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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F079 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
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 positivity

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

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

Who should be imaged at baseline?
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 **does not affect survival** – will this change with the newer drugs?

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!

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

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
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)

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 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

Does Completion Lymphadenectomy Affect Overall Survival?

- **Phase III randomized Dermatologic Cooperative Oncology Group Trial**

- 483 pts randomized 1:1 to Obs vs CLND b/w 2006-2014 following +SLNB
  - **no differences** age, gender, location, ulceration, thickness (med 2.4 mm), # positive nodes, or tumor burden (size) in the SLN(s) - 66% with SLN mets ≤1 mm
  - At mean f/u 35 mos: 15% Obs arm and 8% CLND arm developed regional mets
  - **NO SIG DIFF** in 5 year relapse-free (67%), distant metastasis-free (77%), or melanoma-free (overall) survival (81%); 24% grade 3/4 adverse events CLND

- **Limitations**: 3-y f/u, lower risk tumors in gen

1934 patients with +SLNB assigned to immediate CLND vs nodal observation with ultrasound

- Mean MSS similar in dissection vs obs group (86% at 3 yrs)
- Rate of disease-free survival slightly higher in CLND group (68% vs 63%, P=0.05 at 3 yrs due to increased rate of regional nodal control
- Nonsentinel LN metastasis (11.5% in CLND group) strongly predicted recurrence

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

- SLN tumor burden, # positive nodes, thickness, ulceration predict non-SLN positivity

Faries MB et al. NEJM 2017;376:2211-2222.
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 or trial.”

− DecisionDx® Castle Biosciences, Inc. (others not yet commercially available)

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

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

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!