Performance of a 31-gene expression profile (GEP) test for metastatic risk prediction in cutaneous melanomas (CM) of the head & neck

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Background

- The anatomic complexities of the head and neck region can pose challenges to accurate staging of melanoma by sentinel lymph node (SLN) biopsy, as tumors in this area are associated with higher rates of false negative results compared to other anatomical areas.[1]
- A gene expression profile (GEP) test measures the expression of 31 genes from the primary tumor to classify metastasis risk has been clinically validated.[2,3]
- The GEP test has been shown to improve staging by identifying over 70% of patients, including clinically and pathologically node-negative patients, who develop distant metastasis or die from their disease.[2,3]

Methods

- Of 690 subjects with stage I-III melanoma and long-term follow-up (≥5 years if no event) who were evaluated during the validation of the GEP test, a total of 157 subjects with primary melanoma tumors in the head and neck region were identified. Tumor samples and associated clinical data were collected under an IRB-approved protocol.
- The RT-PCR-based GEP test was performed to determine expression levels of 28 prognostic genes and 3 control genes, and Radial Basis Machine modeling was used to predict binary metastatic risk class for each case (Class 1 vs. Class 2).
- In addition to binary Class, subclassification (A or B) reflects risk refinement based on the proximity of an individual's probability score to the crossover point between Class 1 and 2, with "A" reflecting better and "B" reflecting worse prognosis within a class.
- Recurrence-free survival (RFS; time to regional or distant metastasis), distant metastasis-free survival (DMFS; time to any metastatic event beyond the regional nodal basin) and melanoma-specific survival (MSS; time from diagnosis to death documented as specifically resulting from melanoma) were assessed. Survival rates by SLN status include clinically node negative patients.

References

1. Valsecchi ME, Silbermins D, de Rosa N, et al. JAMA Surgery 2011;29:1479-87.
2. Gerami P, Cook RW, Wilkinson J, et al. Clin Cancer Res 2015;21:175-83.
3. Gerami P, Cook RW, Russell MC, et al. J Am Acad Dermatol 2015;72:780-5 e783.

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Results

Table 1. Patient demographics

	All patients n=157	Class 1 n=79	Class 2 n=78	p value*
Median age (range), years	65 (25-89)	62 (25-89)	66 (25-85)	0.27
Regional and/or distant metastasis	73	19	54	<0.001
Distant metastasis	65	17	48	<0.001
Median time to metastasis/follow-up for nonmets, years	1.4/7.1	1.8/7.5	1.2/6.0	
AJCC stage				<0.001
I	64 (41%)	52 (81%)	12 (19%)	
II	51 (32%)	19 (37%)	32 (63%)	
III	42 (27%)	8 (19%)	34 (81%)	
Breslow thickness				<0.001
Median (range), mm	1.6 (0.2-15.0)	1.0 (0.2-6.0)	2.5 (0.6-15.0)	
≤1 mm	44 (28%)	39 (89%)	5 (11%)	
>1 mm	112 (71%)	40 (36%)	72 (64%)	
Unknown	1 (1%)	0 (0%)	1 (100%)	
Mitotic index				0.002
<1 mm^2	23 (14%)	17 (74%)	6 (26%)	
≥1 mm^2	84 (54%)	32 (38%)	52 (62%)	
Unknown	50 (32%)	30 (60%)	20 (40%)	
Ulceration				<0.001
Absent	92 (59%)	63 (68%)	29 (32%)	
Present	48 (31%)	7 (15%)	41 (85%)	
Unknown	17 (10%)	9 (53%)	8 (47%)	
Node status				<0.001
Negative	118 (75%)	72 (61%)	46 (39%)	
Positive	39 (25%)	7 (18%)	32 (82%)	

*p values indicate statistical differences between Class 1 and Class 2

Table 2. Cox multivariate regression analysis of GEP and other clinicopathologic factors. CI, confidence interval; HR, hazard ratio.

	RFS		DMFS		MSS	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Breslow thickness	1.2 (1.0-1.5)	0.02	1.3 (1.1-1.6)	0.008	1.4 (1.0-1.9)	0.03
Mitotic rate >1/mm^2	1.0 (0.9-1.0)	0.1	0.9 (0.9-1.0)	0.03	0.9 (0.8-1.0)	0.1
Ulceration present	1.2 (0.6-2.5)	0.5	2.0 (0.9-4.2)	0.07	0.9 (0.3-3.1)	0.9
SLN positivity	2.2 (1.1-4.1)	0.02	1.7 (0.8-3.4)	0.1	2.6 (0.8-8.6)	0.1
GEP Class 2	3.0 (1.3-7.1)	0.01	2.5 (1.0-6.3)	0.05	5.4 (0.9-30.6)	0.06

Results

Figure 1. Kaplan-Meier analysis of RFS by GEP subclass and node status. p values indicate statistical differences between Class 1A/Class 2B and node positive/node negative.

