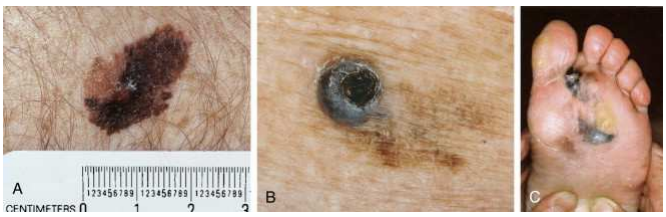


Melanoma Prognostic Factors

Andrea Murina MD
Assistant Professor
Tulane Department of Dermatology
September 25, 2013

- 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

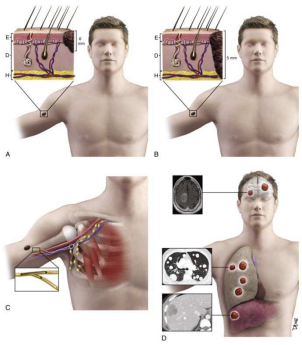
- It is estimated that 76,690 men and women will be diagnosed with and 9,480 men and women will die of **melanoma of the skin** in 2013 in the US.
- On January 1, 2010, in the United States there were approximately 921,780 men and women alive who had a history of melanoma of the skin.

Howlader et al (eds) *SEER Cancer Statistics Review, 1975-2010*, National Cancer Institute. Bethesda, MD,

- 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



Patnana, Madhavi., F.R.C.R. -Oncologic Imaging: A Multidisciplinary Approach, 633-652

Table 1
TNM melanoma classification

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤1.00	a: Without ulceration and mitosis <1/mm^2 b: With ulceration or mitoses ≥1/mm^2
T2	1.01–2.00	a: Without ulceration b: With ulceration
T3	2.01–4.00	a: Without ulceration b: With ulceration
T4	>4.00	a: Without ulceration b: With ulceration
N	Number of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis[a] b: Macrometastasis[b]
N2	2–3	a: Micrometastasis[a] b: Macrometastasis[b] c: In-transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in-transit metastases/satellites with metastatic nodes	
M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, of nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
[a] Micrometastases are diagnosed after sentinel lymph node biopsy.
[b] Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.
Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206; with permission.

Wisco et al. Dermatology Clinics 2012

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

Table 2
TNM melanoma staging

	Clinical Staging[a]				Pathologic Stagingt[b]		
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N > N0	M0	IIIA	T14a	N1a	M0
					T14a	N2a	M0
				IIIB	T14b	N1a	M0
					T14b	N2a	M0
					T14a	N1b	M0
					T1-4a	N2b	M0
					T14a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T14b	N2b	M0
					T14b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

[a] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
[b] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (ie, sentinel lode biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.
Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206; with permission.

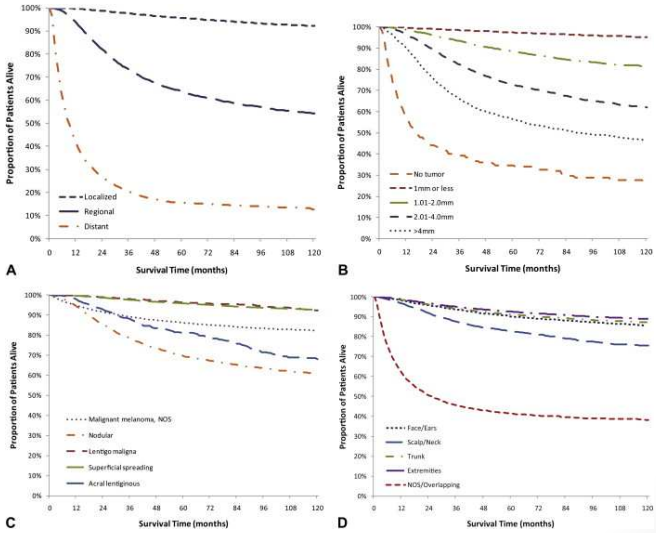
Wisco et al. Dermatology Clinics 2012

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.

Balch CM,. et al, editors. AJCC staging manual. 7th edition. New York: Springer; 2010. p. 325–44.

