Baseline and Surveillance Studies for Cutaneous Melanoma

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Key Aspects of Workup following Melanoma Diagnosis

● **History** - including focused *review of systems*:
  - Constitutional, neurologic, respiratory, hepatic, gastrointestinal, musculoskeletal, skin, lymphatics
  - Pay attention to unanticipated weight loss, general malaise, profound fatigue, headaches or other CNS symptoms

● **Physical Examination**:
  - Total body skin examination
  - Palpation of lymph nodes (regional and distant)
  - Abdominal exam (hepatosplenomegaly)
    • large tumors with satellite, in-transit, or regional nodal metastasis at presentation
    • uveal melanoma
Additional Studies for Workup of the Newly-diagnosed Melanoma Patient

Why do it?

- Assess the extent of disease
- Establish baseline images for future comparison (in patients at risk for relapse)
- Detect clinically occult disease which may affect treatment recommendations
- Define homogeneously-staged patients for clinical trials
Why not perform baseline workup?

- NO GOOD DATA TO SUPPORT IN ASYMPTOMATIC PTS
  - No prospective, randomized trials
  - Most evidence based on retrospective data
- Current tests have relatively insensitive lower limits of resolution
- Cost associated with obtaining baseline studies high
- False positive results associated with:
  - increased patient anxiety
  - increased morbidity with more invasive tests
Hematologic tests lack both high sensitivity and high specificity for melanoma detection

LDH – independent predictor of survival - stage IV only

What about cutaneous melanoma patients?
- 224 patients with CM; screening LDH in 96
- 15% (14/96) had elevated LDH at baseline
- Did not lead to detection of systemic disease, alter surgical management, or correlate with SLN postivity

Serum S-100B
- Further study necessary to assess utility in routine staging
- At present, limited to advanced disease, not routinely used in the US

Baseline Imaging Studies: Chest X-ray

● Multiple studies (retro- and prospective) have found consistent false-positive rates

● **True positive rate extremely low: 0% to 0.5%**

● **Despite availability and low cost, CXR is a highly cost inefficient test** in asymptomatic patients with cutaneous melanoma

● **Routine use not justified at baseline**

Computed Tomography (CT)

- Body CT not useful for detection of occult metastasis in patients with primary cutaneous melanoma

- Most recent study 158 pts, T1b-T3b melanoma, clinically node negative (N0):
  - Chest CT – false positive (FP) rate 87.5%
  - CT abdomen/pelvis - 90.9% FP rate
  - 57 head CTs - 100% FP rate

- NO True Positive Findings!

- Conc: minimal benefit for preoperative CT scans
  - Low yield, high FP rate, no change in surgical management/staging, assoc with additional (invasive) studies, increased patient anxiety

Positron Emission Tomography (PET)

- More sensitive/specific than CT for melanoma staging, but more costly; typically integrated with CT (i.e. PET-CT)
- Highest utility – DISTANT METASTASIS detection in the setting of documented/suspected metastasis (stage III, IV) or for surveillance of metastatic disease
- Positive scan may impact further surgery and/or need for systemic therapy
- Not a substitute for sentinel lymph node biopsy (SLNB) staging in primary melanoma patients

Who should be imaged at baseline?
# Work-up of Primary Melanoma: NCCN Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>NCCN Recommended Workup</th>
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<tbody>
<tr>
<td><strong>Stage 0 (in situ)</strong></td>
<td>None</td>
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<tr>
<td><strong>Stage IA</strong></td>
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</table>
| ≤1 mm thick, no ulceration, mitotic rate <1/mm² | H&P  
Routine imaging/labs not recommended  
Imaging only to evaluate specific signs or symptoms (e.g. ultrasound, CT, PET-CT, MRI) |
| **Stage IB, Stage II** |  |
| (≤1 mm thick with ulceration or mitotic rate ≥1/mm² or >1 mm thick, any characteristic), N0 | H&P  
Routine imaging/labs not recommended  
Imaging only to evaluate specific signs or symptoms (e.g. ultrasound, CT, PET-CT, MRI)  
**SIMILAR TO AAD 2011 GUIDELINES!** |
Baseline and Surveillance Studies (NCCN)

- For all **ASYMPTOMATIC** stage I and II Melanoma (including T4 lesions) at **BASELINE**:
  - LFTs, LDH, CXR, CT and/or PET-CT NOT INDICATED!

- Same true for **SURVEILLANCE**:
  - Routine blood tests not recommended
  - Radiologic imaging (CT, PET/CT, MRI) only indicated to investigate specific signs or symptoms
    - Screening for asymptomatic recurrent/metastatic disease in patients with Stage 0-IIA NOT RECOMMENDED; optional for Stage IIB-IV
    - Consider CXR (lung mets), brain MRI, or PET-CT q3-12 months
    - No imaging for asymptomatic pts of ANY STAGE after 3-5 years!
Site and Timing of Melanoma Relapse

- 429 patients with surgically-resected stage III melanoma, no evidence disease, 1992-2004

- Overall 5-year relapse-free survival:
  - Stage IIIA - 63%
  - Stage IIIB - 32%
  - Stage IIIC - 11%

- Sites of 1st relapse: local/ in-transit (28%), regional nodal (21%), systemic (51%)
  - Radiologic tests detected only 32% of relapses, most by pt or family

- Routine physical exam unlikely to detect 1st relapse after
  - 3 years for stage IIIA, 2 years for stage IIIB, and 1 year for stage IIIC
  - Same true for imaging beyond 3 years for stage IIIA/IIIB & 2 years for IIIC

