Practice gaps in Dermatology: what can we do better for patients with melanoma

Svetomir N. Markovic, M.D, Ph.D
Markovic.svetomir@mayo.edu
Disclosures

• No relevant financial disclosures

• No off-label treatment use discussions
Much has changed in melanoma practice

- **Melanoma 2010**
  - Adjuvant stage III Rx: IFNa
  - Metastatic melanoma: DTIC, IL2

- **Melanoma 2017**
  - Adjuvant stage III Rx: ipilimumab, IFNa
  - Metastatic melanoma: ipilimumab, nivolumab, pembrolizumab, TVEC, vemurafenib, cobimetinib, dabrafenib, trametinib, DTIC, IL2
Where can we do better: survey Mayo Clinic’s practice
Room for improvement

- Diagnostics (primary melanoma of the skin)
  - College of American Pathologists (CAP) reporting template
  - AJCC 7th vs 8th edition
  - Molecular biomarkers of primary melanoma (predicting SLN status, or overall prognosis)
- Follow-up
  - Clinical follow-up guidelines for patients in NED (NCCN)
  - Liquid biopsies (lower cost)
  - Telemedicine
- Therapy
  - Take advantage of experimental therapy
  - Multi-disciplinary approach
  - Toxicity management especially with IO agents
- Standardization
**AJCC official instruction:** "In order to ensure that the cancer care community has the necessary infrastructure in place for documenting 8th Edition stage, the AJCC Executive Committee, in dialogue with the National Cancer Institute (NCI-SEER), Centers for Disease Control and Prevention (CDC), the College of American Pathologists (CAP), the National Comprehensive Cancer Network (NCCN), the National Cancer Data Base (NCDB), and the Commission on Cancer (CoC), made the decision to delay the implementation of the 8th Edition Cancer Staging System to January 1, 2018. All newly diagnosed cases through December 31, 2017 should be staged with the 7th edition."
SLN biopsy

• Standard of care, broad practice
• LN status influences prognosis
• If SLN+, proceed with LAN
  • MSLT-I (WLE w/wo SLN Bx)
  • MSLT-II (WLE+SLN Bx w/wo LAN)
• SLN biopsies are negative in roughly 8 of 10 times
• Can we better predict SLN status?
Final Version of 2009 AJCC Melanoma Staging and Classification

T stage

Stage I and II

N stage

Stage III

JCO 2009; 27(36):6199
Conclusions

Biopsy-based staging of intermediate-thickness or thick primary melanomas provides important prognostic information and identifies patients with nodal metastases who may benefit from immediate complete lymphadenectomy. Biopsy-based management prolongs disease-free survival for all patients and prolongs distant disease-free survival and melanoma-specific survival for patients with nodal metastases from intermediate-thickness melanomas.

Morton et al., NEJM 2014, 370:599
### SLN biopsy

<table>
<thead>
<tr>
<th>T stage</th>
<th>Permanent section + SLN (% of T stage)</th>
</tr>
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<tbody>
<tr>
<td>T1a (n=100)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>T1b (n=47)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>T2a (n=209)</td>
<td>28 (13%)***</td>
</tr>
<tr>
<td>T2b (n=27)</td>
<td>8 (30%)</td>
</tr>
<tr>
<td>T3a (n=84)</td>
<td>24 (29%)</td>
</tr>
<tr>
<td>T3b (n=39)</td>
<td>20 (51%)</td>
</tr>
<tr>
<td>T4a (n=29)</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>T4b (n=25)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Tx (n=11)</td>
<td>6 (55%)</td>
</tr>
<tr>
<td><strong>Overall (n=571)</strong></td>
<td><strong>133 (23%)</strong></td>
</tr>
</tbody>
</table>

**T1** ≤1.0
- a: w/o ulceration and mitosis <1/mm²
- b: with ulceration or mitoses ≥1/mm²

**T2** 1.01–2.0
- a: w/o ulceration
- b: with ulceration

**T3** 2.01–4.0
- a: w/o ulceration
- b: with ulceration

**T4** >4.0
- a: w/o ulceration
- b: with ulceration

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James W. Jakub, MD
Can SLN status be better predicted?

\[ \Delta t: 0-90 \text{ days} \]

Dx Melanoma \rightarrow SLN biopsy

Melanoma included:
- T1 with risk factors (‘thin’ lesions)
- T2 and T3 (‘intermediary’ thickness)
- T4 excluded
- All with SLN biopsy

Risk factors:
1. Ulceration
2. Mitotic rate
3. Age < 40 years

Cohorts (JCO paper):
- **Development**
  - 363 unique consecutive patients
  - Mayo Clinic MN, AZ, FL
- **Validation**
  - 146 unique consecutive patients
  - Mayo Clinic MN, AZ, FL
  - Copenhagen, DK

*Meves et al, JCO, 2015, 33(23):2509*
Clinicopath vs. Clinicopath + Molecular

Development Cohort

Validation Cohort

Meves et al, JCO, 2015, 33(23):2509
Updated Validation Cohort

Cohorts: Validation
- 444 unique consecutive patients
- Mayo Clinic MN, AZ, FL
- Copenhagen, DK
- Zurich, CH

<table>
<thead>
<tr>
<th></th>
<th>SLNB +</th>
<th>SLNB -</th>
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</thead>
<tbody>
<tr>
<td>Model +*</td>
<td>96</td>
<td>79</td>
</tr>
<tr>
<td>Model -</td>
<td>3</td>
<td>266</td>
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<table>
<thead>
<tr>
<th></th>
<th>Σ175</th>
<th>Σ269</th>
<th>Σ444</th>
</tr>
</thead>
<tbody>
<tr>
<td>Σ99</td>
<td>345</td>
<td>444</td>
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</table>

Sensitivity: 97%
Specificity: 77%
PPV: 55%
NPV: 99%

Alexander Meves, MD
Does LAN following + SLN Bx improve survival?

