Melanoma: Updates in Current Management

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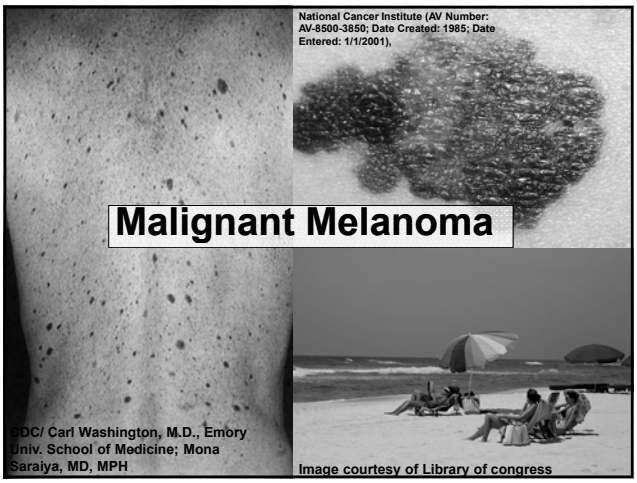
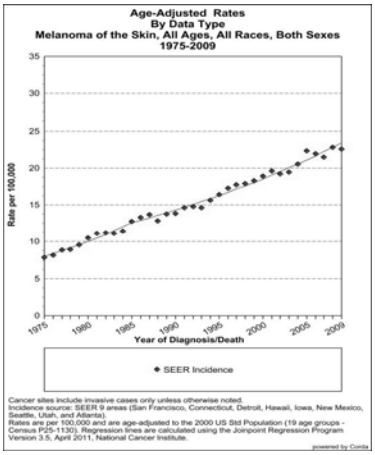


Background

- **Melanoma** is a malignancy of pigment-producing cells located predominantly in the skin, but also eyes, ears, GI tract, mucous membranes
- Accounts for 4% of all skin cancers
- Causes the greatest number of skin cancer-related deaths worldwide
- Early detection is the best means of reducing mortality



American Cancer Society Statistics - 2013

76,690 new cases estimated (45,060 men and 31,630 women)

9,480 melanoma deaths estimated

Incidence Rates by Race

- Whites: 1:50
- Hispanic: 1:200
- Black: 1:1000

Risk Factors

Table 1. Risk factors for developing cutaneous melanoma

Risk factor	Estimated relative risk
High-risk traits	
Xeroderma pigmentosum	1000
Dysplastic nevi, prior melanoma, and familial melanoma	500
Dysplastic nevi, no prior melanoma, and familial melanoma	148
Dysplastic nevi, no PH[a], or FH[b] of melanoma	7–27
Many nevi (≥ 50)	7–54
Caucasian (versus African American)	15–20
Congenital melanocytic nevi (especially large nevi)	17–21
Personal history of melanoma	9
Cutaneous melanoma in first-degree blood relative	8
Low-risk traits	
Dense sun-induced freckles	3–20
Prior history of NMSC	3–17
Immunosuppression	2–8
Other phenotypic traits: red hair, blond hair, blue eyes	1–6
History of severe and painful sunburns	1–6
Sun sensitivity, relative inability to tan	1–5

[a]PH, personal history; [b]FH, familial history.

Benvenuto-Andrade et al. Cutaneous Melanoma: surveillance of patients for recurrence and new primary melanomas. *Dermatologic Therapy. 2005 (18) 423-435*

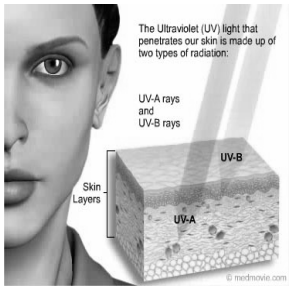
Sun Exposure

UVA radiation (320-400 nm) - penetrates deeper into the dermis. Responsible for sun-induced changes in dermal connective tissue and loss of elasticity (wrinkles, signs of aging)

UVB (290-320 nm) - causes sunburn, induction of increased melanin production in skin

UVA and UVB carcinogenic

Also found in tanning beds

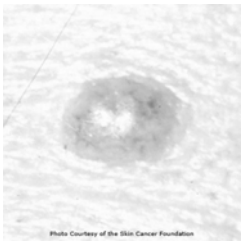


Melanoma: Diagnosis

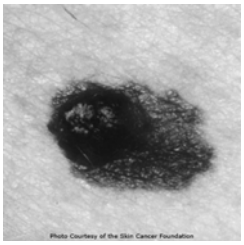
- **Early diagnosis is key to improved outcomes**
- **ABCDE**
  - **Asymmetry**
  - **Border irregularity**
  - **Color**
  - **Diameter**
  - **Evolution**

Asymmetry

- If you could fold the lesion in half, the 2 halves would not match.



