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The Integrated i31-GEP Test Outperforms the MSKCC Nomogram at Predicting SLN Status in Melanoma Patients

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Abstract. *Background/Aim: Sentinel lymph node biopsy (SLNB) for patients with cutaneous melanoma is primarily a prognostic procedure that broadly identifies patients who may have disease progression and may warrant additional intervention. However, 88% of patients undergoing SLNB receive a negative result and of those, some will succumb to their disease. One clinical utility of the integrated 31-GEP test, which combines gene expression data with clinicopathologic factors to provide a personalized, precise risk of SLN positivity, is SLNB guidance. This study compared the i31-GEP for SLNB to a nomogram that predicts SLN positivity using only clinicopathologic factors. Patients and Methods: Patients with T1-T2 tumors and known SLN status (N=465) were analyzed by the i31-GEP for SLNB and a nomogram developed at Memorial Sloan Kettering Cancer Center (MSKCC). A 5% risk threshold was used to conform with national guidelines. Results: In patients with <5% predicted risk, SLN positivity was 2.7% (3/111) for i31-GEP versus 10.0% (11/110, p=0.026) for MSKCC. In each T-category, the i31-GEP maintained a false-negative rate below the 5% risk threshold in those predicted to have a <5% risk, while the MSKCC nomogram did not. Conclusion: Integrating the 31-GEP with traditional factors outperformed a nomogram that uses clinicopathologic factors alone to predict SLN status. Incorporating the i31-GEP into clinical practice could improve identification of patients for SLNB, resulting in better risk-aligned management.*

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In patients with cutaneous melanoma, sentinel lymph node biopsy (SLNB) is an invasive risk stratification procedure. Patients who have a positive SLNB have a higher population-based likelihood of disease progression compared to those with a negative SLNB (1).

The 31-gene expression profile test was developed and validated to identify patients at low (Class 1A), intermediate (Class 1B/2A), and high (Class 2B) risk of disease progression and SLN positivity (2, 3). Recently, the 31-GEP continuous risk score was integrated with clinical and pathological factors using a neural network algorithm to provide a personalized risk of SLN positivity (i31-GEP for SLNB). Combining the 31-GEP risk score with different clinical and pathological factors using Cox regression to predict a patient's risk of tumor recurrence, metastasis, or melanoma-related death [i31-GEP for risk of recurrence (ROR)], demonstrated clinical utility beyond SLN risk predictions, a utility lacking with both the clinicopathologic factor-only nomograms for SLN positivity prediction (4).

The National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma suggest considering patients for SLNB if they have between 5-10% risk of having a positive node [*i.e.*, T1b tumor or a T1a tumor with additional high-risk features, including mitotic rate ≥2/mm^2, lymphovascular invasion (LVI), and young age], and offering SLNB to patients with >10% risk of nodal positivity (T2-T4 tumors) (5). However, using these criteria results in an overall 12% positivity rate and generally <10% positivity rate in T1 tumors (6-12). In addition, it is unclear which patients with T1b-T2a tumors will benefit from SLNB-directed adjuvant therapy because >99% of SLN-positive patients are classified as stage IIIA, most with a tumor burden ≤1.0 mm (13). Most stage IIIA patients will not experience disease progression without any interventions, and it has previously been shown that patients with a low-risk outcome for both i31-GEP for SLNB and i31-GEP for ROR have a >99% 5-year melanoma-specific survival (4, 13).

To better identify candidates for SLNB, Memorial Sloan Kettering Cancer Center (MSKCC) developed a nomogram for predicting SLNB positivity in patients with cutaneous

Table I. *Patient demographics*.

Factor	T1a (n=72)	T1b (n=127)	T2a (n=210)	T2b (n=56)
Age (years), median (range)	57 (22-82)	62 (21-90+)	64 (22-90+)	69 (27-90+)
Mitotic rate (1/mm^2), median (range)	<1 (0-5)	1 (0-15)	2 (0-15)	2 (0-18)
SLN positivity, % (n/N)[1]	5.6% (4/72)	10.2% (14/127)	13.3% (28/210)	23.2% (13/56)
Tumor location, % (n/N)				
Hand and foot	1.4% (1/72)	4.7% (6/127)	2.9% (6/210)	7.1% (4/56)
Head and neck	20.8% (15/72)	19.7% (25/127)	15.7% (33/210)	10.7% (6/56)
Lower extremity	15.3% (11/72)	15.7% (20/127)	19.0% (40/210)	25.0% (14/56)
Upper extremity	19.4% (14/72)	18.9% (24/127)	21.0% (44/210)	17.9% (10/56)
Trunk	41.7% (30/72)	40.9% (52/127)	41.4% (87/210)	39.3% (22/56)
Not specified	1.4% (1/72)	–	–	–
i31-GEP <5%, % (n/N)	56.9% (41/72)	36.2% (46/127)	10.5% (22/210)	3.6% (2/56)
SLN positive, % (n/N)	4.9% (2/41)	2.2% (1/46)	0% (0/22)	0% (0/2)
MSKCC <5%, % (n/N)	73.6% (53/72)	29.9% (38/127)	9.0% (19/210)	0% (0/56)
SLN positive, % (n/N)	7.5% (4/53)	7.9% (3/38)	21.1% (4/19)	–