**Multicenter Selective Lymphadenectomy Trial II (MSLT-II)**

This study is ongoing, but not recruiting participants.
Sponsor: John Wayne Cancer Institute
ClinicalTrials.gov Identifier: NCT00297895

**Purpose:** Subjects must be diagnosed with melanoma. All subjects receive sentinel lymphadenectomy. If the subject is sentinel node positive and meets study requirements, the subject is randomized to receive either: (1) completion lymphadenectomy (2) observation with nodal ultrasound. Subjects are then followed for 10 years.

- Estimated Enrollment: 1925
- Study Start Date: September 2004
- Estimated Study Completion Date: September 2022
- Estimated Primary Completion Date: September 2022 (Final data collection date for primary outcome measure)
Better survival predictions in stage I/II patients

Identification of high-risk cutaneous melanoma tumors is improved when combining the online American Joint Committee on Cancer Individualized Melanoma Patient Outcome Prediction Tool with a 31-gene expression profile based classification

Laura K. Ferris, MD, PhD,a Aaron S. Farberg, MD,b Brooke Middlebrook, BS,c Clare E. Johnson, RN,c Natalie Lassen, PhD,c Kristen M. Oelschlager, RN,c Derek J. Maetzold, BS,c Robert W. Cook, PhD,c Darrell S. Rigel, MD,d and Pedram Gerami, MD,e,f

Pittsburgh, Pennsylvania; New York, New York; Friendswood, Texas; and Chicago, Illinois

Ferris et al., JAAD, Jan 2017
Results: Cox univariate analysis revealed significant risk classification of distant metastasis-free and overall survival (hazard ratio range 3.2-9.4, P < .001) for both tools. In all, 43 (21%) cases had discordant GEP and AJCC classification (using 79% cutoff). Eleven of 13 (85%) deaths in that group were predicted as high risk by GEP but low risk by AJCC.
Clinical follow-up after NED

• Clinical Stage IA, IIA
  • H&P with emphasis on skin and LN
    • Every 6-12 months for 5 years, then annual
  • Routine imaging is not recommended unless symptoms/signs driven
  • Routine blood tests not recommended
  • Educate patient on skin self exam
  • Equivocal LN exam: US should be performed
  • Follow-up schedule influenced by risk of recurrence and family history

• Clinical Stage IIB to IV NED
  • H&P every 3-6 months for 2 years, then 3-12 months for year 3, then annual as clinically indicated
  • Imaging as directed by signs/symptoms; consider every 3-12 months for high risk patients*
  • Routine imaging not recommended beyond 3-5 years
  • Regional LN US every 3-12 months for first 2-3 years
Liquid Biopsy

- Diagnosing tumors via blood tests
- Provide tumor “tissue” when anatomic biopsies are not practical or feasible
- Provide a more global (relevant??) assessment of tumor biology
- Monitor cancer genetics in evolution
- Monitor tumor burden during/after therapy
Cell Free Nucleic Acids

(Nat Rev Onc 2011. 11:426)
BRAF Mutations in Melanoma

- BRAF mutations occur in 40-50% of melanomas

- distribution of BRAF V600 mutations
  - V600E c.1799T>A (80-90%)
  - V600K c.1798_1799delGTinsAA (8%)
  - V600M (1%)
  - V600R (<1%)
Tissue Testing for V600 Mutations

- single analyte or NGS based testing
- long turn around time for test results*
- typically small tissue samples*
- melanin may interfere with PCR
- need for repeat biopsy at recurrence*
**cfDNA BRAF Mutation Detection**

- **47 melanoma patients** with tumors of known BRAF mutation status by routine tissue testing
- Pre-specified acceptance criteria for cfDNA testing
  - no false positives
  - 90% concordance between tissue results and cfDNA results

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<thead>
<tr>
<th></th>
<th>biopsy POS</th>
<th>biopsy NEG</th>
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</thead>
<tbody>
<tr>
<td>cfDNA POS</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>cfDNA NEG</td>
<td>11*</td>
<td>27</td>
</tr>
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- All 11 patients (*) were responding to Rx at time of sample

Minetta C. Liu, MD
Tele-dermatology
Advanced melanoma therapy

- **Multi-disciplinary approach**
  - Tumor boards

- **Always consider clinical trials**
  - Less than 3% of melanoma patients take part on clinical trials
  - Rapidly moving field
  - May options, low cost to patients

- **New drugs, new side effects (skin)**
  - BRAFi/MEKi
  - IO agents
Standardize care

Cancer Center Care Process Model (CPM) Development Process

Disease Group (DG) established
Multidisciplinary & Multisite
Membership specifically to include:
• Pathology
• Radiology
• Others, as appropriate

Update DG membership PRN

Establish annual CPM development goals

Engage Cancer Center NP and
dG members to develop CPM

CPM development with review of all
existing AME content
(incorporated or sunsetting)

Oncology Disease Groups are responsible for
developing CPM content involving their respective
tumor primary across the care continuum … from
screening to surveillance/survivorship

This typically involves identification of
one individual or small group as primary
contact point / resource for the initial
development of the clinical pathway

Involves extensive review of existing national and
society guidelines, primary resources, current
AskMayoExpert content over the course of
multiple meetings with primary author
(multidisciplinary, multisite input)
Summary: we are doing much better, but...

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• **Therapy**
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• **Standardization**
Thank you