Melanoma
Prognostic Factors

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- I have no disclosures.
Objectives

- Review current melanoma staging system and predictive model
- Summarize clinical studies and current reviews on prognostic factors
- Address recent genetic biomarker development

Statistics

- It is estimated that 76,690 men and women will be diagnosed with and 9,480 men and women will die of melanoma of the skin in 2013 in the US.
- On January 1, 2010, in the United States there were approximately 921,780 men and women alive who had a history of melanoma of the skin.

• American Joint Committee on Cancer (AJCC) melanoma staging system defines prognosis based on the standard TNM Classification
  • Tumor
  • Regional Node
  • Distant Metastasis
• Staging → Prognosis → Treatment

**TNM**

• T: describes the primary tumor by its thickness, presence of ulceration and mitotic rate
• N: degree of lymph node involvement, subcategorized by micrometastasis and macroscopic disease
• M: the presence and location of distant metastatic disease
TNM Classification

- Predominately anatomic and pathologic staging
- Breslow thickness is the main prognostic factor
- Mitotic rate has replaced Clark level of invasion in the current staging system
Prognosis Determinations

- American Joint Committee on Cancer (AJCC) Melanoma Staging Database
- Multivariate analysis of 30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma to revise and clarify TNM classifications and stage grouping criteria.
- Melanoma-specific survival curves were generated according to the Kaplan-Meier product-limit method and were compared using the log-rank test.
Unadjusted Kaplan-Meier melanoma specific survival curves

T primary tumor classification

- Breslow depth (tumor thickness) is the main independent prognostic factors to define the local tumor burden.
  - Measured from top of the granular layer down to the lowest tumor cell.
  - Survivability decreases as the depth increases.
  - Mitotic rate and ulceration further subcategorize the Breslow depth to increase its prognostic accuracy.
Tumor thickness is the most powerful prognostic indicator. Wisco et al. Dermatology Clinics 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi-Square Value (1 df)</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
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<tr>
<td>Tumor thickness</td>
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<td>1.56</td>
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</tr>
<tr>
<td>Age</td>
<td>40.8</td>
<td>&lt;.0001</td>
<td>1.16</td>
<td>1.11-1.22</td>
</tr>
<tr>
<td>Gender</td>
<td>32.4</td>
<td>&lt;.0001</td>
<td>0.70</td>
<td>0.62-0.79</td>
</tr>
<tr>
<td>Site</td>
<td>29.1</td>
<td>&lt;.0001</td>
<td>1.38</td>
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</tr>
<tr>
<td>Clark level</td>
<td>8.2</td>
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<td>1.15</td>
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</table>

**Abbreviations:** CI, confidence interval; HR, hazard ratio.

### Breslow thickness and survival

<table>
<thead>
<tr>
<th>Thickness (Breslow)</th>
<th>10 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01mm to 0.5mm</td>
<td>96%</td>
</tr>
<tr>
<td>&gt;6.0 mm</td>
<td>42%</td>
</tr>
</tbody>
</table>
Mitotic Rate

- The mitotic rate is calculated by determining the area in the dermis with the highest number of mitotic figures which is called the “hot spot”.
- The number of mitotic figures is then counted in the hot spot and then extended to adjacent fields for area of $1\text{mm}^2$.
Ulceration

- Ulceration is defined as being present if there is a full-thickness epidermal defect.
- Also reactive changes, such as fibrin deposition and neutrophils; and effacement of the surrounding epidermis or reactive hyperplasia in the absence of trauma or a recent surgical procedure.
- Ulceration predicts a clinically significant lower survival rate for tumors of the same T category, raising them to the next T category’s risk level.

Tumor Classification

- Combining the 3 components of the T classification, the 2009 AJCC melanoma staging 5- and 10-year survival rates range from:

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year survival</th>
<th>10 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>97%</td>
<td>93%</td>
</tr>
<tr>
<td>T4b</td>
<td>53%</td>
<td>39%</td>
</tr>
</tbody>
</table>

(P<.0001)
Nodal Classification

- Number of nodes involved and whether the nodal involvement is microscopic (micrometastasis) versus clinically evident (macrometastasis)
- Number of nodes involved was the most predictive independent factors for survival in patients with regional nodal or in-transit/satellite (stage III) metastatic disease in the Cox multivariate analysis of the melanoma staging database.