Benign



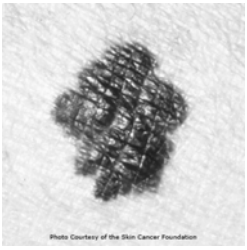
Malignant

Photos Courtesy of the Skin Cancer Foundation

Border

Melanoma often has uneven or blurred borders

Benign

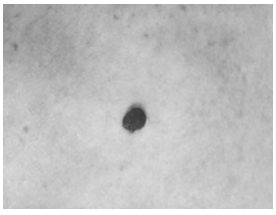


Malignant

Photos Courtesy of the Skin Cancer Foundation

Color

- Melanoma contains mixed shades of tan, brown and black; it can show traces of red, blue or white



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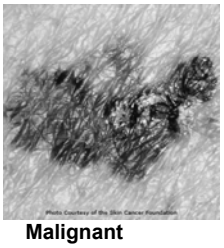
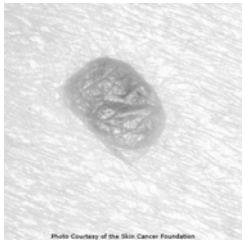


Malignant

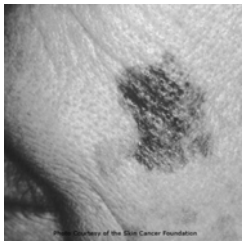
Photos Courtesy of the Skin Cancer Foundation

Diameter

- Melanoma is usually greater than 6 mm (the size of a pencil eraser)



Benign



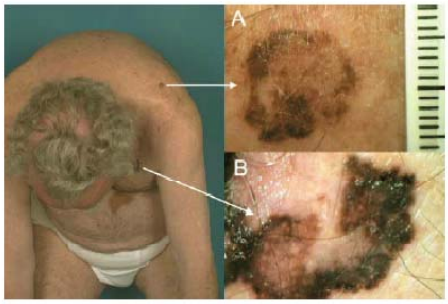
Malignant

Photos Courtesy of the Skin Cancer Foundation

Evolution and other suspicious signs

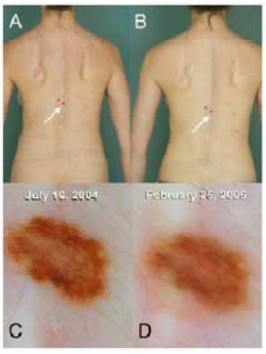
- Changes in appearance, such as spreading of pigment into surrounding skin
- A mole that looks scaly, oozes or bleeds
- Itching, tenderness or pain in a mole
- Brown or black streak under a nail
- Bruise on the foot that does not heal

ABCD: asymmetry, borders, color, diameter > 6mm



Benvenuto-Andrade et al. Cutaneous Melanoma: surveillance of patients for recurrence and new primary melanomas. *Dermatologic Therapy. 2005 (18) 423-435*

E is for Evolution:



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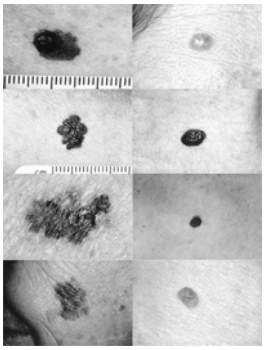
Which lesion should you biopsy??

Malignant Benign



Asymmetry

Border

Color

Diameter

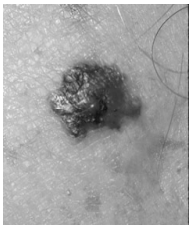
Photos Courtesy of the Skin Cancer Foundation

Histologic Subtypes of Melanoma

Superfical spreading melanoma
Nodular melanoma
Lentigo maligna melanoma
Acral lentiginous

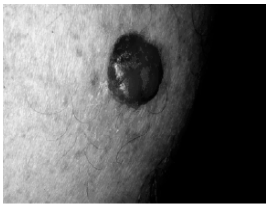
Superficial spreading melanoma

- **Most common subtype (~70%)**
- **Occurs anywhere on the body (non-chronic sun damaged skin)**
- **Derives its name from histologic evidence of lateral growth for a period of time before vertical growth**
- **High incidence of BRAF, PTEN mutations**



Nodular melanoma

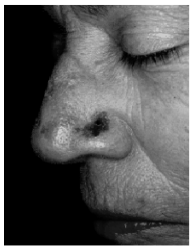
- **Comprise 15-30% of all melanomas**
- **Discrete nodule with dark black pigmentation is typical clinically**
- **Present with clinical and histologic evidence of vertical growth only**



Nodular melanoma Nodular melanomas present as discrete nodules, usually with dark pigmentation. Courtesy of James C Shaw, MD.

