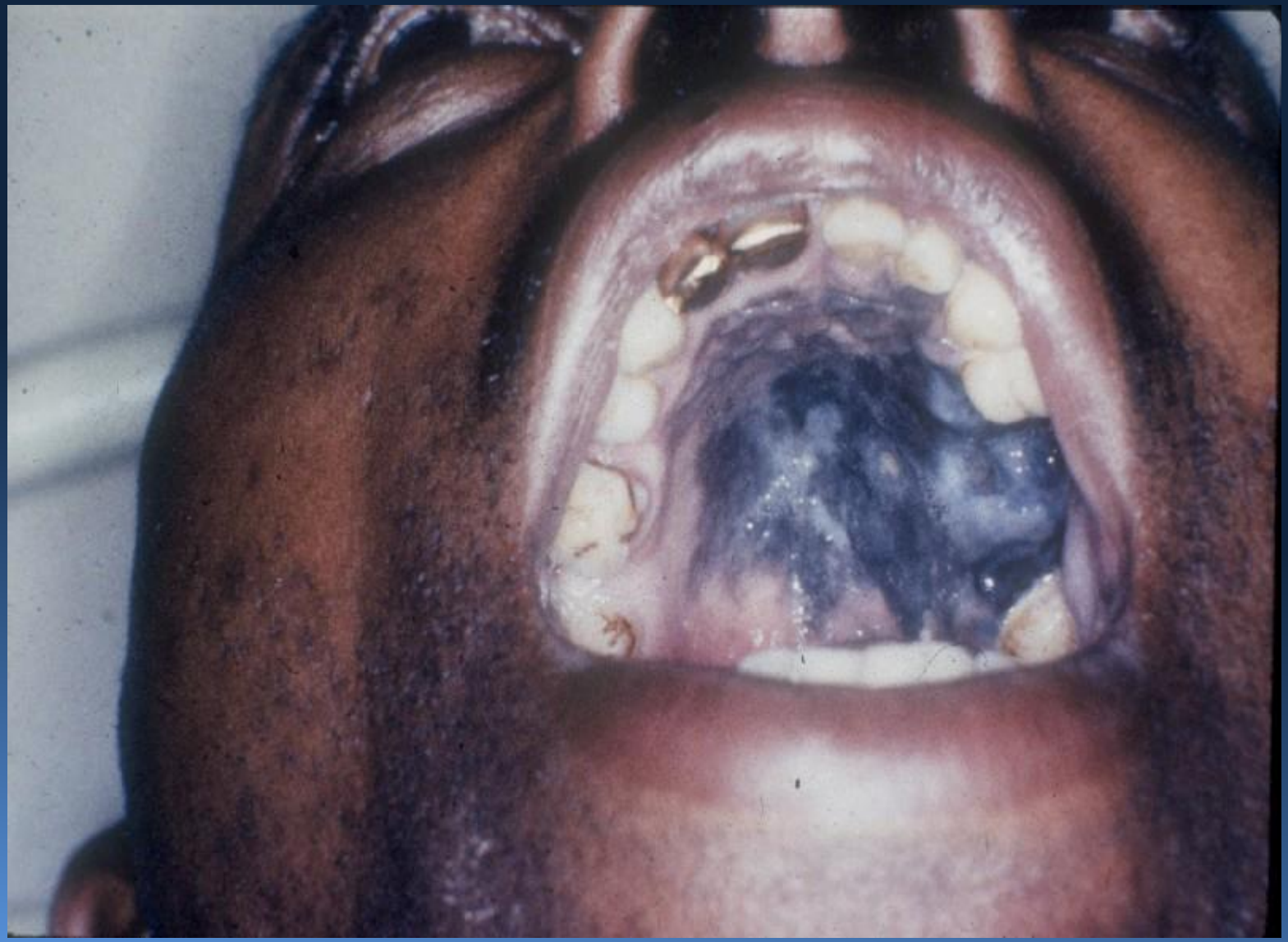
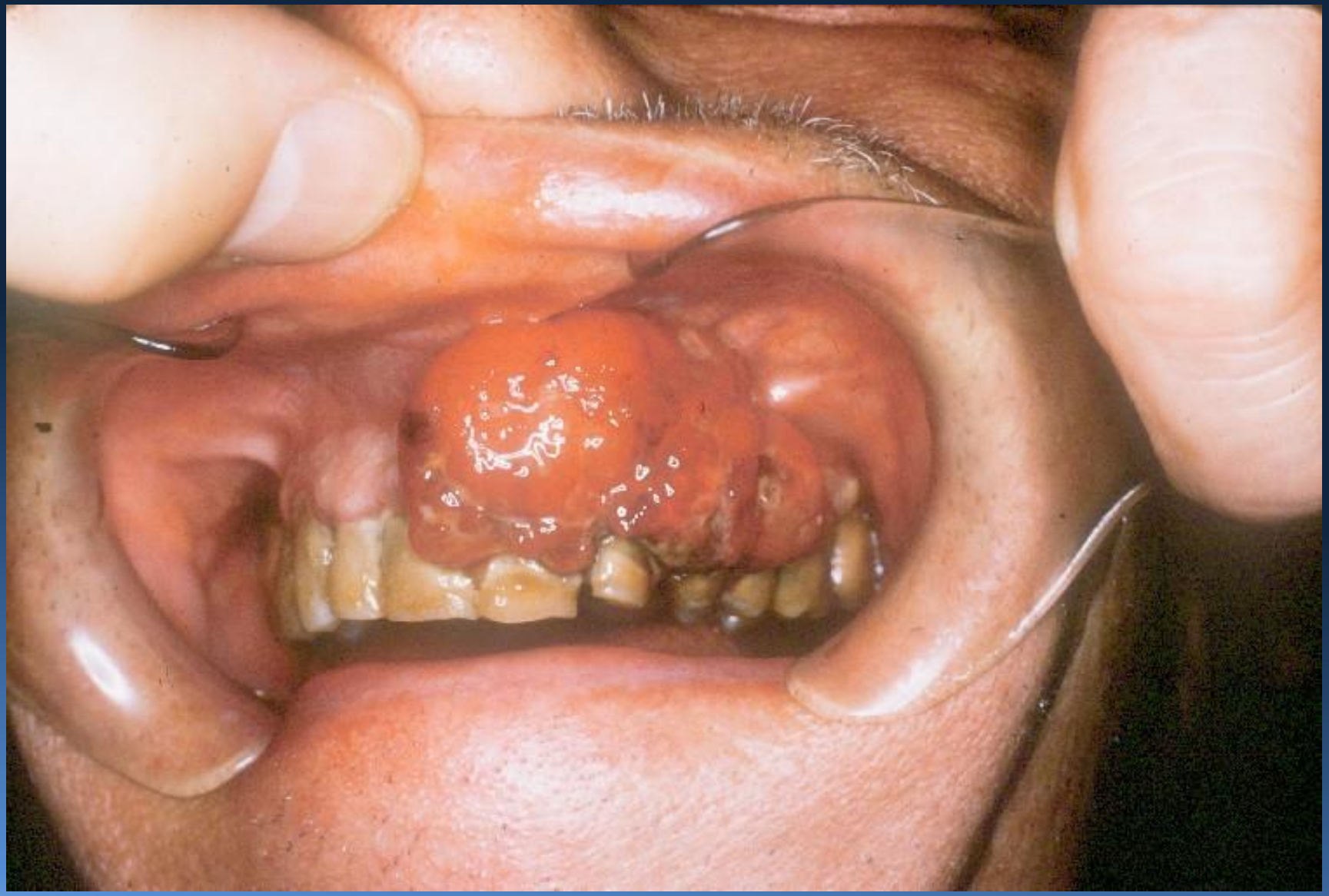
Mucusoal Melanoma