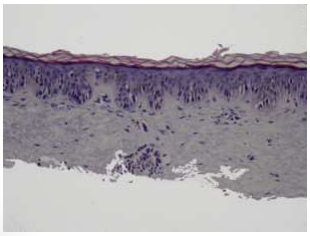
Unadjusted Kaplan-Meier melanoma specific survival curves

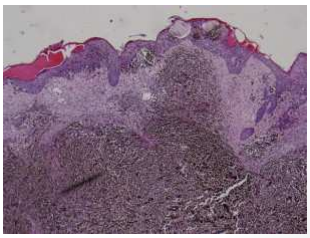


Pollack et al. J Am Acad Dermatol 2011

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.





Breslow A. Ann Surg 1970;172:902–8
Payette MJ et al. J Clin Dermatol 2009;27:53–74..

Table 4
Multivariate Cox regression analysis of prognostic factors in 10,233 patients with localized cutaneous melanoma (stage I and II)

Variable	Chi-Square Value (1 df)	P	HR	95% CI
Tumor thickness	84.6	<.0001	1.25	1.19–1.31
Mitotic rate	79.1	<.0001	1.26	1.20–1.32
Ulceration	47.2	<.0001	1.56	1.38–1.78
Age	40.8	<.0001	1.16	1.11–1.22
Gender	32.4	<.0001	0.70	0.62–0.79
Site	29.1	<.0001	1.38	1.23–1.54
Clark level	8.2	.0041	1.15	1.04–1.26

Abbreviations: CI, confidence interval; HR, hazard ratio.
Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al, editors. AJCC staging manual. 7th edition. New York: Springer; 2010. p. 325–44; with permission.

Tumor thickness is the most powerful prognostic indicator

Wisco et al. Dermatology Clinics 2012

Breslow thickness and survival

Thickness (Breslow)	10 year survival
0.01mm to 0.5mm	96%
>6.0 mm	42%

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 $1mm^2$

Balch CM., et al, editors. AJCC staging manual. 7th edition. New York: Springer; 2010. p. 325–44

Table 7
2008 AJCC melanoma staging database data on mitotic rate and survival

Number of Mitoses/mm²	n	Survival Rate ± SE 5 y	10 y
0–0.99	3312	0.973 ± 0.004	0.927 ± 0.007
1.00–1.99	2117	0.920 ± 0.007	0.842 ± 0.012
2.00–4.99	3254	0.869 ± 0.007	0.754 ± 0.012
5.00–10.99	2049	0.781 ± 0.011	0.680 ± 0.018
11.00–19.99	673	0.695 ± 0.022	0.576 ± 0.027
≥20.0	259	0.594 ± 0.039	0.476 ± 0.050
Total	11,664[a]		

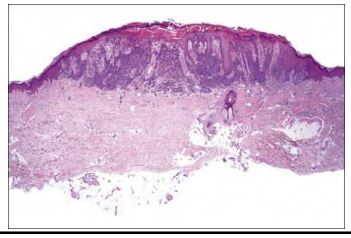
[a] Includes patients with mitosis, tumor thickness, and follow-up information available.

Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al, editors. AJCC staging manual. 7th edition. New York: Springer; 2010. p. 325–44; with permission.

Wisco et al. Dermatology Clinics 2012

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.



Balch CM., et al, editors. AJCC staging manual.7th edition. New York: Springer; 2010. p. 325–44

Tumor Classification

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

(P<.0001)

Stage	5 year survival	10 year survival
T1a	97%	93%
T4b	53%	39%

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.

N	Number of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis[a] b: Macrometastasis[b]
N2	2–3	a: Micrometastasis[a] b: Macrometastasis[b] c: In-transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in-transit metastases/satellites with metastatic nodes	

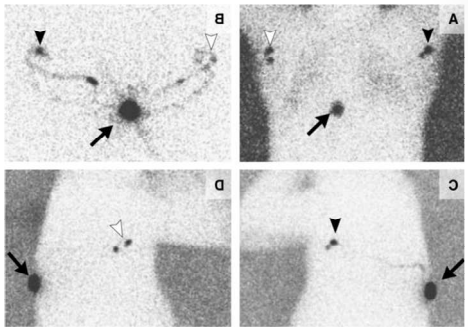
Balch CM, e al. J Clin Oncol 2009;27:6199–206.

