E.E.A.P. Mulder[a,b*], I. Johansson[c,d*], D.J. Grunhagen[a], D. Tempel[e], B. Rentroia-Pacheco[e], J.T. Dwarkasing[e], D. Verver[a], A.L. Mooyaart[f], A.A.M. van der Veldt[b,g], T.E.C. Nijsten[h], C. Verhoef[a], J. Mattsson[i], L. Ny[d,j], L.M. Hollestein[h,**], R. Olofsson Bagge[i,l**]

** Authors have contributed equally and are both considered first author*
*** Authors have contributed equally and are both considered last author*

Departments of [a]Surgical Oncology, [b]Medical Oncology, [g]Radiology & Nuclear Medicine, and [h]Dermatology, Erasmus MC Cancer Institute, Rotterdam, NL; [e]SkylineDx B.V., Rotterdam, NL; Department of [f]Pathology, Erasmus MC, Rotterdam, NL; [k]Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, NL; Departments of [c]Pathology, [i]Surgery, and [j]Oncology, Sahlgrenska University Hospital, Gothenburg, SE; Departments of [d]Oncology and [l]Surgery, Institute of Clinical Sciences at Sahlgrenska Academy, Gothenburg University, Gothenburg, SE.

Using a clinicopathologic and gene expression (CP-GEP) model in Europe to identify stage II melanoma patients at high risk for disease relapse.

Background

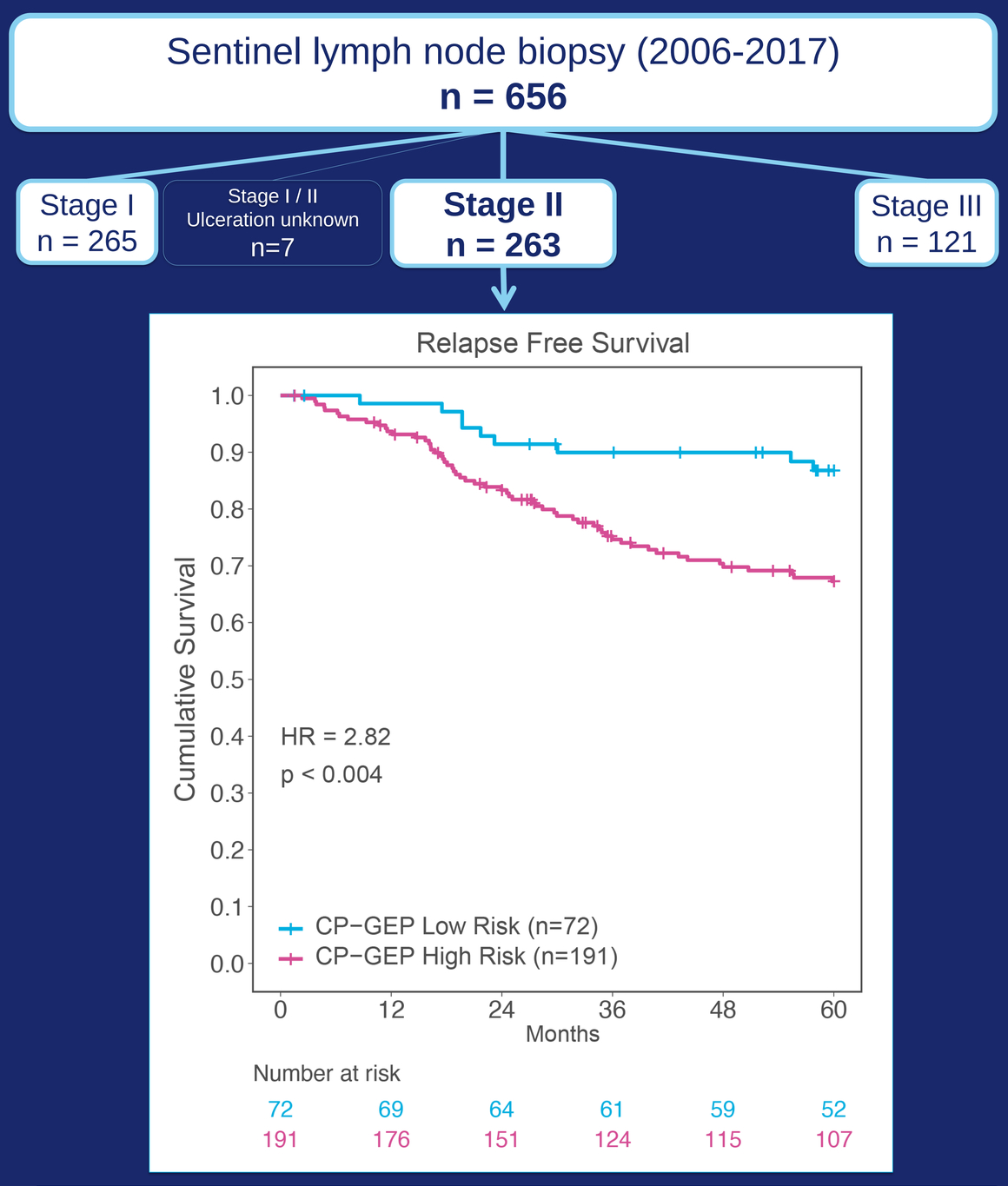
Patients with high-risk stage III melanoma are currently eligible for systemic adjuvant treatment. However, half of the melanoma patients presenting with disease recurrence were initially diagnosed with stage I-II melanoma. To identify patients at high risk for disease relapse in an early stage, new diagnostic tools are in development. One of these potential diagnostic tools is the CP-GEP model, combining clinicopathologic variables and gene expression measurements. The CP-GEP model was shown to be able to identify melanoma patients at high risk for disease relapse in stage IIA, with a five-year relapse-free survival (5y RFS) of 56%, compared to a 5y RFS of 78% in CP-GEP Low Risk patients. Since the CP-GEP model was developed in a US cohort, validation in a European cohort is warranted. This is the first time the CP-GEP model was used in Europe to identify stage II melanoma patients at high risk for disease relapse.