[1]Overall SLN positivity rate=12.5% (58/465). SLN: Sentinel lymph node; MSKCC: Memorial Sloan Kettering Cancer Center.

melanoma, which combines clinical and pathological factors (*i.e.*, age, tumor site, Breslow thickness, Clark level, and ulceration status) and uses logistic regression to predict a patient's risk (14). More recently, the Melanoma Institute Australia (MIA) developed a competitive clinicopathologic-based nomogram that includes age, Breslow thickness, ulceration, tumor subtype, mitotic rate, and lymphovascular invasion (LVI), and showed improved sensitivity and discrimination compared to the MSKCC nomogram (15). However, including tumor subtypes in an SLN prediction model may be problematic due to the well-documented significant discordance in diagnostic subtyping (16, 17). Additionally, Faries *et al*. noted that the 95% confidence intervals (CIs) reported by the MIA nomogram, particularly for thin tumors, are so wide (often ranging from <5% to >15% risk of positivity) as to question the clinical utility of the nomogram (17). A recent analysis of the MIA nomogram showed that in patients with T1-T2 tumors, only 0.9% (5/582) had <5% risk of SLN positivity with an upper 95%CI ≤10%, confirming Faries' concern about the lack of clinical utility of the MIA nomogram for SLNB decision-making (18, 19). Additionally, a recent study found that, compared to the clinicopathologic factor-only nomogram, the i31-GEP for SLNB identified more patients, and with higher confidence, as having <5% risk and an upper 95%CI below 10%, demonstrating superior clinical utility compared to the MIA nomogram (19).

Despite multiple independent and prospective studies confirming the performance of the 31-GEP and i31-GEP (20-25), the NCCN suggests comparisons between clinicopathologic-only tools to the GEP tests be performed to demonstrate that GEP testing provides independent and added value (5). The NCCN recommends comparing GEP tests to clinicopathologic nomograms. A previous study demonstrated the i31-GEP for SLNB outperformed the MIA nomogram in identifying patients at low risk of SLN positivity and with high confidence (19). Therefore, in the present study, we have compared the ability of the i31-GEP for SLNB and the other commonly referenced clinicopathologic nomogram, the MSKCC nomogram, to predict SLN positivity risk.

Patients and Methods

Patients with T1-T2 cutaneous melanoma tumors from a previously published multicenter cohort (18), who had known SLN status, i31-GEP for SLNB test results, and complete clinicopathologic factor information (to enable performance of the MSKCC nomogram) were included in this analysis. Patients were enrolled under one of three Western Institutional Review Board-approved studies from multiple surgical and dermatologic centers. Of the 886 T1-T2 tumors with known SLN status, 421 were not evaluable with the MSKCC nomogram due to the absence of one or more factors needed for analysis by the MSKCC nomogram, 94% of which were due to missing Clark level. The remaining patients (n=465) were retrospectively analyzed with the MSKCC nomogram, and it is therefore unknown whether clinicians had obtained the MSKCC risk score for the patients.

To conform with national guidelines, patients with a predicted risk of <5% were considered low risk and those with a predicted risk of ≥5% were considered high risk. To provide a risk of SLN positivity, the MSKCC nomogram uses patient data for age, tumor site, Breslow thickness, Clark level, and ulceration using logistic regression. The i31-GEP for SLNB incorporates the 31-GEP continuous risk score, Breslow thickness, ulceration status, mitotic rate, and age into a neural network-derived algorithm. The primary accuracy metrics calculated were sensitivity [true positive/(true positive+false negative)] and negative predictive value [NPV: true negative/(true negative+false negative)], both of which consider false-negative results (*i.e.*, predicted risk <5% but had a positive SLN). Secondary accuracy metrics were specificity [true negative/(true negative+false positive)] and positive predictive value [PPV: true positive/(true positive+false positive)]. Because MSKCC does not report 95%Cis, related analysis could not be compared in this study.