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

Nodes	5 year survival	P value
1 micro	71%	<.001
1 macro	50%	
2 micro	65%	<.001
2 macro	43%	
3 micro	61%	<.004
3 macro	40%	
+ 4 micro	36%	
+ 4 macro	36%	



Ross, Merrick I., MD,Gershenwald Jeffrey E., MD - Clinics in Dermatology - Volume 31, Issue 3, 298-310

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).

Buzzell RA et al. J Am Acad Dermatol 1996;34:798–803
Balch CM et al. J Clin Oncol 2001;19:3622–34
Neuman HB et al. Ann Surg Oncol 2008;15:2034–41.

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)

Degree of Metastasis	1 year survival
Distant skin/subcutaneous/LN	62%
Lungs	53%
Other Viscera	33%

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

M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, of nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Other prognostic factors

Table 4
Multivariate Cox regression analysis of prognostic factors in 10,233 patients with localized cutaneous melanoma (stage I and II)

Variable	Chi-Square Value (1 df)	*P*	HR	95% CI
Tumor thickness	84.6	<.0001	1.25	1.19–1.31
Mitotic rate	79.1	<.0001	1.26	1.20–1.32
Ulceration	47.2	<.0001	1.56	1.38–1.78
Age	40.8	<.0001	1.16	1.11–1.22
Gender	32.4	<.0001	0.70	0.62–0.79
Site	29.1	<.0001	1.38	1.23–1.54
Clark level	8.2	.0041	1.15	1.04–1.26

Abbreviations: CI, confidence interval; HR, hazard ratio.
Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al, editors. AJCC staging manual. 7th edition. New York: Springer; 2010. p. 325–44; with permission.

Age

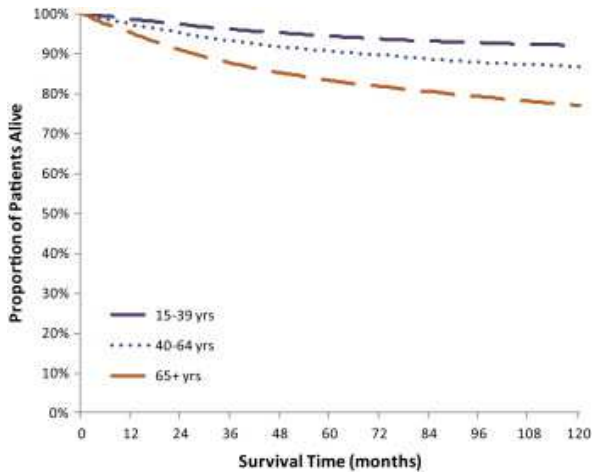
- Age is a highly significant and powerful predictor of survival in melanoma.
- A recent study examined 10,233 patients with localized melanoma and 775 patients with nodal metastases for the AJCC melanoma staging database.
- They found that melanoma is a different biological entity among younger and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

Balch CM et al. Ann Surg Oncol. 2013 Jul 10.

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.

Balch CM et al. Ann Surg Oncol. 2013 Jul 10



Pollack LA et al. J Am Acad Dermatol 2011;65:S78–86

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).

Pollack LA et al. J Am Acad Dermatol 2011;65:578–86

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).

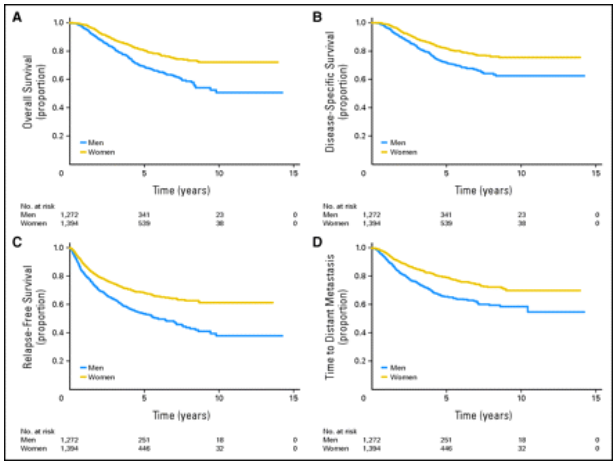
Joosse A et al. J Invest Dermatol 2011;131:719–26

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.