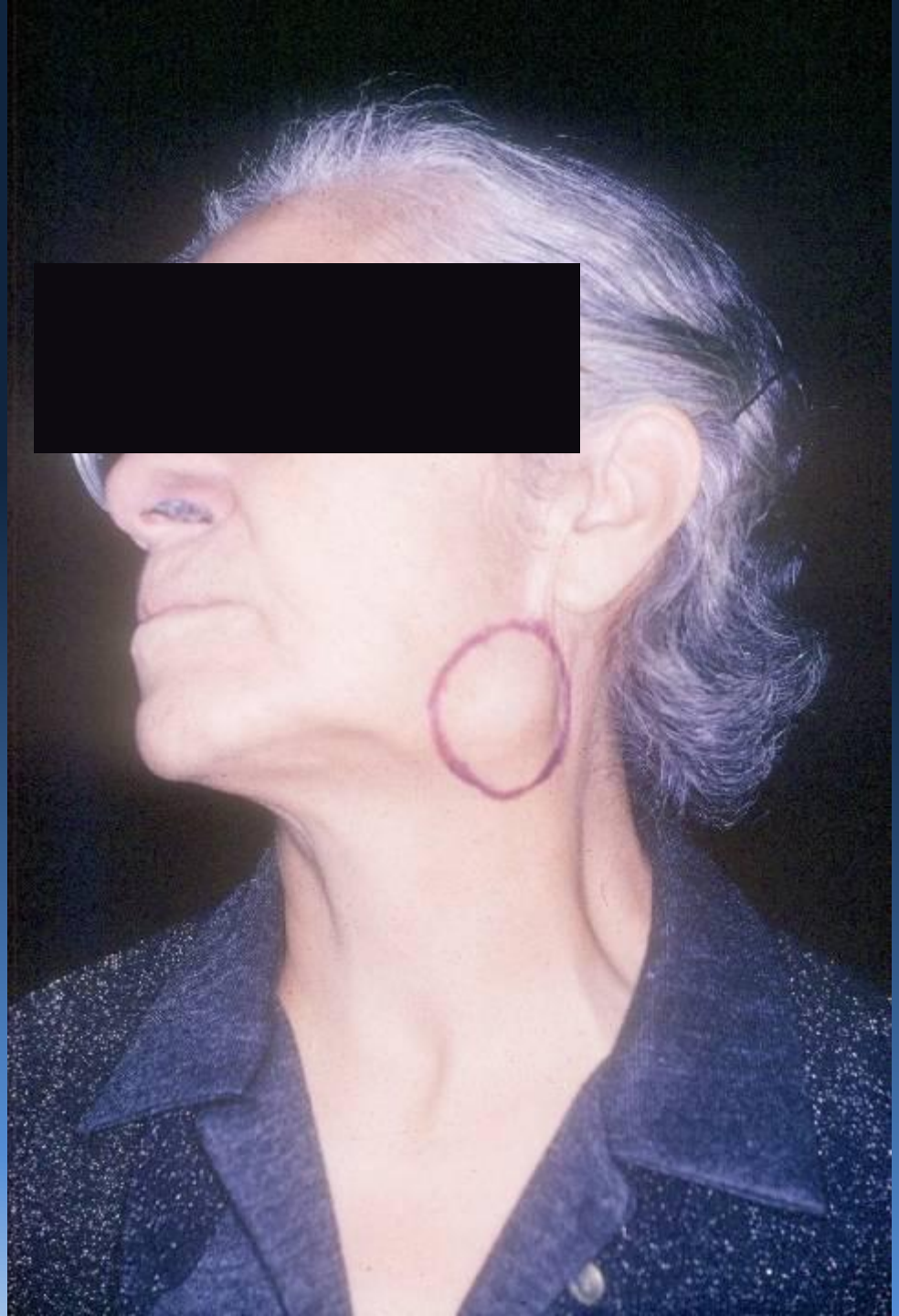








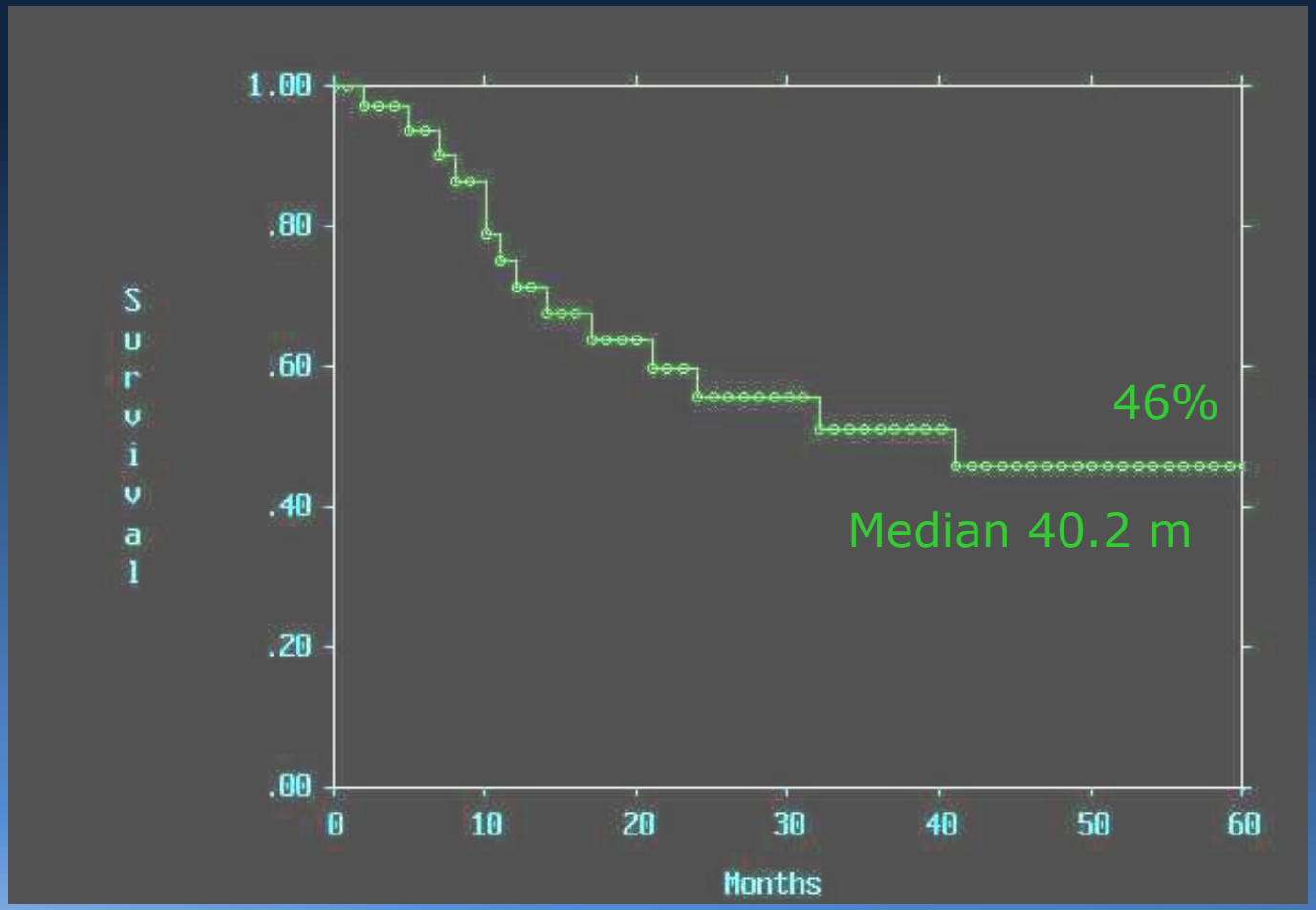