Table II. *True-to-false-negative sentinel lymph node biopsy (SLNB) ratio.*

Analysis method	Ratio (true-to-false-negative SLNB†)
T-category (Standard)	17:1 (68/4)
MSKCC (Clinical and pathological factors only)	9:1 (99/11)
i31-GEP for SLNB (31-GEP integrated with clinical and pathological factors)	36:1 (108/3)

†True-to-false negative ratios suggest that for every 100 patients avoiding SLNB based on the different methods, approximately 5.5 would have had a positive SLN using T-category, 10 would have had a positive SLN using MSKCC, which is worse than prediction using T-category alone, and 2.7 would have had a positive SLN using i31-GEP for SLNB, which is better than prediction using T-category alone. MSKCC: Memorial Sloan Kettering Cancer Center.

Table III. *Accuracy metrics.*

Prediction method	Sensitivity	NPV	Specificity	PPV
MSKCC	81%	90%	24%	13%
i31-GEP for SLNB	95%	97%	27%	16%

SLNB: Sentinel lymph node biopsy; MSKCC: Memorial Sloan Kettering Cancer Center; NPV: negative predictive value; PPV: positive predictive value.

To determine the number of patients per 100 who would avoid SLNB but would have a positive SLN, the ratio of true-to-false-negative results was compared between T-category, MSKCC, and the i31-GEP for SLNB. A false negative or true negative test result by MSKCC or the i31-GEP for SLNB was defined as a predicted SLN positivity risk <5% and an actual positive or negative SLN, respectively. Similarly, a false-negative or true-negative test result by T-category was defined as a T1a tumor and a positive or negative SLN, respectively. A 5% risk threshold was used to conform with NCCN standards for avoiding SLNB, and a 19:1 true-to-false negative ratio was considered the acceptable ratio of balancing avoiding SLNB and missing a positive SLN [*i.e.,* a 5% (1/20) positivity rate had the patients undergone SLNB]. The Chi-squared test was used to compare the false negatives between the i31-GEP and the MSKCC nomogram.

Results

The overall SLN positivity rate was 12.5% (58/465) in the study population (Table I). SLN positivity rate was 5.6% (4/72) in patients with T1a tumors, 10.2% (13/127) in patients with T1b tumors, 13.3% (28/210) in patients with T2a tumors, and 23.2% (13/56) in patients with T2b tumors (Table I). Among patients with T1a tumors (low risk), 68 had a negative SLN (true negative), and 4 had a positive SLN (false-negatives), resulting in a 17:1 (68/4) true-to-false-negative ratio, consistent with a 5% risk threshold (19:1 ratio) (Table II). This 17:1 ratio means that for every 100 patients avoiding SLNB using T-category, 5.5 would have had a positive SLN.

The MSKCC nomogram identified 23.7% (110/465) of patients as having a <5% predicted risk of a positive SLN. Among those considered to have <5% predicted risk, 48.2% (53/110) had a T1a tumor, with an actual 7.5% (4/53) SLN positivity rate; 34.5% (38/110) had a T1b tumor, with an actual 7.9% (3/38) SLN positivity rate; 19% (19/110) had a T2a tumor, with an actual 21.1% (4/19) SLN positivity rate; and 0% (0/119) had a T2b tumor. The overall SLN positivity rate in patients with <5% risk by MSKCC was 10% (11/110). Using the MSKCC nomogram resulted in a 9:1 true-to-false-negative ratio (99/11) (Table II). These data suggest that for every 100 patients avoiding SLNB using the MSKCC nomogram, 10 would have had a positive SLN.

The i31-GEP for SLNB identified 23.9% (111/465) of patients as having a <5% predicted risk of a positive SLN. Among those considered low-risk by the i31-GEP for SLNB, 36.9% (41/111) had a T1a tumor, with an actual 4.9% (2/41) positivity rate; 41.4% (46/111) had a T1b tumor, with an actual 2.2% (1/46) positivity rate; 19.8% (22/111) had a T2a tumor, with an actual 0% (0/22) positivity rate; and 1.8% (2/111) had a T2b tumor, with an actual 0% (0/2) positivity rate. The overall SLN positivity rate in patients considered to have <5% risk by the i31-GEP for SLNB was 2.7% (3/111), significantly (p=0.026) lower than the MSKCC nomogram. Using the i31-GEP for SLNB resulted in a 36:1 true-to-false-negative ratio (108/3) (Table II). The 36:1 ratio means that for every 100 patients avoiding SLNB using the i31-GEP for SLNB, 2.7 would have had a positive SLN, well below the 5% threshold established by national guidelines. The i31-GEP for SLNB had higher sensitivity (95% *vs.* 81%) and NPV (97% *vs.* 90%) than the MSKCC nomogram (Table III). When analyzing SLN positivity rates using a 10% threshold, those predicted by the i31-GEP for SLNB to have ≤10% risk had a 9.6% SLN positivity (30/311), while the MSKCC nomogram had an 11.4% (41/359) SLN positivity rate (data not shown).