Lentigo maligna melanoma

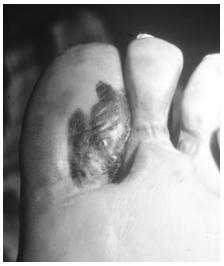
- **~ 5% of melanomas**
- **Arises from *in situ* melanoma on sun-damaged skin**
- **Usually head or neck**
- **High incidence of KIT mutations**



Lentigo maligna melanoma Lentigo maligna melanoma usually arises in areas of sun-damaged skin, particularly on the head and neck. Courtesy of James C Shaw, MD.

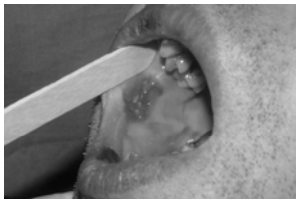
Acral Lentiginous Melanoma

- **~ 2-10% of melanomas**
- **Most common subtype in dark-skinned individuals**
- **Involves palms, soles, and nail beds**
- **More aggressive than other types – ? due to depth at diagnosis**
- **High incidence of KIT mutations**



Mucosal Melanoma- where the "sun don't shine"

- **Rare, but can occur on almost any mucosal surface**
- **2x higher in whites vs blacks**
- **Head/neck (ie nasal, sinus, mouth), female genital tract, anorectal region, urinary tract**
- **KIT mutations**



Melanoma: Diagnosis

Excisional biopsy (elliptical, punch, or saucerization): 1-3 mm margin, avoid larger margin to permit accurate lymphatic mapping

Full thickness incisional or punch: attempt to perform in clinically thickest portion of lesion

Melanoma: Diagnosis

Avoid shave biopsy: may compromise pathologic diagnosis and complete assessment of thickness

Path report should include depth of invasion in mm, Clark's level, presence or absence of ulceration, mitotic count, and status of peripheral and deep margin

Phases of Growth

Radial Growth Phase- tumor cells proliferate at the dermal-epidermal junction, tumor expands radially

- Lesions are confined to epidermis, may have superficial involvement of dermis

Vertical Growth Phase- lesion invades deeper into dermis, development of palpable nodule

- *Nodular type of melanoma has only VGP

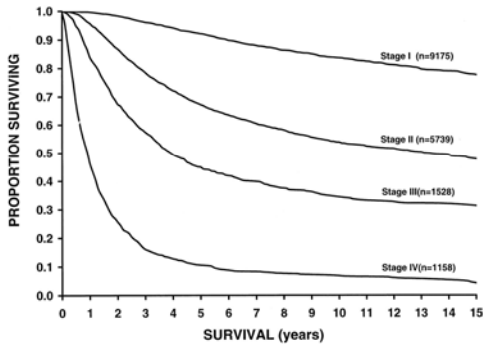
Prognostic Factors

- **Localized disease:**
  - Breslow thickness
  - presence of ulceration
  - Mitotic count
- **Regional disease:**
  - tumor burden (# of positive nodes)
  - Macroscopic vs microscopic positive nodes
  - Extension into extranodal soft-tissue
- **Other (worse prognosis): mucosal/ocular lesions, male, older age**

Survival & Stage

Stage at Diagnosis	Stage Distribution	5 yr Survival
Localized (confined to primary site – stage I, II)	84%	98%
Regional (spread to regional LN -stage III)	8%	62.1%
Distant	4%	15.9%
Unknown (unstaged)	4%	76%

Fifteen-year survival curves comparing localized melanoma (stages II and I), regional metastases (stage III), and distant metastases (stage IV)



Balch, C. M. et al. J Clin Oncol; 19:3635-3648 2001
JOURNAL OF CLINICAL ONCOLOGY

Melanoma: surgical care

Wide Excision of the primary lesion

Nodal assessment

Surgical Margins

Tumor Thickness	Recommended margin
– In situ	– 0.5 cm
– ≤ 1 mm	– 1 cm
– 1.01 – 2 mm	– 1 – 2 cm
– 2.01 – 4 mm	– 2 cm
– > 4 mm	– 2 cm

