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Original Research

Risk stratification using the Merlin Assay (CP-GEP) in an independent cohort of 930 patients with clinical stage I/II melanoma who did not undergo sentinel lymph node biopsy

Teresa Amaral [a,b,*], Eftychia Chatziioannou [b], Alica Nuebling [b], Lena Nanz [b], Tobias Sinnberg [b], Heike Niessner [a,b], Tim Arentsen [c], Romy Ruiter [c], Jvalini Dwarkasing [c], Alexander M. Eggermont [d,e], Ulrike Leiter [a,b], Lukas Flatz [a,b], Stephan Forchhammer [b]

[a] Skin Cancer Center, Department of Dermatology, Eberhard Karls University of Tuebingen, Germany
[b] Department of Dermatology, University of Tuebingen, Germany
[c] SkylineDX B.V., Rotterdam, Netherlands
[d] University Medical Center Utrecht & Princess Maxima Center, Utrecht, Netherlands
[e] Comprehensive Cancer Center Munchen of the Technical University Munich & Ludwig Maximilians University, Munich, Germany

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ABSTRACT

Purpose: More than 80 % of patients with melanoma are diagnosed without nodal metastasis, but most of those who relapse or die from melanoma are initially diagnosed as low risk early-stage. Here we investigate the ability of the Merlin Assay to stratify patients who did not undergo sentinel lymph node biopsy (SLNB) for their risk of recurrence.

Patients and methods: 930 patients with clinical stage I/II primary cutaneous melanoma from the University of Tuebingen diagnosed between 2000 and 2020 were analyzed. None of the patients included underwent SLNB. The Merlin Assay combines patient age at diagnosis, Breslow thickness, and gene expression of eight specific genes from the primary tumor. Risk output labels are High Risk and Low Risk.

Results: Clinicopathological gene expression profile (CP-GEP) identified 879 patients as Low Risk and 51 patients as High Risk. The 10-year RFS (HR 20.07; $p < 0.001$) and DMFS (HR 19.39; $p < 0.001$) were significantly higher in CP-GEP Low Risk versus High Risk patients. Similar results were observed in 10-year MSS (HR 35.85; $p < 0.001$). CP-GEP analysis of lentigo maligna melanoma and acral lentiginous melanoma showed that the performance of assay was independent of melanoma histological subtypes.

Conclusion: This study shows that CP-GEP has the potential to stratify patients with early-stage melanoma who did not undergo SLNB based on their risk of recurrence. Patients with CP-GEP Low Risk have a significantly better long-term survival. CP-GEP shows to be promising for guiding SLNB referral and may support melanoma care by optimizing personalized treatment plans and potential surveillance regimens.

1. Introduction

Sentinel lymph node biopsy (SLNB) is the gold standard for staging primary cutaneous melanoma and pivotal in the decision making of subsequent patient care. However, SLNB is an invasive surgery with a proportion of patients experiencing postoperative complications such as infection and seroma [1,2]. Of all patients that undergo SLNB surgery, approximately 80–85 % are SLNB negative [3–5]. Patients with thin melanomas, in particular clinical stage IA patients, may not undergo SLNB surgery based on ineligibility according to (inter)national clinical guidelines [6–9] or other considerations such as frailty, co-morbidities, tumor location and patients decision or preference. In addition, SLNB positivity rates are low in patients with thin melanomas and may not prove justifiable given the invasive nature of the SLNB procedure, risk of complications, and burden on healthcare system [10–13]. Post operative lymphedema, in particular, can be persistent and can cause long-term decreased quality of life [14]. Despite the long-term favorable survival of patients with stage I melanoma [15], it was shown that the patients

* Correspondence to: Skin Cancer Center, Department of Dermatology, Liebermeisterstrasse. 25, Tuebingen 72 076, Germany.
E-mail address: teresa.amaral@med.uni-tuebingen.de (T. Amaral).

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with thin melanomas who relapse or even die of melanoma represent a large group in absolute numbers [16,17]. Moreover, currently there are no systemic therapies available for stage I-IIA patients, i.e., patients with either SLNB negative or who did not undergo SLNB. Since these constitute a significant portion of patients that eventually relapse or die of melanoma, better risk stratifying tools that are able to identify patients at high risk for recurrence or even death are warranted [18,19]. On the other extreme, overtreatment of early-stage melanoma patients is an important aspect, further underscoring the need for selection [20].

