Challenges in Melanoma Diagnosis and Management

Winter Clinical Dermatology Conference - Hawaii

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REFERENCES

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Darrell S. Rigel, MD
Challenges in Melanoma Diagnosis and Management

Castle – A, H, I

Cancer USA - 2017

Skin Cancer USA - 2017

More Skin Cancers than all other cancers combined

Melanoma - USA

Melanoma - USA

Rigel et al, NYU Melanoma Cooperative Group, 2017
**Melanoma – US 2017**

- **Invasive** = 87,100
- **In-situ** = 63,410

**US Cancer Statistics, 2017**

<table>
<thead>
<tr>
<th>Estimated New Cases</th>
<th>Male</th>
<th>Female</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>252,710</td>
<td>30%</td>
<td>252,710</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>134,950</td>
<td>14%</td>
<td>134,950</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>94,210</td>
<td>8%</td>
<td>94,210</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>81,280</td>
<td>7%</td>
<td>81,280</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>33,981</td>
<td>3%</td>
<td>33,981</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>20,790</td>
<td>2%</td>
<td>20,790</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>23,260</td>
<td>2%</td>
<td>23,260</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>9,700</td>
<td>1%</td>
<td>9,700</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>15,260</td>
<td>2%</td>
<td>15,260</td>
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<tr>
<td>All Sites</td>
<td>536,158</td>
<td>100%</td>
<td>536,158</td>
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</tbody>
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**US Melanoma % Annual Incidence Change by gender**

- **1975-85:** Male 5.4%, Female 5.5%
- **1985-2005:** Male 3.2%, Female 2.4%
- **2005-13:** Male 0.4%, Female 0.3%

Siegel et al., Ca J Clinics, 2017
Melanoma incidence was higher among females (age-adjusted incidence rate = 9.74) vs. males (age-adjusted incidence rate = 5.77) and increased with age.

Increases occurred over time for Females but not Males.

Conclusions:
- These data suggest areas for etiologic research around gene-environment interactions and the need for targeted cancer control activities specific to adolescents and young adult populations.

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For Melanoma:

Skin Cancer Deaths US - 2017

Over 1 American dies of Melanoma every hour

Do factors relating to Melanoma Incidence = those related to Melanoma Mortality?

For Melanoma:

Incidence ≠ Mortality

<table>
<thead>
<tr>
<th>Melanoma</th>
<th>Pancreatic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Death %</td>
<td>High Death %</td>
</tr>
<tr>
<td>Early detection effective</td>
<td>Early detection rare</td>
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<tr>
<td>Incidence ≠ Mortality</td>
<td>Incidence = Mortality</td>
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Melanoma Prevention

Primary

Secondary

<table>
<thead>
<tr>
<th>Melanoma</th>
<th>Pancreatic Cancer</th>
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<tbody>
<tr>
<td>Highest Incidence</td>
<td>Highest Mortality</td>
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<td>Highest Incidence</td>
<td>Highest Mortality</td>
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<tr>
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<td>CT</td>
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**UV and Melanoma**

*MM Incidence* is the measure of UV exposure behavior and MM development.

*MM mortality* is a measure of access to care and early detection.

Therefore, when evaluating melanoma prevention, we need to look at both types of prevention to be effective.

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**Comparison of Regional and State Differences in Melanoma Rates in the United States: 2003 vs 2013**

- The Northeast, specifically New England, is the only US geographic region in which most states experienced a reduction in both death and incidence rates.
- Strong skin cancer prevention programs likely played a role in this region’s success such as an initiative which funded sunscreen dispensers in public and recreational areas throughout Boston and other New England cities.
- **Conclusion:**
  - Such programs may enhance public awareness about skin cancer and may suppress the continual rise in melanoma.

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**Cost-Effectiveness of Skin Surveillance Through a Specialized Clinic for Patients at High Risk of Melanoma**

- Decision-analytic model to compare the costs and benefits of specialized surveillance vs. standard care over a 10-year period.
- Specialized surveillance through the High Risk Clinic was both less expensive and more effective than standard care.
- Mean saving was $6,828 (95% CI, $5,564 to $8,092) per pt.
- Mean quality-adjusted life-year gain was 0.31 (95% CI, 0.27 to 0.35).
- Main drivers of the differences were detection of melanoma at an earlier stage resulting in less extensive treatment and a lower annual mean excision vs. standard care.
- **Conclusions:**
  - Specialized surveillance was a cost-effective strategy for the management of individuals at high risk of melanoma.