Melanoma Surveillance

- Careful Hx and PE detect most metastases, **NOT surveillance studies**
  - Labs almost never sole indicator of metastatic disease
  - LDH- staging value only for stage IV melanoma – AT TIME OF DIAGNOSIS

- Extensive radiologic scans (CT/ MRI/ PET/ skeletal survey) generally **not** of value in asymptomatic pts

- Presymptomatic detection of stage IV melanoma **does not affect survival** – **will this change with the newer drugs?**

Intensive Imaging for High-risk Melanoma

- Prospective study 290 pts with stage IIB, IIC, III melanoma
  - underwent intensive imaging and clinical surveillance
- 114 (39%) developed metastasis – MEDIAN 1.4 years
  - Imaging (CT C/A/P, brain MRI q 6 mos x 5 years) detected 67% metastasis (mostly distant)
  - Clinical exam (pt or provider) detected 49% (mostly skin, LNs)

Limitations - NO assessment of:
- patient outcomes (e.g. improved survival due to imaging detection)
- cost-effectiveness
- potential patient harms (adverse effects of false positive findings)

Common Follow-up Recommendations for All Patients

- At least annual skin exam for life

- Educate all patients in:
  - regular skin self-examination, lymph node self-exam for invasive disease

- Surveillance regional nodal ultrasound may be considered in patients:
  - with equivocal LN exam
  - who were offered but did not undergo SLNB
  - in whom SLNB not possible/successful
  - with a positive SLNB who did not undergo complete lymph node dissection (CLND)
  - Not a substitute for SLNB or CLND!

Role of Ultrasound (US) in Regional Nodal Basin Follow-up

● Prospective study (1288 pts) demonstrated higher sensitivity (89%) compared to clinical examination (71%)
  – Provided earlier diagnosis of in-transit and regional LN metastasis after initial surgery

● Meta-analysis: US superior to palpation for assessment of regional lymph node metastasis and surveillance of regional LN fields
  – When clinical findings equivocal and/or clinical suspicion is high

● Meta-analysis: 74 studies, 1990-2009, 10,528 patients
  – Ultrasonography superior to CT, PET, and PET-CT for detecting lymph node metastases
  – Increased Radiology adoption of ultrasound for this purpose nec in the US!

# Primary Melanoma Surveillance

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| **Stage 0 (in situ)** | - At least annual skin exam for life (ALL PATIENTS)  
- Educate patient in regular self skin exam (ALL PATIENTS) |
| **Stage IA-IIA NED (no evidence disease)** | - H&P (with emphasis on nodes and skin) every 6-12 mo x 5 y, then annually as clinically indicated  
- At least annual skin exam for life  
- Educate patient in regular self skin and LN exam (stage IA-IV)  
- Routine blood tests/radiologic imaging to screen for asymptomatic recurrent/metastatic disease **not recommended** |
| **Stage IIB-IV NED (no evidence disease)** | - H&P (emphasis on nodes and skin)  
  - Every 3-6 mo for 2 yr, then  
  - Every 3-12 mo for 3 yr, then annually as clinically indicated  
- Routine blood tests not recommended  
- Consider CT, brain MRI, and/or PET-CT every 3-12 mos to screen for recurrent/metastatic disease (**category 2B**)  
- Routine radiologic imaging **not recommended after 3-5 y** |
AAD Guidelines 2011

● **Baseline:**
  - No baseline lab or imaging studies in asymptomatic patients with newly-diagnosed primary melanoma of any thickness

● **Surveillance:**
  - Surveillance labs/imaging studies have low yield for metastatic detection and high false-positive rates
  - Regular clinical follow-up and interval patient self exam of skin and regional LNs
  - History and PE findings direct need for further studies to detect metastatic disease
  - No clear f/u interval – at least annual history and PE with attention to skin and lymph nodes

What About Newer Molecular Techniques?

● “While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is NOT RECOMMENDED outside of a clinical study (trial).”
  - myPath®, Myriad Genetics, Inc.
  - DecisionDx®, Castle Biosciences, Inc.

● Somatic mutational analysis (BRAF, NRAS, KIT) recommended if patients are being considered for either routine treatment or clinical trials, but not in the absence of metastatic disease
  - “BRAF testing of the primary cutaneous melanoma is not recommended unless required to guide systemic therapy.”
Patient Follow-up Considerations

- Opinions vary regarding appropriate follow-up

- **Follow-up schedule** influenced by:
  - Risk of disease recurrence and new primary melanoma
  - Previous primary melanoma; h/o atypical nevi
  - Family history
  - Patient anxiety

- **Optimal duration of follow-up controversial**
  - Probably not cost effective to follow patients intensely after 5-10 years
  - *Lifetime dermatologic surveillance recommended* due to risk of second primary melanoma (4-8%)
  - Frequency of dermatologic surveillance based on individual risk factors
Conclusions

- Patient history and thorough physical examination are the key components of initial workup and surveillance in the melanoma patient.

- Following surgical resection, **regular CLINICAL follow-up** is the most important means of detecting local, regional and distant disease.

- Surveillance imaging recommendations may change as **adjuvant therapies for lower stage disease** evolve.
How to Access the NCCN Guidelines

● GO to: NCCN Clinical Practice Guidelines in Oncology – NCCN.org

● For Health Care Professionals:
  – www.nccn.org/professionals/physician_gls/

● Click on “NCCN Guidelines for Treatment of Cancer by Site”

● Then on “MELANOMA” - PDF File: “NCCN Guidelines”

● Register with email address and create account - FREE!