CP-GEP has previously shown to be able to risk stratify patients who did not undergo SLNB (n = 80 patients) [21]. Here, we investigated the performance of CP-GEP risk stratification in this same population but in a larger cohort.

2. Methods

2.1. Study population

The cohort for analysis consisted of 930 patients with clinical stage I/II cutaneous melanoma diagnosed between 2000 and 2020 from the University of Tuebingen who did not undergo SLNB. A total of 993 patient formalin-fixed paraffin-embedded (FFPE) primary tumor samples were available from the Central Malignant Melanoma Registry that met inclusion criteria, of which 930 were processed and analyzed (Fig. 1). Data analysis was based on the American Joint Committee on Cancer (AJCC) 8th edition staging system. The study was approved by the Ethics Commission of the Eberhard Karls University Tuebingen (653/2020B0) and conducted in accordance with consensus ethical principles derived from international ethical guidelines, including the Declaration of Helsinki.

2.2. CP-GEP

CP-GEP combines clinicopathologic features (patient's age at diagnosis and Breslow thickness) with the expression of eight genes from the primary tumor (*ITGB3, PLAT, SERPINE2, GDF15, TGFBR1, LOXL4, CXCL8,* and *MLANA)*, and two housekeeping genes (*RLP0* and *ACTB*) measured by quantitative reverse transcription polymerase chain reaction using the ΔCt method [22]. CP-GEP model has a binary output: Low Risk or High Risk. FFPE blocks from each primary tumor were retrieved from the dermato-pathology archives and a total of 50 micron was used as input for the gene expression profiling. Of 993 patients, the study excluded samples failing to meet the necessary quality and quantity (n = 61) and samples failing to meet clinical criteria (n = 2) leading to a final cohort of 930 patients (Fig. 1).

2.3. Statistical methods

Prognostic value of CP-GEP was evaluated by using Kaplan-Meier curves - stratification on CP-GEP output labels: Low Risk versus High Risk for disease recurrence. The primary clinical endpoint was recurrence-free survival (RFS). Distant metastasis-free survival (DMFS), melanoma specific survival (MSS) and overall survival (OS) were also reported. Calculation of the hazard ratio (HR) with a 95 % confidence interval (CI) was done using a Cox proportional hazards regression model, with the corresponding Wald p-value < 0.05 (two-sided) indicating statistical significance. The median follow-up was calculated based on reverse Kaplan-Meier estimator via R package prodlim (version 2019.11.13). Wald tests were used to assess the significance of the difference based on CP-GEP risk. Log-log CI were computed for 5-year and 10-year survival rate estimates. Analyses were performed using R (version 3.6.1). Patient characteristics were analyzed using the gtsummary R package (version 1.3.3). Survival analyses were performed with survminer (version 0.4.6) and survival (version 3.1.8) R packages.

3. Results

3.1. Study population

Of 930 patients with clinical stage I/II melanoma 879 patients were classified as Low Risk and 51 patients as High Risk. The median Breslow thickness was 0.5 mm (interquartile range [IQR]: 0.40–0.70 mm). Most patients had stage IA disease totaling 91 % (847 patients). The median age was 64 years (IQR: 52–75 years), 41 % were females, and ulceration was absent in most tumors (94 %). Most common histological types in this cohort were superficial spreading melanoma (SSM; 72 %) and lentigo maligna melanoma (LMM; 19 %) (Table 1).

3.2. CP-GEP performance for long-term outcome in patients that did not undergo SLNB

The median follow-up time for the whole cohort, calculated using the reverse censoring method, was 165 months (IQR, 116, 217); for RFS was 141 months (IQR 85,195), for DMFS was 136 months (IQR, 84, 193) and for MSS was 137 (IQR, 84,193).