Margins of >2cm do not improve rate of local recurrence, disease-free survival, or overall survival, but they do increase the risk of requiring a skin graft or flap closure of the defect

How and When to Manage the Draining Lymph Node Basin

Elective Versus Therapeutic Lymph Node Dissection

Therapeutic lymph node dissection

"watch and wait"

- **Delayed until the time of nodal recurrence**
- **Avoided LND complications in node-negative patients.**
- **Strategy assumes there will be no evidence of distant metastatic disease at the time of nodal recurrence – not necessarily**

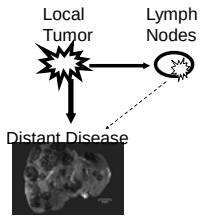
Elective Versus Therapeutic Lymph Node Dissection

Elective lymph node dissection

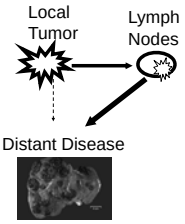
"search and destroy"

- **Performed at the time of WLE.**
- **80% of patients were node-negative.**
- **Survival advantage in retrospective studies.**

REGIONAL LYMPH NODES
Is it better to find nodal disease early?

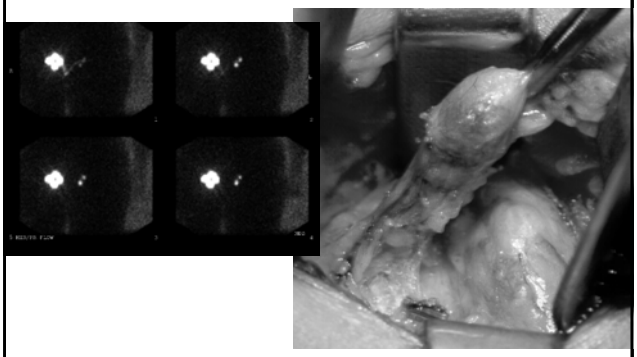


•Hypothesis: Most patients with nodal disease already have distant disease.
•Removal of regional nodes has minimal impact on survival



•Hypothesis: Orderly progression of disease from primary site to lymph nodes then distant sites
•Removal of lymph nodes prevents mets, improves survival

Revolution circa 1994: Sentinel lymph node biopsy



Video: Injection and Lymphoscintigraphy

Video: Surgical Sentinel Lymph Node Biopsy

When do we do Sentinel Lymph Node Biopsy?

- **NCCN recommendations:**
  - **SLN biopsy for patients with melanoma > 1mm regardless of characteristics. Standard of care.**
  - **For lesions 0.75-1.0 mm, consider SLN biopsy if there are aggressive features such as:**
    - **Ulceration**
    - **Clark level IV or V**
    - **(Satellitosis)**
    - **(Regression)**
    - **(Young Age)**
    - **(High Mitotic Rate)**

Some consider SLNbx for these, too

The Case for Sentinel Lymph Node Biopsy

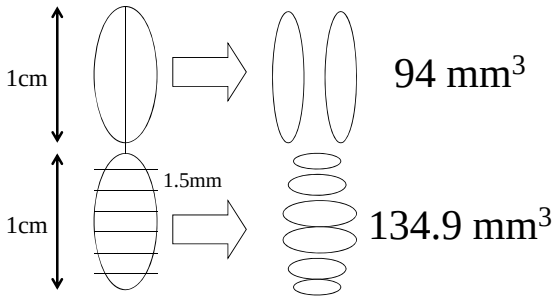
Better pathologic examination
Powerful predictor of survival – risk stratification allows for individualization of Treatment

Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal Recurrence

Avoid complications from ELND for node negative patients

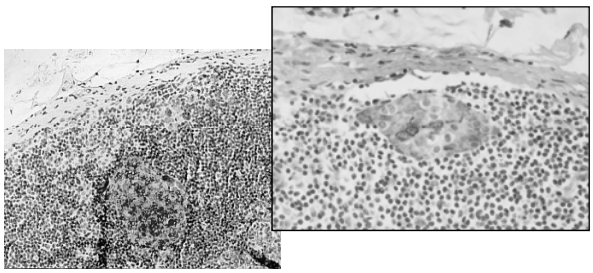
Survival benefit to SLNBx?

Increased cross-sectional area examined with serial sectioning.



Sabel et al. Surgery 2000;128:556-63.