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**Indoor Tanning in Diverse US Youth**

- Data from 2015 Youth Risk Behavior Survey.
- Non-heterosexual youths are at increased risk for skin cancer.
- Non-heterosexual youths (White, Hispanics and Blacks) have an increased usage of tanning beds.
- Non-heterosexual black youths have a higher tanning usage than white females.
Indoor Tanning in Diverse US Youth

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- Non-heterosexual youths are at increased risk for skin cancer
- Non-heterosexual youths (White, Hispanics and Blacks) have an increased usage of tanning beds
- Non-heterosexual black youths have a higher tanning usage than white females
- Conclusions:
  - Need to incorporate sexual orientation and ethnicity when developing skin cancer prevention programs for youth

Blashill et al., JAMA Dermatol. 2016

Early MMs Increasing Faster Than Advanced MMs

- 26,736 people diagnosed with thin melanomas
- 20-year survival was 96%
- Most influential determinants of prognosis were thickness ≥ 0.75 mm (HR 4.33 vs. tumors < 0.25 mm) and patient age at diagnosis >65 years (HR 2.6) vs. age <25 years.
- Acral lentiginous and nodular tumors, male gender, tumor site on the scalp or neck, or tumor invasion of the entire papillary dermis each independently increased the risk of dying from thin invasive melanoma
- Conclusions:
  - Clinical vigilance is warranted for patients with thin melanomas

Green et al., J Clin Oncol, 2014

Population-Based 20-Year Survival Among People Diagnosed With Thin Melanomas

- 2,243 patients with thin MMs (<1mm) were retrieved from databases at 6 centers with 124 mons follow up
- Worst prognosis categories were age >60 years, Breslow thickness >0.75 mm, Mitotic Rate≥ 1, ulceration, presence of LVI, and regression ≥ 50%.
- Breslow thickness >0.75 mm, Mitotic Rate≥ 1, ulceration, and LVI were significantly associated with SLN+.
- Conclusions:
  - Mortality associated with thin melanomas
  - Pts need to be followed closely

Maurichi et al., J Clin Oncol, 2014

Prediction of Survival in Patients With Thin Melanoma: Results From a Multi-Institution Study

- More people die from thin melanomas than thick melanomas
- 4,218 Australians who died from melanoma between 1990 and 2009, thin melanomas (<1mm) accounted for 23% of melanoma deaths overall
- More people died from thin melanomas (296 deaths, 23%) than from thick melanomas more than 4 mm in thickness (186 deaths, 14%) or from metastatic presentations (207 deaths, 16%).
- Conclusions:
  - More people with thin melanomas die than with thick melanomas because there are so many more thin lesions

Whiteman and Olsen, WCCS 2014

Melanoma US by Disease Stage

- 96% Localized
- 11% Regional
- 3% Distant

Pollack et al., J Amer Acad Dermatol, 2011
**Recurrence Probability by Stage**

Turner et al, J Clin Oncol, 2011

**Invasive MM US Cases by Thickness**

SEER 1992-2003

Landow et al, SID poster, 2016

**Invasive MM US Deaths by Thickness**

SEER 1992-2003

Landow et al, SID poster, 2016

**Detection of Occult Invasion in Melanoma In Situ**

- Unequivocal MMIS without associated nevi or regression was identified using a consecutive sample of 33 cases
- 3 sequential slides were stained with H&E and melan-A.
- Melan-A–stained slides showing definitive invasion were double-stained with Sry-related HMG-box gene 10 (SOX10) to confirm the melanocytic nature of the cells
- Occult invasive melanoma was detected in 11 of 33 consecutive cases (33%) of previously diagnosed MMIS
- 6 of 11 melanomas (55%) were diagnosable only by immunohistochemistry
- Conclusions:
  - History and physical examination including regional lymph nodes, education, and surveillance recommendations should be based on a very low, but not zero, risk of metastasis for MMIS

Bax et al. JAMA Dermatol, 2016

**Pathology Review of Thin MM and MMIS**

Impact on Treatment Decisions

- Overall pathologic discordance rate in diagnosis 4% (15/420 pts)
- Overall change in tumor staging rate 24% (97/405 pts)
- Changes in surgical excision margins in 12% of pts (52/420 pts)
- Decision about performing a sentinel lymph node biopsy in 16% of pts (67/420 pts)
- Conclusions:
  - Review of thin MM or MMIS by an expert dermatopathologist results in frequent, clinically meaningful alterations in diagnosis, staging, prognosis, and surgical treatment

Santillan et al, J Clin Oncol, 2010

**Impact of Genetics on Melanoma Diagnosis and Prognosis**

Santillan et al, J Clin Oncol, 2010
What does the myPath test do?

- Premise: Benign and malignant melanocytic lesions behave differently (invasion, metastasis, immune function etc.) and this is associated with expression of different (and/or different amounts of) RNAs.
- Identified a panel of 23 genes that are differentially expressed in benign and malignant melanocytic lesions and has developed a myPath test that
  - purifies RNA from the tissue;
  - quantifies how much of each of the 23 RNAs is expressed; and
  - applies a mathematical algorithm to objectively determine if the lesion is benign or malignant based on the expression pattern.

