Prospective multicenter evaluation of a clinicopathologic and gene expression profile test to predict sentinel node status in T1-T3 cN0 melanoma: updated MERLIN_001 trial

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Introduction

Guidelines recommend staging melanoma patients with sentinel lymph node biopsy (SLNB) for a predicted risk of SLN metastasis ≥10% and considering SLNB for 5-10% risk. A gene expression profile (GEP)-based test that accurately identifies patients with a low risk of SLN metastasis would help refine patient selection for SLNB, but current guidelines advise against using GEP for SLN risk prediction absent prospective trial data. This blinded prospective multicenter study evaluated the performance of a test combining clinicopathologic factors (age, Breslow thickness) with an 8-gene GEP (CP-GEP test) for predicting SLN status in patients undergoing SLNB.

Methods

Eligible patients with pT1-T3 cN0M0 cutaneous melanoma undergoing clinically indicated SLNB were prospectively enrolled in 11 melanoma referral centers in the United States. T1a patients could only be enrolled if at least one high risk feature was present: age <40, mitotic count ≥2 mm^2, or presence of lymphovascular invasion. The CP-GEP was performed on formalin-fixed, paraffin-embedded tissue from the primary tumor biopsy and results reported in binary fashion as Low or High Risk. The primary endpoint was negative predictive value (NPV) in Low Risk patients. Preplanned analyses included assessment by T substage and age.

Results

The GEP was successfully performed in 97.7% of samples. 1,755 patients of these patients underwent SLNB (17.6% SLN-positive); 37% were classified as Low Risk. Among all patients classified as Low Risk, the SLN was positive in 7.1% for an NPV of 92.9% (95% CI 90.7-94.8%). High Risk patients were SLN positive in 23.8%. Most T1b patients (67.6%) were Low Risk, with an NPV of 94.8% (95% CI 91.7-96.9%); fewer T2a patients were Low Risk (36.7%), with an NPV of 91.8% (95 CI 87.7-94.9%). The SLN positive rate in clinical stage IB patents classified as Low Risk (49.3% of all stage IB) was 6.6%, with an NPV of 93.4% (95% CI 91.1-95.3%). In clinical stage IIA/B, only 7.6% of patients were designated as Low Risk (17.1% SLN-positive). Test performance was consistent across age subgroups, including a SLN positive rate in Low Risk patients ≥65 years old of 6.6% (95% CI 4.2-9.7%).

Conclusion

In the first prospective multicenter blinded trial of a GEP prediction tool for SLN status, the CP-GEP test reliably identified patients with <10% risk of SLN metastasis, suggesting its potential to more precisely estimate individual patient risk of a SLN metastasis and inform shared decision-making for SLNB.

	SLN Positive Rate (95% CI)
Overall (n=1755)	17.6%
Low Risk (n = 650)	7.1% (5.2-9.3%)
High Risk (n = 1105)	23.8% (21.3-26.4%)
Clinical Stage IB (n = 1176)	12.5%
Low Risk (n = 580)	6.6% (4.7-8.9%)
High Risk (n = 596)	18.3% (15.3-21.6%)
Clinical Stage IIA/IIB (n = 539)	29.5%
Low Risk (n = 41)	17.1% (7.2-32.1%)
High Risk (n = 498)	30.5% (26.5-34.8%)
Age ≥ 65 yo (n = 828)	14.6%
Low Risk (n = 349)	6.6% (4.2-9.7%)
High Risk (n = 479)	20.5% (16.9-24.4%)