IHC in Sentinel Lymph Node Biopsy

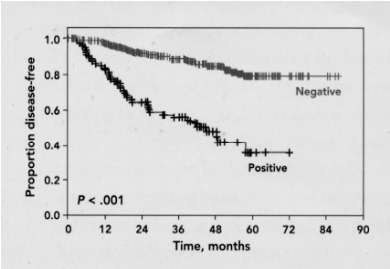


The Case for Sentinel Lymph Node Biopsy

- Better pathologic examination
- Powerful predictor of survival – risk stratification allows for individualization of treatment
- Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence
- Avoid complications from ELND for node negative patients
- Survival benefit to SLNBx?

Prognosis Associated with Sentinel Node Status

SLN status is the most powerful independent prognostic factor predicting survival, individualizing treatment



Disease-free survival stratified by SLN status

Gershenwald et al, J Clin Oncol 1999

The Case for Sentinel Lymph Node Biopsy

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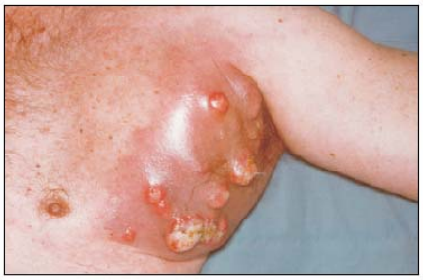
Loss of Local Control



From Fife K, Thompson JF. Lymph-node metastases in patients with melanoma: what is the optimum management? Lancet Oncol 2001;2:614-621

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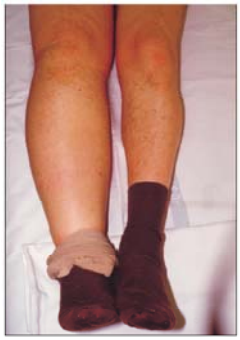
Risks vs Benefits: Lymphedema after ELND….lymph nodes were negative



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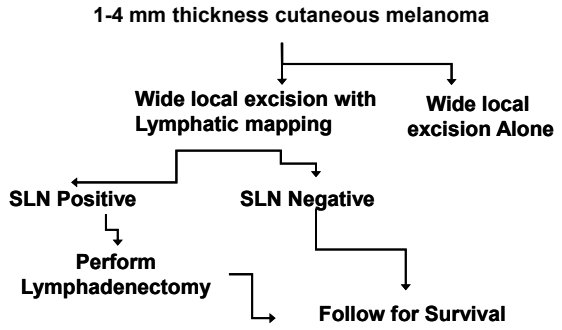
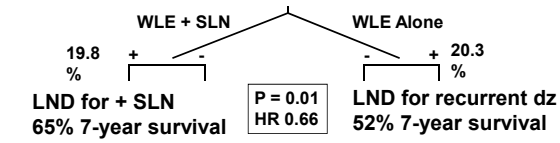
Multicenter Selective Lymphadenectomy Trial -I



Interim Results- MSLT I

2001 patients with melanoma >1.0mm or Clark IV

1339 patients with melanoma between 1.2 and 3.5mm Melanoma Specific Survival



Average # nodes: 1.6
Pts. with >4 nodes: 5%
In Transit Recurrence: 8%

Average # nodes: 3.4
Pts. with >4 nodes: 27%
In Transit Recurrence: 9%

7.4 % False Negative Rate

ASCO, 2005

Management of Positive Lymph Nodes

- **Positive Sentinel Node**
- **Standard of Care = Completion Lymph Node Dissection**
- **Palpable Lymph Node in a patient with a primary melanoma, or a history of melanoma**
- **FNA to get a tissue diagnosis**
- **If confirmed to be melanoma, staging work-up indicated to rule out distant metastatic disease**
- **If no distant disease, lymph node dissection**

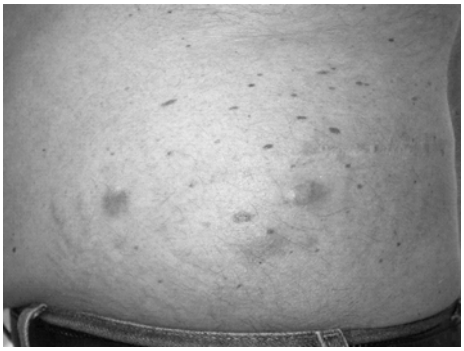
Multicenter Selective Lymphadenectomy Trial - II

- **+ SLNbx patients randomized to CLND vs nodal observation (with clinical examinations and ultrasound) to determine if CLND improves relapse rate or survival**