<table>
<thead>
<tr>
<th>N</th>
<th>Number of Metastatic Nodes</th>
<th>Nodal Metastastic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>N1</td>
<td>1</td>
<td>a: Micrometastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis</td>
</tr>
<tr>
<td>N2</td>
<td>2–3</td>
<td>a: Micrometastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: In-transit metastases/satellites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>without metastatic nodes</td>
</tr>
<tr>
<td>N3</td>
<td>4+ metastatic nodes, or matted nodes, or in-transit metastases/satellites with metastatic nodes</td>
<td></td>
</tr>
</tbody>
</table>

Sentinel Lymph Node Biopsy

- Recommended for tumors >1mm Breslow depth
- Can be considered in patients with thin melanomas 0.75mm-1mm.
- Currently is only a staging and prognostic tool.
- There has not been proven therapeutic or survival benefit.
- The Multicenter Selective Lymphadenectomy Trial II will determine whether sentinel lymph node positivity followed by complete lymph node dissection (CLND) improves survival vs CLND after clinically detected nodes.
Nodal Classification

<table>
<thead>
<tr>
<th>Nodes</th>
<th>5 year survival</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 micro</td>
<td>71%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 macro</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>2 micro</td>
<td>65%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 macro</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>3 micro</td>
<td>61%</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>3 macro</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>+4 micro</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>+4 macro</td>
<td>36%</td>
<td></td>
</tr>
</tbody>
</table>

Metastasis Classification

- Melanoma is capable of spreading to any distant site
- The most common locations are the skin, soft tissues, lung, liver, brain, bone, and gastrointestinal tract.
- When analyzing prognosis by anatomic metastatic site, significant differences were found only when the sites are arranged into 3 categories:
  - distant skin/subcutaneous tissue/distant lymph nodes (M1a),
  - the lungs (M1b),
  - or any other visceral site (M1c).
Metastasis Classification

- Based on the 2008 AJCC melanoma staging database of 7972 patients with stage IV melanoma, survival was clinically significant at the 1-year mark with reported rates of 62%, 53%, and 33% for the 3 categories, respectively (P<.0001)

<table>
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<th>Degree of Metastasis</th>
<th>1 year survival</th>
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<tr>
<td>Distant skin/subcutaneous/LN</td>
<td>62%</td>
</tr>
<tr>
<td>Lungs</td>
<td>53%</td>
</tr>
<tr>
<td>Other Viscera</td>
<td>33%</td>
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LDH

- Only checked in patients with metastatic disease
- If elevated, survival rates decrease regardless of the site of distant metastatic disease.
- Upstages any metastatic patient to M1c classification

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<th>M</th>
<th>Site</th>
<th>Serum LDH</th>
</tr>
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<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>NA</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, of nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
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Other prognostic factors

Table 4

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Abbreviations: CI, confidence interval; HR, hazard ratio.
Adapted from Balch CM, Gershenwald JE, Soong SJ, et al.

Age

- Age is a highly significant and powerful predictor of survival in melanoma.
- A recent study examined 10,233 patients with localized melanoma and 775 patients with nodal metastases for the AJCC melanoma staging database.
- They found that melanoma is a different biological entity among younger and older patients, after controlling for all other variables.
Age

- Patients younger than 20 years of age had:
  - Primary tumors with slightly more aggressive features,
  - A higher incidence of sentinel lymph node metastasis,
  - But, paradoxically, more favorable survival than all other age groups.
- Patients >70 years old had:
  - Primary melanomas with the most aggressive prognostic features,
  - More likely to be head and neck primaries,
  - Were associated with a higher mortality rate than the other age groups.
  - Surprisingly, however, these patients had a lower rate of sentinel lymph node metastasis per T stage.
- Among patients between the two age extremes, clinicopathologic features and survival tended to be more homogeneous.
Gender

• Overall, men have a greater risk for having advanced disease with a poorer outcome.
• Using 68,495 invasive melanoma cases diagnosed from 1992 to 2005 in the SEER database, the risk of death for women was lower than for men (HR 0.76, 95% CI, 0.71–0.81).