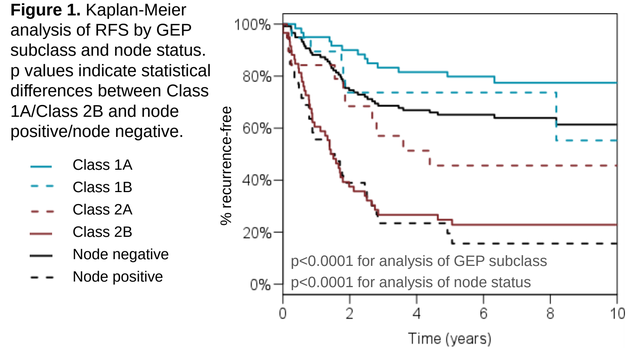


Figure 2. Kaplan-Meier analysis of DMFS by GEP subclass and node status. p values indicate statistical differences between Class 1A/Class 2B and node positive/node negative.

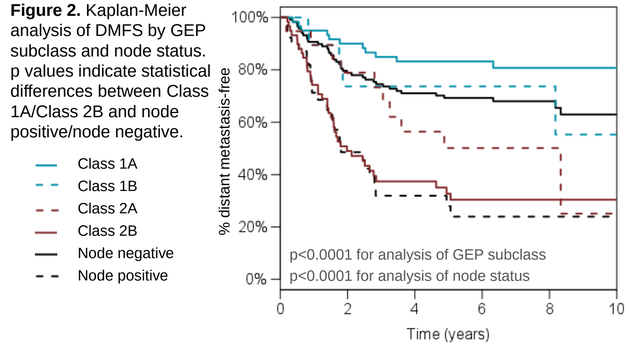
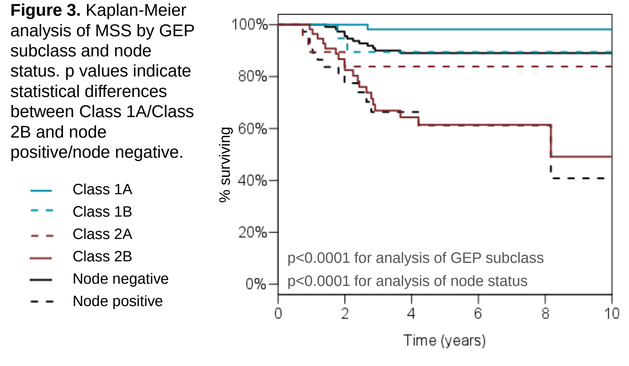


Figure 3. Kaplan-Meier analysis of MSS by GEP subclass and node status. p values indicate statistical differences between Class 1A/Class 2B and node positive/node negative.



Results

Table 3. 5-year RFS, DMFS and MSS rates according to subclass (Class 1A, 1B, 2A, or 2B).

	RFS		DMFS		MSS	
	5-yr rate (95% CI)	Events (rate)	5-yr rate (95% CI)	Events (rate)	5-yr rate (95% CI)	Events (rate)
Class 1A (n=60)	80% (70-91%)	13 (22%)	83% (74-93%)	11 (18%)	98% (95-100%)	1 (2%)
Class 1B (n=19)	74% (56-96%)	6 (32%)	74% (56-96%)	6 (32%)	90% (77-100%)	2 (11%)
Class 2A (n=19)	46% (28-76%)	10 (53%)	50% (31-80%)	10 (53%)	84% (69-100%)	3 (16%)
Class 2B (n=59)	25% (16-39%)	44 (75%)	33% (22-48%)	38 (64%)	61% (49-78%)	19 (32%)

Table 4. Five-year RFS, DMFS and MSS rates including 95% confidence intervals (CI) by GEP Class (n=157), node status (n=110), and both methods in combination (n=110).

	5-yr RFS (95% CI)	5-yr DMFS (95% CI)	5-yr MSS (95% CI)
Class 1 (n=79)	78% (70-88%)	81% (73-90%)	96% (92-100%)
Class 2 (n=78)	30% (21-42%)	37% (27-50%)	68% (57-80%)
Node neg (n=118)	65% (57-74%)	69% (61-78%)	89% (83-95%)
Node pos (n=39)	20% (10-40%)	28% (16-49%)	61% (46-82%)
Class 1/Node neg (n=41)	83% (75-92%)	85% (77-93%)	96% (91-100%)
Class 1/Node pos (n=7)	29% (9-92%)	43% (18-100%)	100% (100-100%)
Class 2/Node neg (n=30)	37% (25-54%)	45% (32-62%)	78% (66-92%)
Class 2/Node pos (n=32)	19% (8-42%)	24% (11-50%)	50% (33-78%)

Conclusions

- In a cohort of head and neck melanoma patients, GEP Class 2 identified 74% of patients who had a distant metastasis and 88% of patients who died from their disease.
- Patients with a low-risk (Class 1A) result showed lower RFS, DMFS, and MSS event rates than those with node-negative status.
- Patients with a high risk (Class 2B) result had similar RFS, DMFS and MSS rates as those with node-positive status.
- GEP testing could be a clinically useful tool for patients with melanoma of the head and neck following a node-negative result to identify those patients who may still be at high risk for metastasis.