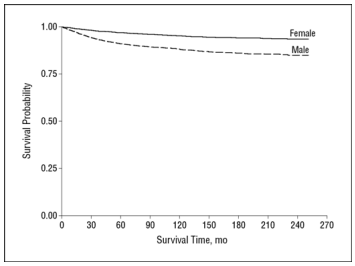
Joosse A et al. J Invest Dermatol 2011;131:719–26
Joosse A et al. J Clin Oncol. 2013 Jun 20;31(18):2337-46

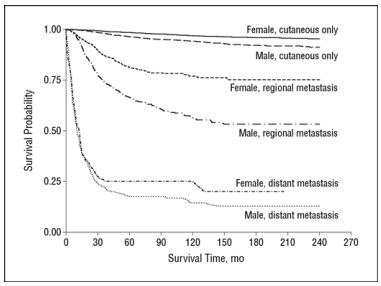
Gender



Gender

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





Gamba CS et al. JAMA Dermatol. 2013 Jun 26:1-8

Site

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

Site	5 year Melanoma Specific Survival
Face/Ears	90.2%
Trunk	91.2%
Extremities	92.5%
Scalp/Neck	82.5%

Pollack La et al. J Am Acad Dermatol 2011;65:S78–86.

Site

Site	5 year survival	10 year survival
Scalp/Neck	83.1%	76.2%
All others	92.1%	88.7%

- 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.

Site

- 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).

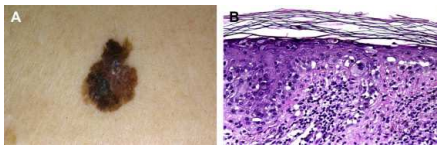
Lachiewicz AM et al. Arch Dermatol 2008; 144:515–21

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.



SURVIVAL			
1-Year	2-Year	5-Year	10-Year
99.8 %	99.6 %	98.1 %	95.9 %
(99.7 % - 100 %)	(99.3 % - 99.8 %)	(97.4 % - 98.8 %)	(94.4 % - 97.4 %)

Cockerell, Clay J., MD - Dermatologic Clinics - Volume 30, Issue 3, 445-468

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.

Brewer JD et al. Arch Dermatol 2011;147:790–6

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.

Rodrigues LK,et al. Arch Dermatol 2002;138:765–70

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.

Jhaveri MB, Clin Obstet Gynecol 2011;54:537–45.

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.

Wu Xc et al. J Am Acad Dermatol 2011;65:S26–37

Genetic Biomarkers

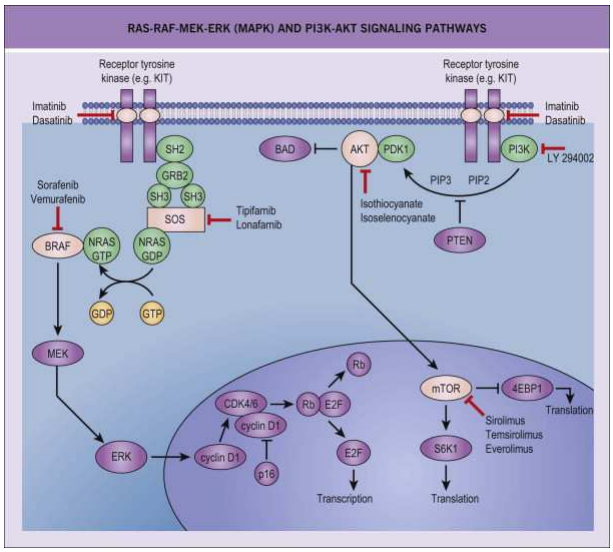
- There has been increasing data on melanoma biomarkers and specifically identifying prognostic genetic biomarkers.
- The genes involved in the genetic pathways that lead to melanoma have become a prime target for emerging therapies and may have significance in prognosis.
- The current most promising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

Long GV et al. J Clin Oncol 2011;29:1239–46.
Flaherty KT et al.N Engl J Med 2010;363:809–19.

BRAF pathway



Garbe, Claus,Bauer, Jürgen - Dermatology, 1885-1914

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.