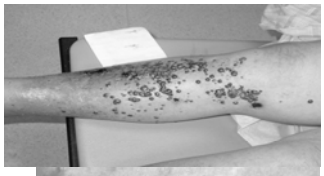
Adjuvant Therapy for Melanoma

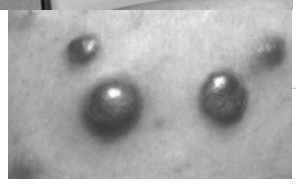
- **Risk of recurrence after surgery:**
  - **60% for T4N0M0**
  - **75% for regional node metastases**
- **Only proven therapy in the adjuvant setting is IFN α-2b, but its use is controversial**
  - **Intergroup Trials E- 1684, 1690, 1694 showed RFS benefit to high dose IFN α-2b; OS benefit noted in E-1684 and E1694.**
- Consider for patients with resected melanoma at high risk for recurrence (> 4mm thick and/or node +)

Local Recurrence



In-Transit Melanoma





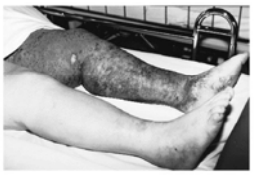
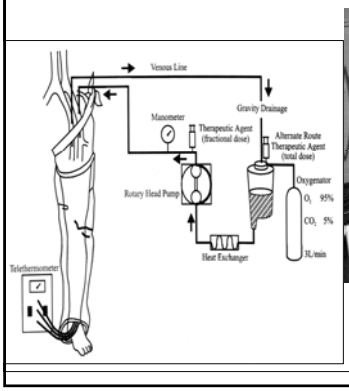


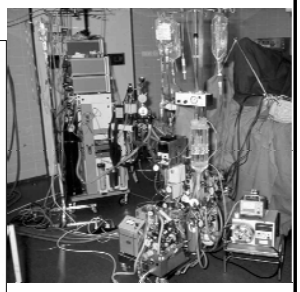
Image courtesy of NEJM

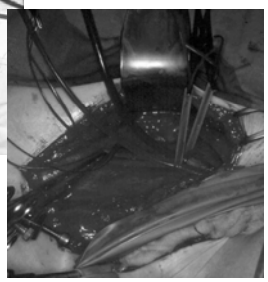
Management of In-Transit Disease

- **Confirm pathologically with FNA, biopsy**
- **Treatment options:**
  - **Excise to clear margins, consider SLN bx**
  - **Intratumoral BCG or IFN or IL-2 or Rose Bengal, etc…**
  - **CO2 Laser Ablation**
  - **Hyperthermic Isolated Limb Perfusion**
  - **Radiation**
  - **Clinical Trial**
  - **Systemic Chemotherapy**

Isolated perfusion circuit

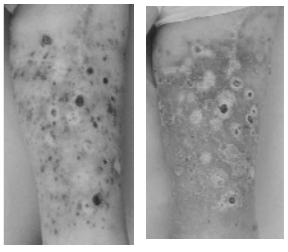




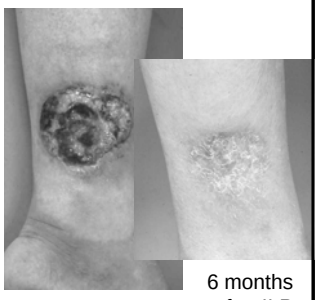


Iliac cannulation

Melanoma treated by melphalan ILP

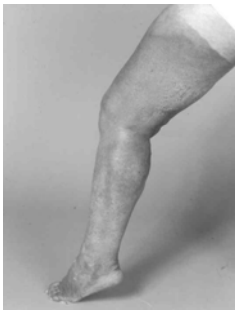


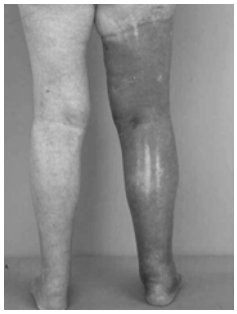
6 weeks after ILP



6 months after ILP

Normal toxicity reaction





Isolated Limb Infusion

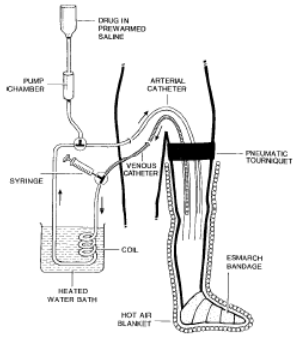
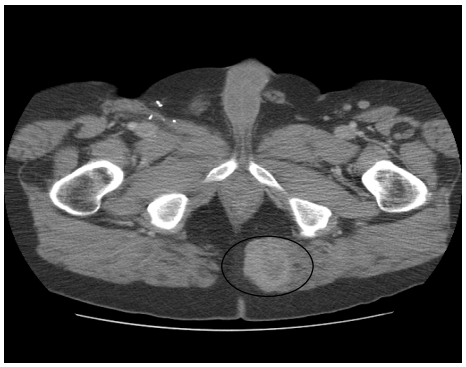


Fig. 1. Schematic diagram of the isolated limb infusion (ILI) circuit. (Reprinted with permission of Regional Cancer Treatment.)

