Validation of a Model Combining Clinicopathologic Risk Factors and a Gene Expression Profile to Identify Primary Melanoma Patients Who Can Safely Forgo Sentinel Lymph Node Biopsy

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Background

- The sentinel lymph node biopsy (SLNB) procedure has gained importance now that primary cutaneous melanoma (PCM) patients with a positive sentinel lymph node are considered candidates for adjuvant systemic therapy.[1]
- SLNB is an invasive procedure, and approximately 80% of patients have no nodal metastasis. Many SLNB negative patients are exposed to invasive surgery but enjoy no discernible therapeutic benefit.[2,3]
- There is a need for a non-invasive test to accurately identify PCM patients who may forgo the SLNB procedure due to low risk of nodal metastasis.
- Previously, a clinicopathological and gene expression profile model (CP-GEP model) has been developed to identify PCM patients who can safely forgo SLNB. Moreover, a validation of the CP-GEP model in a European cohort has been reported.[4,5]

Objective

Validation of the CP-GEP model to identify primary melanoma patients who can safely forgo SLNB surgery.

Method & Design

- Patients who underwent SLNB at Mayo Clinic or West Virginia University within 90 days of PCM diagnosis (2004-2019) (Table 1).
- RNA was extracted from formalin-fixed paraffin-embedded diagnostic PCM biopsy tissue and reverse transcribed into cDNA.
- Gene expression of 8 target genes involved in melanoma metastasis (MLANA, GDF15, TGFBR1, CXCL8, LOXL4, PLAT, SERPINE2, ITGB3) and two housekeeping genes (RLP0 and B-ACT) were analyzed using RT-qPCR.[4]
- The CP-GEP model combines Breslow thickness and patient age with the expression of eight genes to classify patients as CP-GEP High Risk or CP-GEP Low Risk for nodal metastasis.

Table 1: Patient and tumor characteristics US cohort

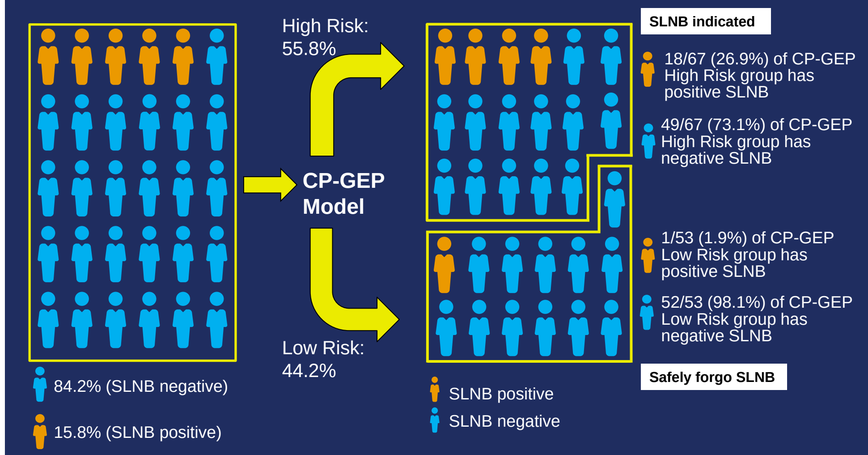
Characteristic	SLNB negative (N=130)	SLNB positive (N=32)
Male gender, n (%) (84 – 51.9%)	72 (55.4%)	12 (37.5%)
Age at primary melanoma diagnosis (years), Mean (SD)	56.2 (16.4)	55.1 (16.8)
Breslow depth (mm), n (%)		
0.5 – 1	57 (43.8%)	5 (15.6%)
1.1 – 2	44 (33.8%)	14 (43.8%)
2.1 – 4	18 (13.8%)	10 (31.3%)
> 4	11 (8.5%)	3 (9.4%)
Ulceration, n (%)		
Present	27 (20,8%)	10 (31.3%)
Absent	103 (79,2%)	22 (68,8%)
Mitotic rate type, n (%)		
Absent	36 (27.7%)	2 (6.3%)
1 – 6	79 (60.8%)	20 (62.5%)
> 6	15 (11,5%)	10 (31.3%)
Location, n (%)		
Head and neck	21 (16.2%)	5 (15.6%)
Trunk	50 (38.5%)	11 (34.4%)
Upper extremity	31 (23.8%)	5 (15.6%)
Lower extremity	23 (17.7%)	10 (31.3%)
Acral	5 (3.8%)	1 (3.1%)
Clark level, n (%)		
III	19 (14.6%)	0 (0.0%)
IV	89 (68.5%)	18 (56.3%)
V	3 (2.3%)	2 (6.3%)
Unknown	19 (14.6%)	12 (37.5%)
CP-GEP High Risk (108 – 66.7%)	77 (59.2%)	31 (96.9%)
CP-GEP Low Risk (54 – 33.3%)	53 (40.8%)	1 (3.1%)

Table 2: Performance CP-GEP Model in US cohort

T-Stage	n	Prevalence (%)	SENS (%)	SPEC (%)	NPV (%)	PPV (%)	SLNB Reduction Rate (%)
All	162	19.8	96.9	40.8	98.1	28.7	33.3
T1	62	8.1	80.0	66.7	97.4	17.4	62.9
T2	58	24.1	100.0	31.8	100	31.8	24.1
T3	28	35.7	100.0	5.6	100	37.0	3.6
T4	14	21.4	100.0	N/A	N/A	21.4	0.0
T1 & T2	120	15.8	94.7	51.5	98.1	26.9	44.2

Performance of the CP-GEP model stratified by T-stages with (n) is number of patients, (SENS) is the specificity, (SPEC) is the specificity, (NPV) is the Negative Predictive Value, (PPV) is the Positive Predictive Value. Also, shown is the performance of the CP-GEP model for the combined T1-T2 group of PCM patients.

Figure 1: Potential SLNB reduction rate for T1 & T2 melanoma using the CP-GEP Model



The CP-GEP Model shows a potential SLNB reduction rate of 44.2% for T1&T2 melanoma patients with a NPV of 98.1%.

Results

Cohort:

- Overall, 32/162 (19.8%) of patients had a positive sentinel lymph node.
- At diagnosis, the median patient age was 56 years.
- Most patients had thin to intermediate melanoma thickness (0.5 – 2 mm).
- 62/162 (38.2%) presented with T1 melanoma and 58/162 (35.8%) presented with T2 melanoma with a prevalence of 15.8%

CP-GEP:

- 108 patients (66.7%) were labeled CP-GEP High Risk and 54 patients (33.3%) were labeled CP-GEP Low Risk.
- 53 SLNB negative patients were identified as CP-GEP Low Risk.
- In patients with T1 to T2 melanoma, the combined CP-GEP model is able to achieve an SLNB reduction rate of 44.2%, while maintaining a high negative predictive value of 98.1%.

Conclusions

Validation study of the CP-GEP model based on age, Breslow thickness and primary melanoma gene expression of 8 genes:

- A non-invasive and validated molecular tool that is able to predict nodal metastasis in an US cohort which can be used to identify PCM patients who can safely forgo SLNB.
- The CP-GEP model is a promising tool for patient care, preventing unnecessary surgery in a large group of melanoma patients.

References

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Disclosures

A.B Yousaf has no conflict of interest.

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