The median RFS, DMFS, MSS and OS for the whole cohort was not reached. For all patients, the 5- and 10 year RFS rate was 93 % and 92 % (95 % CI, 91 %-95 %; 90 %-93 %); the 5- and 10-year DMFS rate was 98 % and 96 % (95 % CI, 96 %-98 %; 95–97 %); the 5- and 10-year MSS rates were 98 % and 97 % (95 % CI, 97 %-99 %; 96 %-98 %) and the 5- and 10-year OS rates were 88 % and 78 % (95 % CI, 86 %-90 %; 75 %-

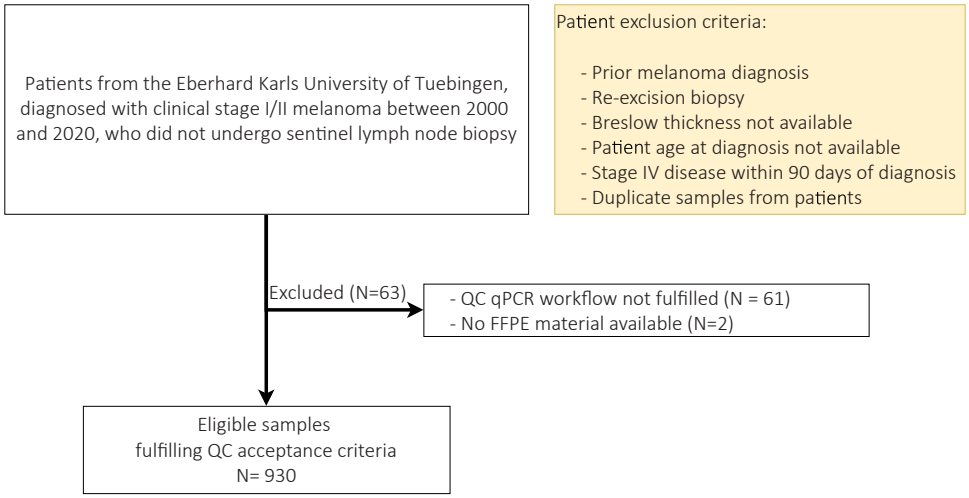

Fig. 1. Cohort diagram.

Table 1
Patient and tumour characteristics (n = 930 patients).

Characteristic	All Patients (N = 930)	CP-GEP Low Risk(N = 879)	CP-GEP High Risk(N = 51)
Sex			
Female	379 (40.8 %)	353 (40.2 %)	26 (51.0 %)
Male	551 (59.2 %)	526 (59.8 %)	25 (49.0 %)
Age, Years	64 (52, 75)	63 (51, 75)	80 (68, 87)
Breslow Thickness (median, IQR; in mm)	0.50 (0.40, 0.70)	0.50 (0.40, 0.70)	3.60 (2.20, 5.60)
SLNB Finding			
Unknown	930 (100.0 %)	879 (100.0 %)	51 (100.0 %)
Biopsy Location			
Head neck	206 (22.2 %)	188 (21.4 %)	18 (35.3 %)
Trunk	407 (43.8 %)	402 (45.7 %)	5 (9.8 %)
Upper extremities	136 (14.6 %)	128 (14.6 %)	8 (15.7 %)
Lower extremities	180 (19.4 %)	160 (18.2 %)	20 (39.2 %)
Other	1 (0.1 %)	1 (0.1 %)	0 (0.0 %)
Histologic Type			
Superficial spreading	665 (71.5 %)	648 (73.7 %)	17 (33.3 %)
Nodular	13 (1.4 %)	1 (0.1 %)	12 (23.5 %)
Lentigo maligna	180 (19.4 %)	172 (19.6 %)	8 (15.7 %)
Acral lentiginous	43 (4.6 %)	33 (3.8 %)	10 (19.6 %)
Other	14 (1.5 %)	11 (1.3 %)	3 (5.9 %)
Unknown	15 (1.6 %)	14 (1.6 %)	1 (2.0 %)
Clark Level			
Unknown	930 (100.0 %)	879 (100.0 %)	51 (100.0 %)
Ulceration			
Absent	873 (93.9 %)	852 (96.9 %)	21 (41.2 %)
Present	44 (4.7 %)	15 (1.7 %)	29 (56.9 %)
Unknown	13 (1.4 %)	12 (1.4 %)	1 (2.0 %)
Clinical Stage			
IA	847 (91.1 %)	842 (95.8 %)	5 (9.8 %)
IB	21 (2.3 %)	17 (1.9 %)	4 (7.8 %)
IIA	16 (1.7 %)	5 (0.6 %)	11 (21.6 %)
IIB	15 (1.6 %)	3 (0.3 %)	12 (23.5 %)
IIC	18 (1.9 %)	0 (0.0 %)	18 (35.3 %)
Unknown	13 (1.4 %)	12 (1.4 %)	1 (2.0 %)
T Category			
T1	9 (1.0 %)	8 (0.9 %)	1 (2.0 %)
T1a	714 (76.8 %)	714 (81.2 %)	0 (0.0 %)
T1b	133 (14.3 %)	128 (14.6 %)	5 (9.8 %)
T2	4 (0.4 %)	4 (0.5 %)	0 (0.0 %)
T2a	21 (2.3 %)	17 (1.9 %)	4 (7.8 %)
T2b	2 (0.2 %)	0 (0.0 %)	2 (3.9 %)
T3a	14 (1.5 %)	5 (0.6 %)	9 (17.6 %)
T3b	12 (1.3 %)	3 (0.3 %)	9 (17.6 %)
T4a	3 (0.3 %)	0 (0.0 %)	3 (5.9 %)
T4b	18 (1.9 %)	0 (0.0 %)	18 (35.3 %)