Prognostication in Melanoma: “Holy grail” in melanoma biology

Problems with Histologic Variables and Prognosis

- Inability to apply to partial biopsies in many cases. AJCC recommendations based on excisions
- Stages are confusing; difficult to understand for both patients and physicians
- Many criteria are subjective, ie, ulceration, regression, Clark’s levels, vertical growth phase, Breslow’s thickness, vascularity, presence of TIL
- Some criteria cannot be quantified, ie, ulceration: reported as “present or absent”
- Questions about mitoses
- Ignores host immunity and other host factors
- A more objective, more accurate method is sorely needed

Currently, most significant prognostic techniques for melanoma are AJCC criteria and Sentinel Lymph Node status

What if we could non-invasively identify patients who will have aggressive disease?
Genetic Testing to Assist in Prognosis of Melanoma

- FDA approved test developed by Castle Biosciences, Friendswood, Texas
- Uses formalin-fixed, paraffin-embedded tissue
- Quantifies expression of 31 genes from primary tumor to develop a Gene Expression Profile (GEP)
- Applies a validation algorithm to classify patients as Class 1 (low) vs Class 2 (high) risk of developing metastatic disease within 5 years
- Could be early “reflex” test for melanoma to suggest prognosis if becomes practical and cost effective

GEP

- Uses formalin-fixed, paraffin-embedded tissue
- Quantifies expression of 31 genes from primary tumor
- Applies a validation algorithm
- Classifies patients as low vs. high risk

Class 1 test result:
Low Risk of metastasis within 5 years

Class 2 test result:
High risk of metastasis within 5 years

31 GEP Melanoma Analysis Summary

- This analysis shows that both SLNB positive status and DecisionDx-Melanoma Class 2 are important predictors of DMFS and OS.
- SLNB identified ~30% of patients who died, but 70% of patients who died were SLNB negative.
- Performing the 31 GEP-Melanoma assay in the SLNB negative cohort identified over 80% of those SLNB negative patients who developed distant metastasis and died.

Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: randomized trial survival analysis

- Previously published randomized trial (same researchers) of narrow (1 cm) versus wide (3 cm) excision margins in pts with thick cutaneous MMMs showed narrow margins were associated with an increased frequency of locoregional relapse
- Current guidelines advise a 2 cm margin for MMM >2 mm in thickness
- Multicenter trial at 59 hospitals
- 900 pts with one primary localized MM greater than 2 mm in Breslow thickness on the trunk or limbs (excluding palms or soles) were randomly assigned (1:1) to receive surgery with either a 1 cm or 3 cm excision margin following an initial surgery

Hayes et al, Lancet Oncol, 2016
Management of MM by US Dermatologists

- Email survey of US Dermatologists (n=510, 8% response rate) performed in August 2015
- Asked questions on how they evaluated and managed MM

Farberg et al. JAAD, 2016

Practice Setting Validation

<table>
<thead>
<tr>
<th>Setting</th>
<th>MM Survey</th>
<th>AAD Data</th>
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<tr>
<td>Academic/University</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>Dermatology Group</td>
<td>16%</td>
<td>10%</td>
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<tr>
<td>Multispecialty</td>
<td>45%</td>
<td>48%</td>
</tr>
<tr>
<td>Solo</td>
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<td>26%</td>
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</tbody>
</table>

Farberg et al. (AAD), 2016

Experience Validation: Years in Practice (YIP)

<table>
<thead>
<tr>
<th>YIP</th>
<th>MM Survey</th>
<th>AAD Data</th>
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<tbody>
<tr>
<td>0-10 YIP</td>
<td>27%</td>
<td>35%</td>
</tr>
<tr>
<td>11-39 YIP</td>
<td>52%</td>
<td>49%</td>
</tr>
<tr>
<td>31+ YIP</td>
<td>21%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Farberg et al. JAAD, 2016

Geographic Validation: Zip Code First Digit

<table>
<thead>
<tr>
<th>Zip Code First Digit</th>
<th>MM Survey</th>
<th>AAD Data</th>
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<tbody>
<tr>
<td>0</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>1</td>
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<td>13%</td>
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<td>2</td>
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<td>7</td>
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<td>8</td>
<td>3%</td>
<td>5%</td>
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<tr>
<td>9</td>
<td>9%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Farberg et al. (AAD), 2016