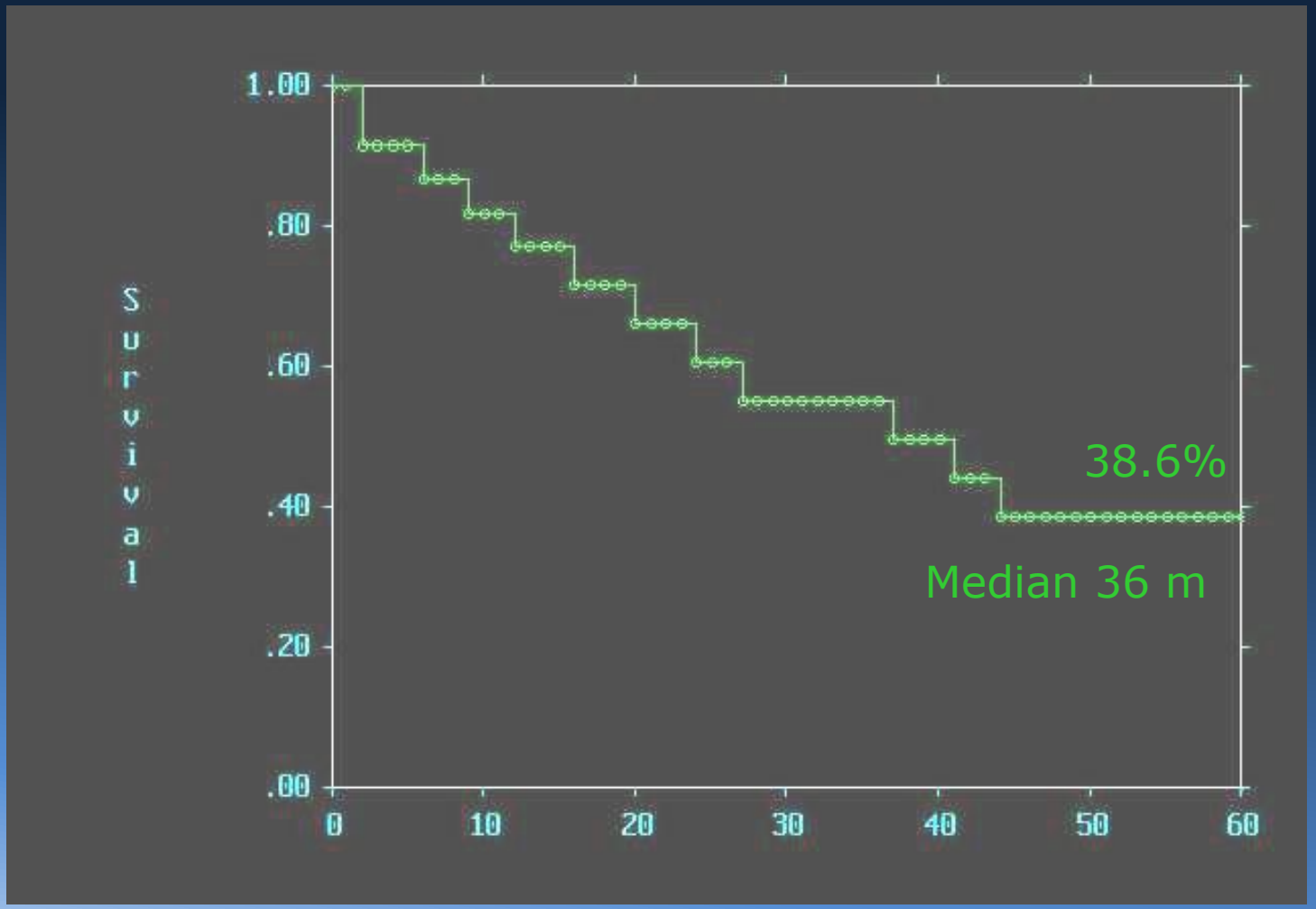
MSKCC Patients

- 1978 - 1998
- Complete clinical data on 59 patients
- Sinonasal melanomas = 35
- Oral melanomas = 24

Sinonasal Melanoma Cause-specific Survival



Oral Melanoma
Cause-specific Survival



A good physician
treats the disease;
a great physician
treats the patient
who has the disease.