Methods

This study included patients with cutaneous melanoma patients aged ≥18 years who underwent sentinel lymph node biopsy (SLNB) at the Erasmus MC Cancer Institute (The Netherlands) and Sahlgrenska University Hospital (Sweden) between January 2006 and December 2017. The CP-GEP model combines clinicopathologic features (age and Breslow thickness) with the expression of eight target genes (*ITGB3, PLAT, SERPINE2, GDF15, TGFBR1, LOXL4, CXCL8 and MLANA*) in the primary tumor, that has already been excised. Patients were stratified according to their risk of relapse: CP-GEP High Risk or CP-GEP Low Risk, using a predefined cut-off value. The primary clinical endpoint of this study was 5y RFS.

Results

In total, 656 stage I-III patients were included in the study. Patients had a median age of 58 years (interquartile range [IQR] 47-69) and the median Breslow thickness was 1.9 mm (IQR 1.3-3.3). In the majority of patients who underwent SLNB, no SLN metastasis was found (i.e. stage I-II melanoma, n=535). Among all stage II patients (n=263), 5y RFS was 73% (95% CI: 67-78). CP-GEP stratification of these stage II patients resulted in a 5y RFS of 87% (95% CI: 76-93, CP-GEP Low Risk, n=72) versus 67% (95% CI: 60-74, CP-GEP High Risk, n=191) (HR 2.82, *p<0.004*). In comparison, 5y RFS in patients with nodal metastasis (stage III melanoma patients) was 53% (95% CI: 43-61).



	N	Events RFS	5-years RFS, 95%CI	
Stage II	263	67	72.8%	[66.7-77.9]
CP-GEP Low Risk	72	9	86.8%	[76.1-92.9]
CP-GEP High Risk	191	58	67.3%	[59.8-73.7]
Stage III	121	54	52.8%	[43.2-61.4]

Conclusions

The CP-GEP model is a non-invasive tool that can adequately identify stage II cutaneous melanoma patients at high risk for disease relapse within five years, as demonstrated in this European cohort. These results indicate the possible added value of using the CP-GEP model in current clinical practice. CP-GEP High Risk patients may benefit from therapeutic interventions or enhanced surveillance.

e.e.a.p.mulder@erasmusmc.nl