Metastatic Disease

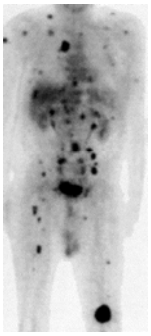


Metastatic Disease

- **M1a – skin, subcutaneous, distant lymph node basin**
- **M1b - pulmonary**
- **M1c – visceral mets OR any distant mets + elevated LDH**

Management of Stage IV Melanoma

- **Complete and thorough physical examination**
- **Radiologic Examination to Document Location and Number of Lesions**
  - **MRI of brain**
  - **CT of chest/abd/pelvis**
  - **PET scan (^{18}F-PET)**
- **Consider Surgical Excision**
- **Systemic Therapy If Not Resectable**



Survival After Complete Resection of M1a Disease

Author	Study	Year	n	5-year
Markowitz	LN	1991	72	38%
Markowitz	Soft Tissue	1991	60	49%
Gadd	LN	1992	199	11%
Barth	All Sites	1995	281	14%

Factor most predictive of survival: Disease-Free Interval (>12-18 months)

Survival After Complete Resection of M1b Disease (Pulmonary)

Author	Year	n	5-year
Karp	1990	29	5%
Gorenstein	1991	59	25%
Harpole	1992	98	20%
Tafra	1995	106	27%
Leo	2000	282	22%

Factors most predictive of survival: Disease-Free Interval and # of metastatic lesions excised

Strategies for Systemic Therapy for Metastatic Melanoma

Traditional Antineoplastic Chemotherapy

Dacarbazine (DTIC)

- Overall response rates 10-15%
- CR in up to 3%

Temozolomide

- a derivative of DTIC that is absorbed orally and possesses significant CNS penetration

Immunotherapy

We know that human tumors can be immunogenic

- **Increased cancers in setting of immunosuppression – transplant recipients, HIV**
- **Improved survival in many cancers with increased lymphocyte infiltration**
- **Unknown primary melanoma thought to be due to immune eradication of primary tumor; improved survival stage-for-stage vs known primaries**
- **Reports of spontaneous resolution of tumors**
- **Dr. Coley's toxins**

Factors Responsible for the Antitumor Response

Innate Immunity (non-specific)

- **Phagocytosis**
- **Complement fixation**
- **NK-mediated killing**

Adaptive Immunity (specific)

- **Cell-Mediated Immunity**
- **Humoral Immunity**

Clinical Translation: Ways to Induce Antitumor Immunity

- **Passive Immunotherapy**
  - **Adoptive transfer of tumor-specific activated T-cells**
  - **Administration of anti-tumor antibodies**
    - **Rituxan, Herceptin**
- **Active Immunotherapy**
  - **Non-specific**
    - **Interferon**
    - **BCG administered in 4 lymph node basins**
  - **Specific**
    - **Intralesional BCG**
    - **Vaccination**

High Dose IL-2

- Nonspecific, active immunotherapy
- Given by IV bolus injection q 8h
- Two cycles of a maximum of 14 doses each, separated by 2 weeks off
- Results in profound lymphocytic infiltrates in tissues, "cytokine cascade"
- Side effects:
  - **General: initial fever/chills, hypotension, tachycardia, oliguria (capillary leak)**
  - **Organ specific autoimmune type reactions: nausea, vomiting, diarrhea, dermatitis, confusion, agitation, myocarditis,**
- Overall Clinical Response rate of 15-16% in patients with metastatic melanoma; some long term CRs

Proof of Principle: Specific Antitumor Immunity

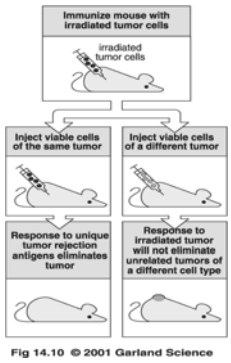


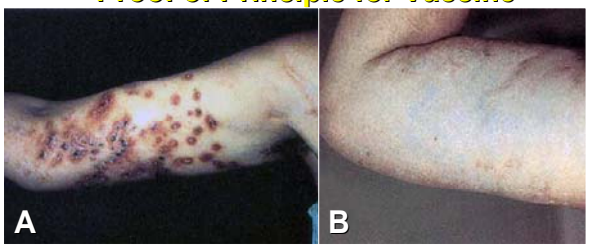
Fig 14.10 © 2001 Garland Science

- Mice immunized with an irradiated tumor and then challenged with live cells from the same tumor were able to reject these tumor cells
- Mice challenged with a live but unrelated tumor were not protected and developed tumor outgrowth
- Protection Study

Immunity to methylcholanthrene-induced sarcomas. J Natl Cancer Inst 1957; 18(6): 769.