81 %), respectively (Supplementary Figure 1 and Table 2).

For patients with CP-GEP Low Risk, the 10-year RFS rate was 95 % versus 38 % for patients with CP-GEP High Risk (95 % CI, 93 %-96 %; 23 %-52 %; HR 20.07; $p < 0.001$). Similarly, CP-GEP Low Risk patients had significantly better 10-years DMFS (98 % vs. 70 %; HR 19.44; $p < 0.001$), MSS (99 % vs. 67 %; HR 35.85; $p < 0.001$) and OS rates (80 % vs. 38 %; HR 5.59; $p < 0.001$), compared to the High Risk group (Fig 2A-D and Table 2).

At 5-years, CP-GEP captured 12 deaths in the CP-GEP High Risk group out of a total of 16 melanoma specific deaths, yielding a sensitivity of 75 % (48 %-93) and specificity of 96 % (94 %-97 %); at 10-years, CP-GEP captured 13 deaths in the CP-GEP High Risk group out of a total of 23 melanoma specific deaths, yielding a sensitivity of 57 % (35 %-77 %) and specificity of 96 % (94 %-97 %).

3.3. CP-GEP prognostication in histological subtype analysis

CP-GEP was also used to risk stratify patients considering the histological subtypes LMM and acral lentiginous melanoma (ALM). In 180 patients with LMM, 172 were identified as Low Risk and 8 as High Risk. The 10-years RFS rate was 89 % for Low Risk vs 43 % for High Risk (95 % CI, 83 %-93 % and 10 %-73 %; HR 8.79; $p < 0.001$). Similar results were observed for DMFS, MSS and OS. For the 43 patients with

Table 2
5- and 10-year survival analysis for the whole cohort and for CP-GEP Low Risk and CP-GEP High Risk. Relapse-free survival (RFS), distant metastasis-free survival (DMFS), melanoma specific survival (MSS) and overall survival (OS).

	5-year RFS		10-year RFS		5-year DMFS		10-year DMFS		5-year MSS		10-year MSS		5-year OS		10-year OS	
Stratification	Events	(95 %CI)	Events	(95 %CI)	Events	(95 %CI)	Events	(95 %CI)	Events	(95 %CI)	Events	(95 %CI)	Events	(95 %CI)	Events	(95 %CI)
Complete cohort	62	93.1 [91.2–94.6]	72	91.7 [89.6–93.3]	22	97.6 [96.3–98.4]	31	96.2 [94.6–97.3]	16	98.2 [97.1–98.9]	23	97.2 [95.8–98.1]	113	87.8 [85.6–89.8]	193	77.9 [75.0–80.5]
CP-GEPLow Risk	34	96.0 [94.4–97.1]	44	94.5 [92.7–95.9]	9	98.9 [98.0–99.4]	18	97.6 [96.1–98.5]	4	99.5 [98.8–99.8]	10	98.6 [97.4–99.3]	85	90.3 [88.2–92.1]	162	80.2 [77.2–82.8]
CP-GEP High Risk	28	37.5 [23.2–51.8]	28	37.5 [23.2–51.8]	13	70.2 [53.8–81.7]	13	70.2 [53.8–81.7]	12	70.3 [53.1–82.2]	13	66.8 [49.0–79.6]	28	44.9 [31.0–57.9]	31	38.4 [25.1–51.6]