Melanoma Surgical Margins

<table>
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<tr>
<th>Thickness</th>
<th>Margins</th>
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</thead>
<tbody>
<tr>
<td>In-situ</td>
<td>5 millimeters</td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>1 centimeter</td>
</tr>
<tr>
<td>1 – 2 mm</td>
<td>1 – 2 centimeters</td>
</tr>
<tr>
<td>&gt;2 mm</td>
<td>2 centimeters</td>
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</tbody>
</table>

Surgical margins for melanoma in-situ

- 1072 patients with 1120 MMIS was studied. All lesions were excised by Mohs micrographic surgery with frozen-section examination of the margin.
- The minimal surgical margin was 6 mm, and the total margin was calculated by adding an additional 3 mm for each subsequent stage required.
- 86% of MMIS were successfully excised with a 6-mm margin; 9 mm removed 98.9% of MMIS.
- The superiority of 9-mm to 6-mm margins was significant (P < .001).
- Conclusions:
  - 5-mm margins for MM in-situ may be inadequate

Kunishige et al., J Am Acad Dermatol, 2012
Accuracy of initial shave biopsy as a predictor of final stage in pts with thin melanomas

- 81 thin melanomas (≤ 1mm) diagnosed via shave biopsy with positive deep and/or lateral margins
- Four cases (5%) had a change in stage or T level.
- Conclusions:
  - In the majority of cases (95%) the thickness from shave biopsy is predictive of the final stage

Misdiagnosis of Melanoma by Type of Biopsy
Negative impact of punch biopsy on accurate dx

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Punch Biopsy</th>
<th>Shave Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
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<tr>
<td>Tumor thickness</td>
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<td>Depth of Invasion</td>
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<td>Overall outcome</td>
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<td>Cox Regression</td>
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Management of MM by US Dermatologists

- Email survey of US Dermatologists (n=510, 8% response rate) performed in August 2015
- Asked questions on how they evaluated and managed MM
- Conclusions:
  - Guidelines only partially followed
  - Large differences in approaches
  - Differences in approaches by experience
  - Educational opportunity exists
  - Maybe guidelines may be need to be reviewed/revised

Challenges and Controversies in Treating Advanced Disease
**Targeting Approaches to Systemic MM**

- **BRAF inhibitors**
  - Interrupts the B-Raf/MEK step on the activation pathway – if the B-Raf has the V600E mutation
- **MEK inhibitors**
  - Inhibits the mitogen-activated protein kinase enzymes MEK1 and/or MEK2
- **PD-1 blockers**
  - Programmed death 1 (PD-1) receptor is a negative regulator of T-cell effector mechanisms that limits immune responses against cancer
- **CTLA-4 antibodies**
  - CTLA-4 inhibits T cell responses

**Safety Profile of Nivolumab Monotherapy: Pooled Analysis of Patients With Advanced MM**

- 576 patients, 71% experienced any-grade treatment-related AEs (most commonly fatigue [25%], pruritus [17%], diarrhea [13%], and rash [13%])
- 10% experienced grade 3 to 4 treatment-related AEs
- AEs (occurring in 49% of patients) were most frequently skin related
- Conclusions:
  - Treatment-related AEs with nivolumab monotherapy were primarily low grade, and most resolved with established safety guidelines

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**Programmed Death-Ligand 1 (PD-L1) and MM**

- Response to the Anti–Programmed Death 1 Antibody Pembrolizumab in MM
- 451 MM patients received pembrolizumab
- 344 (76%) had PD-L1–positive tumors
- Higher response rate and longer PFS (HR 0.76) and OS (HR 0.76) was observed ($P < .001$).
- Conclusions:
  - PD-L1 expression in pretreatment tumor biopsy samples was correlated with response rate, PFS, and OS
  - However, patients with PD-L1–negative tumors may also achieve durable responses

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**Pembrolizumab Better Than Ipilimumab in MM Regardless of PD-L1 Expression**

- 834 patients, of which 80% were PD-L1-positive and 18% were PD-L1-negative
- Pembrolizumab Better Than Ipilimumab Regardless of PD-L1 Expression
- Conclusions:
  - PD-L1 expression was associated with improved outcomes with pembrolizumab vs ipilimumab

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**Psychoeducational Intervention to Reduce Fear of Cancer Recurrence in Pts with a Prior MM**

- Pts with a MM hx commonly report a fear of cancer recurrence (FCR)
- Participants were randomly assigned to intervention (n = 80) or usual care (n = 84) using a newly developed psychoeducational resource with 3 telephone-based psychotherapeutic sessions over a 1 month period timed in accordance with dermatologic appointments.
- At 6 months, the intervention group reported significantly lower FCR severity, trigger, and distress scores than the control group in the baseline-adjusted models
- Conclusions:
  - This evidence-based psychoeducational intervention was effective in reducing FCR and stress and increasing melanoma-related knowledge in people concerned about recurrence or new melanoma