Surgery Branch - NCI 1967

Intralesional BCG: Proof of Principle for Vaccine



Recurrent Melanoma — Complete Regression 5 Yrs Later

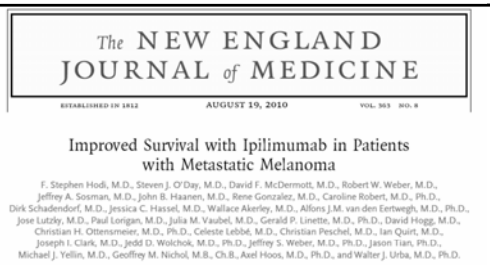
Morton et al, Surgery, 1970

Tumor Vaccination Strategies

Vaccine Type	Advantages	Disadvantages
Autologous Tumor Cell Vaccine	• Patient specific – potential to generate immunity against any antigens, known or unknown, expressed by the patient's tumor • Possibility of generating humoral and cellular antitumor immunity	• Not widely applicable. • Requires adequate tumor tissue for manufacture. • Time-consuming and technically challenging manufacturing process. • Fluctuations in the panel of antigens expressed on a patient's tumor render the vaccine ineffective
Allogeneic Tumor Cell Vaccine	• Widely applicable. • Patient's tumor tissue need not be available. • Potentially targets humoral and cellular immunity	• Not patient specific. • Response may be dictated by the similarity of patient's tumor cells to tumor cells comprising the vaccine • Moderately complex/demanding preparation
Peptide Vaccine	• Acellular technique. • Possibility of developing an "off the shelf" vaccine. • Potentially widely applicable • Known epitopes simplify immunologic monitoring	• Important tumor regression peptides must be known. • Tumor escape is problematic when only one or two peptides are administered as part of a vaccine • HLA restriction • Only generates cellular immunity
Dendritic Cell (DC) Vaccine	• Utilizes potent antigen-presenting cells that are the final common pathway for generation of antitumor immunity • Can be loaded with tumor antigens through a variety of techniques.	• Requires leukapheresis and ex-vivo culture and processing with multiple opportunities for contamination. • Yield can be variable and patient dependent.

Overcoming Tolerance to Self Antigens

- **CTLA4-Blockade**
  - **Cytotoxic T-lymphocyte antigen 4, attenuates and limits emerging T-cell responses, prevents autoimmunity**
  - **Neutralizing antibody to CTLA-4 results in unopposed positive co-stimulation of T-cells which overcomes peripheral tolerance to self antigens**
  - **Results in autoimmunity to normal self antigens (resulting in side effect profile – (- itis), and also to "self" tumor antigens**



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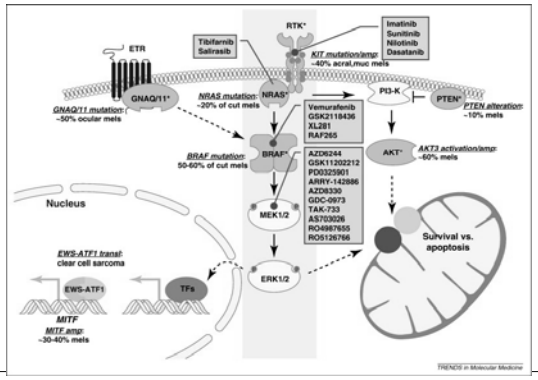
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

- **Ipilimumab + peptide vaccine: median survival 10 mo**
- **Ipilimumab alone : median survival 10.1 mo**
- **Peptide vaccine alone : median survival 6.4 mo**

Targeted Therapy for Melanoma



Targeted Therapy for Melanoma

BRAF Inhibitors

- **Activating mutations in BRAF (V600E) in ~ 50% of melanoma patients**
- **Clinical trials showing tumor regression ant stabilized disease in > 50% of patients with advanced melanoma**
- **Resistance to BRAF inhibition is a problem, investigating combination with other pathway inhibitors such as MEK, P13k/akt, mTOR**