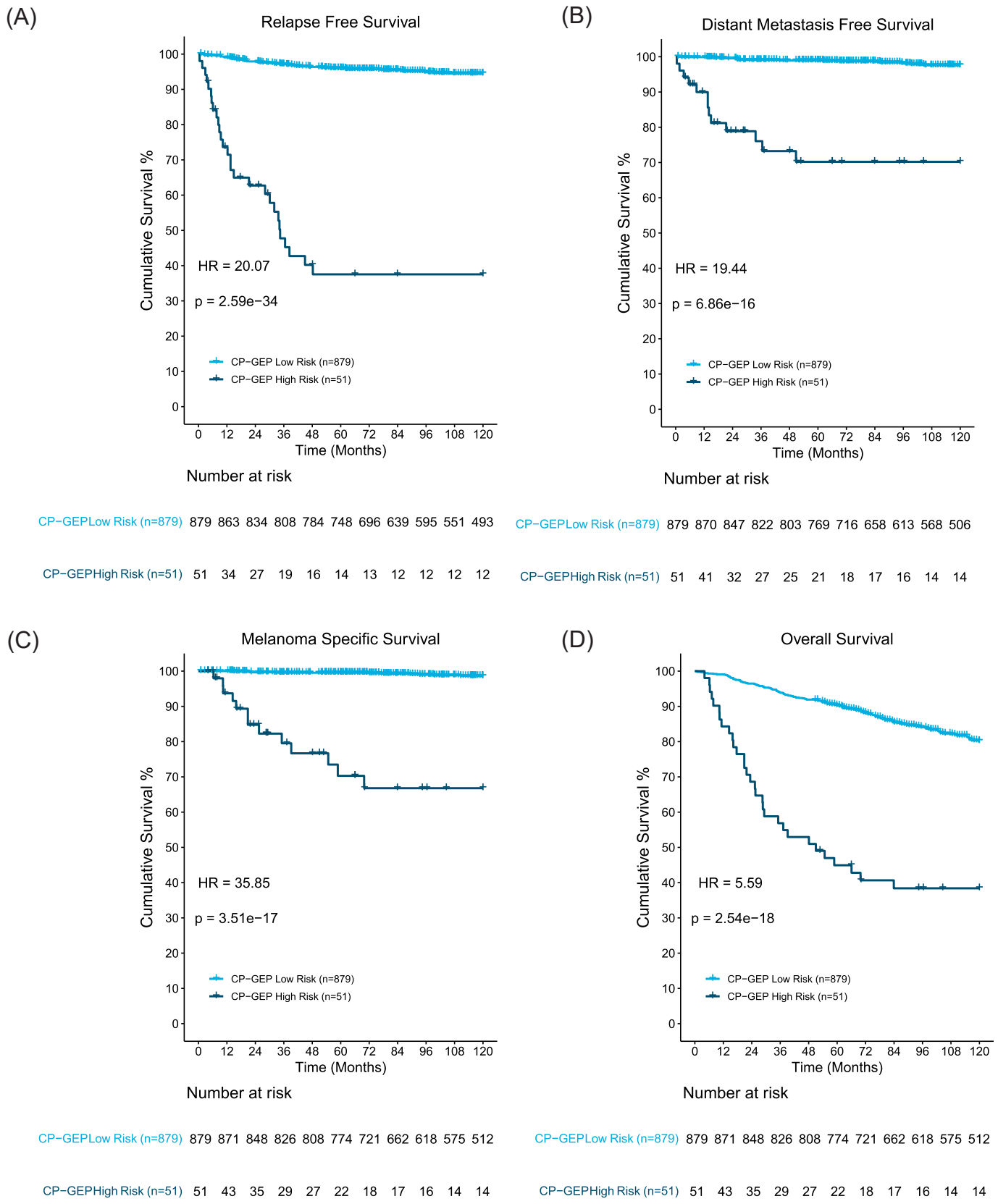

Fig. 2. A-D – Kaplan-Meier analysis of the 930 patients who did not undergo sentinel lymph node biopsy, stratified by CP-GEP. Survival endpoints were relapse-free survival (RFS – 2A), distant metastasis-free survival (DMFS – 2B), melanoma specific survival (MSS - 2 C) and overall survival (OS – 2D) at ten-years of follow-up. CP-GEP Low Risk (light blue curve); CP-GEP High Risk (dark blue curve). For each of the endpoints we report the hazard ratio (HR), and the corresponding p-value calculated with Wald test.

ALM, 33 were risk stratified as Low Risk and 10 as High Risk. The 10-years RFS rate was 71 % vs 0 %, for Low Risk vs High Risk, respectively (95 % CI, 52 %-84 % and NA; HR 5; $p < 0.01$). Two patients in the High Risk group died of melanoma while none in the Low Risk group did (Table 3).

4. Discussion

Previously we showed that CP-GEP was able to risk stratify patients (n = 80) who did not undergo SLNB [21]. In this larger cohort, which did not include the previously mentioned 80 patients, we confirm the initial results showing that CP-GEP risk stratifies patients with early-stage melanoma who did not undergo SLNB based on their risk of recurrence and death from melanoma. We observe that CP-GEP Low Risk patients have significantly better long-term survival compared to CP-GEP High Risk patients, including longer MSS, a valuable survival endpoint in this early setting. In fact, most MSS deaths were identified in patients classified as CP-GEP High Risk.

ALM known to be a more aggressive subtype of melanoma is often diagnosed in later stages [23]. Our data show that patients with ALM and CP-GEP High Risk may need a more intensive follow-up, as in our cohort all deaths were identified in this sub-group. At the same time, it may be possible to adjust the intensity and frequence of follow-up in patients with LMM and CP-GEP Low Risk, considering their long-term excellent prognosis, compared to the LMM CP-GEP High Risk group.

