Work-up/Follow-up: Baseline and Surveillance Studies for Cutaneous Melanoma Patients

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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S017- Translating Evidence into Practice: Primary Cutaneous Melanoma Guidelines

DISCLOSURES

I do not have any relevant relationships with industry.
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, including around biopsy site
  - Palpation of lymph nodes (regional and distant)
  - Consider abdominal exam for:
    - large tumors with satellite, in-transit, or regional nodal metastasis at presentation
    - uveal melanoma
Additional Studies for Workup of Newly-diagnosed Pts

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 studies?

- NO good data to support in **asymptomatic patients**
  - 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 and morbidity** from more invasive tests
Screening Bloodwork

- Available lab 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 or recommended in the US

Baseline Imaging Studies: Chest X-ray

- Multiple studies (retro- and prospective) have found consistent false-positive rates.
- True positive rate 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.

Baseline Computed Tomography (CT)

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

- Study of 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 costly/invasive studies, increased patient anxiety

Positron Emission Tomography (PET)

- More sensitive/specific than CT for melanoma staging, but more costly; usually integrated with CT

- Highest utility:
  - detection of DISTANT METASTASIS in the setting of suspected melanoma recurrence
  - extent of disease work-up for documented recurrence
  - surveillance of metastatic (stage III/IV disease)

- Positive scan may impact further surgery and/or need for systemic therapy

- Not a substitute for sentinel lymph node biopsy (SLNB) in primary melanoma patients

Melanoma Work-Up/ Follow-up

- Careful Hx and PE detect metastasis, **NOT** baseline or surveillance studies
  - Labs never sole indicator of metastatic disease; CXR rarely
  - 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 **not associated with improved survival** –this may change with newer therapies

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 57% metastasis (mostly distant)
  - Clinical exam (patient or provider) detected 49% (mostly skin, LNs)

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

NCCN: Baseline and Surveillance Studies

For all STAGE I and II Melanoma (including T4 lesions) at BASELINE:

- ROUTINE imaging/lab tests not recommended (e.g. LFTs, LDH, CXR)
- Imaging (CT scan, PET/CT, MRI) at baseline only to evaluate specific signs or symptoms

Same true for SURVEILLANCE:

- Routine blood tests not recommended
- Radiologic imaging (CXR, CT, PET/CT, brain MRI) indicated to investigate specific signs or symptoms
  - Screening for asymptomatic recurrent/metastatic disease in Stage IA, IB, IIA pts not recommended
  - Optional for Stage IIB-IV pts - consider CXR, brain MRI, or PET-CT q3-12 months
  - No tests recommended for asymptomatic pts of ANY STAGE after 3-5 years!

AAD CPG 2011 and 2018

● 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 recommended

Propective 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 United States!

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 (at baseline or in follow-up)
  - 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 pathologic information provided by SLNB or CLND
CLND following a +SLNB does not appear to affect overall survival

- Phase III randomized Dermatologic Cooperative Oncology Group Trial
  - Limitations: only 3-yr f/u, lower risk tumors in gen, no Head/Neck melanomas

- Multicenter Selective Lymphadenectomy Trial II (MSLT-2)
  - Lymphedema observed in 24% of pts s/p CLND vs 6.3% obs group
  - Conclusion: immediate CLND increases rate of regional disease control but NOT melanoma specific survival

- NCCN guidelines – Active nodal basin surveillance or CLND

What About Newer Molecular Techniques?

- **NCCN:** “While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate 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 or trial.”
  - Newer prognostic molecular techniques **should not replace** standard staging procedures
  - 31-gene prognostic GEP: not a substitute for SLNB; more data needed to incorporate into staging schemes

- **AAD:** “Insufficient evidence to recommend routine molecular profiling assessment for baseline prognostication.
  - Molecular classification **should not be used** to alter management outside of current guidelines (NCCN/AAD)
  - Criteria for and utility of prognostic molecular testing, including GEP, in aiding clinical decision making (e.g., SLNB eligibility, surveillance intensity, imaging, and/or therapeutic choice) **needs to be evaluated** in the context of a clinical study or trial.

Baseline Testing for Oncogenic Mutations

- **NCCN:** Somatic mutational analysis (BRAF, NRAS, KIT, NTRK) recommended if patients are being considered for either routine treatment or clinical trials, but not in the absence of metastatic disease
  - Can be done on metastatic and not primary tissue

- **AAD:** Mutational analysis for BRAF or multigene testing of the primary lesion **not recommended** for CM patients who are NED unless required to guide systemic therapy or consideration of clinical trials

- **NEW:** BRAF mutation testing is recommended for patients with stage III melanoma at high risk for recurrence for whom future BRAF-directed therapy may be an option
  - includes patients eligible for adjuvant dabrafenib/trametinib
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
# AAD 2018 Melanoma Follow-up Schedule

Table XV. Suggested surveillance intervals and follow-up tests

<table>
<thead>
<tr>
<th>CM stage</th>
<th>Follow-up interval and duration</th>
<th>Examination</th>
<th>Radiologic* tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 MIS</td>
<td>At least every 6-12 mo for 1-2 y; annually thereafter</td>
<td>Physical examination with emphasis on assessment for local recurrence, particularly for the LM subtype, and full skin check to ascertain for new primary CM</td>
<td>None</td>
</tr>
<tr>
<td>Stage IA-IIA</td>
<td>Every 6 to 12 mo for 2-5 y; at least annually thereafter</td>
<td>Comprehensive history (review of systems) and physical examination, with specific emphasis on the skin and regional LNs</td>
<td>None</td>
</tr>
<tr>
<td>Stage IIB and higher</td>
<td>Every 3-6 mo for the first 2 y; at least every 6 mo for 3-5 y and at least annually thereafter</td>
<td>Comprehensive history (review of systems) and physical examination, with specific emphasis on the skin and regional LNs</td>
<td>May be performed for up to 3-5 y†</td>
</tr>
</tbody>
</table>

*CM, Cutaneous melanoma; LM, lentigo maligna; LN, lymph node; MIS, melanoma in situ.

*Including chest radiography (to screen for lung metastasis); computed tomography of the chest, abdomen, and pelvis; brain magnetic resonance imaging; and/or positron emission tomography—computed tomography. The frequency of imaging depends on the risk of recurrence.

†Highest risk period for relapse.
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 node-negative 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!