Gender

• In another study investigating gender’s influence in cutaneous melanoma, 11,774 melanoma cases were analyzed for survival and disease progression by gender.
• This study found that women compared with men had a
  • HIGHER
    • Melanoma Specific Survival (HR 0.62, 95% CI, 0.56–0.70).
  • LOWER risks of
    • Progression (HR 0.68, 95% CI, 0.62–0.75),
    • Lymph node metastasis (HR 0.58, 95% CI, 0.51–0.65),
    • And visceral metastasis (HR 0.56, 95% CI, 0.49–0.65).

Gender

- In a study of 2,672 patients with Stage I or II melanoma, women have a consistent independent advantage in
  - Overall survival (adjusted HR 0.70)
  - Disease specific survival (adjusted HR 0.74)
  - Time to lymph node metastasis (adjusted HR .70)
  - Time to distant metastasis (adjusted HR 0.69)
- This was calculated to be a 30% relative prognostic advantage of female compared to male patients with melanoma.
- A similar study using 2,734 Stage III patients, continued to show female advantage even after metastasis to lymph nodes and distant sites.


Gender

- A recent study similarly supported a female survival advantage in adolescents and young adults with melanoma.

![Graph showing survival probability over time for different gender groups.]

Site

- Presence of a melanoma on an axial site conferred a worse prognosis than an extremity site.

<table>
<thead>
<tr>
<th>Site</th>
<th>5 year Melanoma Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face/Ears</td>
<td>90.2%</td>
</tr>
<tr>
<td>Trunk</td>
<td>91.2%</td>
</tr>
<tr>
<td>Extremities</td>
<td>92.5%</td>
</tr>
<tr>
<td>Scalp/Neck</td>
<td>82.5%</td>
</tr>
</tbody>
</table>

![Graph showing survival probability over time for different sites.]

Patients with scalp/neck melanoma died of melanoma at an increased rate (HR 1.84, 95% CI, 1.62–2.10) compared with the rate of patients with extremity melanomas.

<table>
<thead>
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<th>5 year survival</th>
<th>10 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp/Neck</td>
<td>83.1%</td>
<td>76.2%</td>
</tr>
<tr>
<td>All others</td>
<td>92.1%</td>
<td>88.7%</td>
</tr>
</tbody>
</table>

Using the SEER database during the years of 1992 to 2003 to further explain the aggressiveness of the scalp and neck location, patients with scalp and neck melanomas were:

- older (mean age at diagnosis, 58.8 vs 55.1 years),
- With thicker tumors (median thickness, 0.80 mm vs 0.63 mm),
- more commonly men (74% vs 54%),
- ulcerated (7% vs 5%),
- positive lymph nodes (7% vs 4%),
- classified as a nodular melanoma (10% vs 8%) or a lentigo maligna melanoma (12% vs 6%),

compared with melanomas in the face/ears, trunk, and extremities (P<.001 for all comparisons).
Prediction Tool

• The AJCC has created an online melanoma prediction tool (www.melanomaprognosis.org) to more accurately determine melanoma prognosis for localized and regional disease.
• The prediction tool expands on the AJCC melanoma staging system by generating a prognostic analysis based on the patient’s individual characteristics.
• There is a similar online predictor tool at http://www.lifemath.net/cancer/melanoma/outcome/

Sample patient

• 25 year old female with 1.0 mm Breslow, no ulceration on the leg. No lymph node involvement.

<table>
<thead>
<tr>
<th>Survival</th>
<th>1-Year</th>
<th>2-Year</th>
<th>5-Year</th>
<th>10-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year</td>
<td>99.8%</td>
<td>99.6%</td>
<td>98.1%</td>
<td>95.9%</td>
</tr>
<tr>
<td>(96.7% - 100%)</td>
<td>(96.3% - 99.8%)</td>
<td>(97.4% - 96.8%)</td>
<td>(94.4% - 97.4%)</td>
<td></td>
</tr>
</tbody>
</table>
## Sample patient

**Classification:** T1 N0 M0 AJCC Stage: Stage X  
**Cancer Mortality:** 5.3% 15-year Kaplan-Meier Cancer Death Rate  
**Life Expectancy:** The average life expectancy of women this age who do not have cancer is 56.4 years. (81 years total)  
**Years of Life Lost:** This cancer shortens that average life expectancy by 2.8 years.