Discussion

The decision to perform SLNB should be weighed in patients with cutaneous melanoma according to potential benefits and risks. Potential access to adjuvant therapy if a positive SLN is discovered could have life-saving implications. However, most patients will have a negative SLN, and most patients with stage I disease who have a positive SLN will be re-staged as stage IIIA, which has a 5-year survival rate of 93% without any adjuvant therapy (26). Further, for patients with thicker tumors (T3b-T4), SLNB may no longer be required for adjuvant therapy eligibility, and some argue that Breslow thickness alone is more predictive of poor outcomes than SLN status based on the analysis of each factor's hazard ratio (1, 27, 28). An analysis by Marchetti *et al*. showed that to find one additional patient who would go on to die from melanoma, compared to using clinicopathological features only, one would need to perform 142 SLNBs, after accounting for the potential harms of unnecessary SLNBs (29). Finally, SLNB does not predict who will respond to adjuvant therapy (30, 31).

Based on these limitations, the overuse of SLNB is a concern, and additional methods that predict which patients with cutaneous melanoma will have poor outcomes are needed. Studies have investigated the prognostic ability of various clinical features to provide better prognostication than standard staging alone (32, 33). A recent analysis found that the MIA and MSKCC nomograms did not provide an overall net benefit to selecting patients for SLNB (34). Additionally, the MSKCC nomogram was developed including Clark level; however, following the nomogram's development, mitotic rate replaced Clark level in staging criteria and guidelines only recommend inclusion of Clark level in pathology reports for nonulcerated lesions ≤1 mm in which mitotic rate is not determined (5). Because Clark level has not been included in guidelines for many years, it is very frequently omitted from the pathology report, questioning the utility of a nomogram that uses data not collected in many current reports.

A recent publication demonstrated that clinicians using the 31-GEP test to guide SLNB decision-making in patients with T1a-T2 tumors performed significantly fewer SLNBs compared to a contemporary cohort who did not use the 31-GEP to aid in SLNB decisions (35). However, evaluating the 31-GEP and the recently available i31-GEP for SLNB compared to alternative nomograms to select for SLNB can confirm the clinical value of incorporating *versus* not incorporating the 31-GEP/i31-GEP for SLNB into clinical practice. The ability of the i31-GEP for SLNB to reclassify patients into a risk category with a more definitive biopsy guideline demonstrates high utility for SLNB decision-making. In addition, a separate analysis by Marchetti *et al*. demonstrated that the i31-GEP for SLNB added benefit in patients with T1-T2 tumors compared to performing SLNB on all patients, which would result in a clinically meaningful reduction in SLNB procedures (36).

The current study showed that the i31-GEP for SLNB outperformed the nomogram developed by MSKCC in patients with T1-T2 tumors overall and in each T-category subgroup (Table I). The high sensitivity and NPV of the i31-GEP for SLNB show that patients considered low risk can have higher confidence of a negative SLN compared to relying upon the T-stage category or MSKCC nomogram result recommendations. In patients with T1 tumors, for whom guidance on the clinical decision to perform SLNB is least clear, the i31-GEP for SLNB could have reduced the number of SLNBs by 43.7%, compared with standard NCCN SLNB guidance using AJCC staging, while maintaining a low false-negative rate (Table I).

Limitations of the study are its retrospective design and the inherent limitations therein, including potential selection bias in study recruitment; however, the overall SLNB positivity rate was 12.5%, which is similar to previously published rates of 12% and suggests the cohort is not skewed regarding the overall risk level (6). In addition, only patients with all the necessary factors for analysis by the MSKCC nomogram could be included in the study, and it cannot be ruled out that a different data set could provide different results; however, as previously published, the MIA nomogram has previously been shown to outperform the MSKCC nomogram, and the i31-GEP has been shown to outperform the MIA nomogram (15, 19).

Conclusion

Similar to the recently published comparison of the i31-GEP and the MIA nomogram (19), the present study showed that the i31-GEP for SLNB also outperformed the MSKCC nomogram. These data are consistent with those from previous studies demonstrating the clinical utility of the 31-GEP and i31-GEP for SLNB to reduce unnecessary SLNBs, change management decisions concerning clinical visit frequency and imaging, and provide prognostic information independent from traditional staging factors. Incorporating the i31-GEP into clinical practice may help improve the accurate identification of patients for SLNB, thereby aiding in better risk-aligned management.

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Conflicts of Interest

BJM is an employee and stock/options holder at Castle Biosciences, Inc. MT and AMG have no related conflicts of interest.

Authors' Contributions

BJM designed the research, analyzed the data, and wrote the manuscript. MT, BJM, and AMG interpreted the data and revised the manuscript. All Authors read and approved the final manuscript.

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