Viros A et al. PLoS Med 2008;5:941–51.

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.

Long GV,. J Clin Oncol 2011;29:1239–46

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

- 1. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206.
- 2. Balch CM, Soong SJ, Gershenwald JE, et al. Age as a prognostic factor in patients with localized melanoma and regional metastases. *Ann Surg Oncol*. 2013.
- 3. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: Validation of the american joint committee on cancer melanoma staging system. *J Clin Oncol*. 2001;19(16):3622-3634.
- 4. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg*. 1970;172(5):902-908.
- 5. Brewer JD, Christenson LJ, Weaver AL, et al. Malignant melanoma in solid transplant recipients: Collection of database cases and comparison with surveillance, epidemiology, and end results data for outcome analysis. *Arch Dermatol*. 2011;147(7):790-796.
- 6. Brewer JD, Christenson LJ, Weaver AL, et al. Malignant melanoma in solid transplant recipients: Collection of database cases and comparison with surveillance, epidemiology, and end results data for outcome analysis. *Arch Dermatol*. 2011;147(7):790-796.
- 7. Buzzell RA, Zitelli JA. Favorable prognostic factors in recurrent and metastatic melanoma. *J Am Acad Dermatol*. 1996;34(5 Pt 1):798-803.
- 8. Flaherty KT. Is it good or bad to find a BRAF mutation? *J Clin Oncol*. 2011;29(10):1229-1230.
- 9. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med*. 2010;363(9):809-819.
- 10. Gamba CS, Clarke CA, Keegan TH, Tao L, Swetter SM. Melanoma survival disadvantage in young, non-hispanic white males compared with females. *JAMA Dermatol*. 2013:1-8.
- 11. Jhaveri MB, Driscoll MS, Grant-Kels JM. Melanoma in pregnancy. *Clin Obstet Gynecol*. 2011;54(4):537-545.
- 12. Joosse A, Collette S, Suciu S, et al. Sex is an independent prognostic indicator for survival and relapse/progression-free survival in metastasized stage III to IV melanoma: A pooled analysis of five european organisation for research and treatment of cancer randomized controlled trials. *J Clin Oncol*. 2013;31(18):2337-2346.
- 13. Joosse A, de Vries E, Eckel R, et al. Gender differences in melanoma survival: Female patients have a decreased risk of metastasis. *J Invest Dermatol*. 2011;131(3):719-726.
- 14. Lachiewicz AM, Berwick M, Wiggins CL, Thomas NE. Survival differences between patients with scalp or neck melanoma and those with melanoma of other sites in the surveillance, epidemiology, and end results (SEER) program. *Arch Dermatol*. 2008;144(4):515-521.
- 15. Lasithiotakis K, Leiter U, Meier F, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. *Cancer*. 2008;112(8):1795-1804.
- 16. Livestro DP, Kaine EM, Michaelson JS, et al. Melanoma in the young: Differences and similarities with adult melanoma: A case-matched controlled analysis. *Cancer*. 2007;110(3):614-624.
- 17. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol*. 2011;29(10):1239-1246.
- 18. Neuman HB, Patel A, Ishill N, et al. A single-institution validation of the AJCC staging system for stage IV melanoma. *Ann Surg Oncol*. 2008;15(7):2034-2041.
- 19. Payette MJ, Katz M,3rd, Grant-Kels JM. Melanoma prognostic factors found in the dermatopathology report. *Clin Dermatol*. 2009;27(1):53-74.
- 20. Pollack LA, Li J, Berkowitz Z, et al. Melanoma survival in the united states, 1992 to 2005. *J Am Acad Dermatol*. 2011;65(5 Suppl 1):S78-86.
- 21. Viros A, Fridlyand J, Bauer J, et al. Improving melanoma classification by integrating genetic and morphologic features. *PLoS Med*. 2008;5(6):e120.
- 22. Wisco OJ, Sober, AJ. Prognostic Factors for Melanoma. Dermatology Clinics. 2012: 469-485
- 23. Wu XC, Eide MJ, King J, et al. Racial and ethnic variations in incidence and survival of cutaneous melanoma in the united states, 1999-2006. *J Am Acad Dermatol*. 2011;65(5 Suppl 1):S26-37.