## Other factors

- Transplant patients  
- HIV patients  
- Pregnant patients  
- Race  
- Genetic Biomarkers
Transplant

- A review of melanoma in transplant patients compared SEER melanoma data with organ transplant case series data.
- 724 melanoma cases from 638 transplant patients after receiving a solid organ were reviewed, representing the largest series of cases to date.
- This study showed that 3-year overall survival, regardless of Breslow thickness or the Clark level, was worse in all post-transplant patients with melanoma.

HIV

- Patients who are HIV positive with melanoma follow a similar pattern as solid organ transplant patients.
- A study found a significant reduction of overall survival compared with matched controls.
- There was no association between CD4 cell counts and tumor thickness.
- However, there was an inverse relationship between CD4 cell counts and time to first melanoma recurrence.
- This suggests a more aggressive course with an increased risk of mortality among patients who are HIV positive with melanoma.
Pregnancy

- Retrospective reviews from cases of melanoma in pregnant women from the 1970s and 1980s indicated a survival disadvantage in pregnant women.
- However, after controlling for age, race, stage, and tumor thickness, no significant difference is found.
- The overall survival is not significantly different for melanoma diagnosed before, during, or after pregnancy compared with age-matched non-pregnant women.

Race

- Melanoma occurs most commonly among whites (95%)
- A higher percentage of advanced and thicker melanomas occur among nonwhite individuals.
- A recent study calculated the MSS of different ethnic groups with invasive melanoma in the United States, using 288,741 melanoma cases from 1999 to 2006.
- Whites and Hispanics had lower rates of melanomas thicker than 4mm (5% and 8%, respectively) compared with 11% in each of the other racial groups.
- Overall 5-year MSS was lowest for blacks (78.2%), followed by Asian/Pacific Islanders (80.7%), American Indian (84.9%), and highest for whites (90.0%).
- The 5-year MSS was similar for localized melanoma among all racial and ethnic groups except blacks, which was slightly lower,
- There were no significant differences in the 5-year MSS for advanced melanomas.
Genetic Biomarkers

- There has been increasing data on melanoma biomarkers and specifically identifying prognostic genetic biomarkers.
- The genes involved in the genetic pathways that lead to melanoma have become a prime target for emerging therapies and may have significance in prognosis.
- The current most promising prognostic genetic biomarker is the BRAF oncogene.

BRAF

- The BRAF oncogene, encodes a serine-threonine protein kinase, is found in the Ras/mitogen activated protein kinase (MAPK) pathway.
- Mutated BRAF has been reported to be present in 33% to 47% of primary melanomas and 41% to 55% of metastatic melanomas.
- The mutated BRAF oncogene has been aggressively studied because its presence is successfully used by the new targeted molecular therapies.
BRAF pathway

BRAF and NRAS

- In a recent study, BRAF and NRAS oncogene mutation status was evaluated in 302 archived tissue samples of primary cutaneous melanoma.
- This study showed no overall prognostic value in melanomas with a BRAF mutation (codon 600) compared to wild-type BRAF.
BRAF

- In a similar recent study evaluating 197 patients with metastatic melanoma, a comparison of melanomas with the two most common BRAF mutations (V600E and V600K) with wild-type BRAF was conducted.
- Of the 197 patients, 48% of the patients were found to have a BRAF mutation.
- The most significant (P<.05) associations found in mutated BRAF melanomas were:
  - histopathologic subtype (superficial spreading or nodular melanoma),
  - presence of mitoses,
  - single or occult primary melanoma,
  - truncal location,
  - age less than 50 years at the time of diagnosis.
- Similar to previous studies regarding the prognostic value of BRAF, this study found that there was no significant difference in the DFI between mutated BRAF and wild-type BRAF.

Conclusions

- Keys to the prognosis in melanoma patients are multifactorial.
- The strongest prognostic factors are features of the primary tumor, namely Breslow depth, mitotic rate, and ulceration.
- Other factors such as age, gender, and other patient characteristics also influence the prognosis.
- Research is now focused on genetic biomarkers that may better predict the behavior of the melanoma cells and have a significant prognostic value.
References