Currently, SLNB serves as the gateway to adjuvant therapy for patients with stage III cutaneous melanoma, and stage IIB/IIC in selected countries. While constituting a large group of patients that eventually die of melanoma, patients with thin melanomas who did not undergo SLNB, and patients with stage I-IIA with negative SLNB have no access to adjuvant therapy [16,17]. These data show that SLNB negativity is not synonymous with low risk of disease recurrence or even death from melanoma [24]. For patients who, due to diverse reasons (e.g., ineligible according to guidelines, health, age, tumor location, risk of complications, among others), do not receive SLNB, correct TMN classification is not possible due to missing SLN status, making the path to treatment often not accessible. Taken together, these data support the need for better risk stratification tools to identify those at high risk for disease relapse or death [22,25–30]. Besides, the melanoma community also needs to better identify those patients with extremely low risk, for which further interventions are not needed.

Risk stratification assays, including CP-GEP, may support such personalized treatment decisions, which in turn may lead to a decrease in healthcare costs, allowing healthcare providers and resources to be reallocated [21,30,31]. Our results show that for patients with a classification of CP-GEP Low Risk forgoing SLNB surgery may be discussed. This would decrease the risk of surgical complications, potentially reducing the number of visits to the hospital, and the number of follow-ups. In a small interventional study with 45 patients diagnosed with mostly thin melanomas, 23 of 29 patients with CP-GEP Low Risk score decided to forgo SLNB surgery [32]. On the other hand, patients with CP-GEP High Risk could be considered to have a more intensified patient pathway, including offering access to (neo)adjuvant therapy, SLNB, and more frequent follow-up. Next steps necessarily include prospective interventional studies in which CP-GEP is used as a screening tool to select, or deselect, patients with melanoma for (neo) adjuvant therapy. One such study could use CP-GEP risk stratification as a rule-in test for patients with early-stage melanoma who are not eligible for SLNB.

To our knowledge this is the largest cohort of patients who didn't undergo SLNB used to test such a risk stratification tool. Other strengths from this analysis include the long median follow up time, which is extremely important in the early setting, the detailed annotated dataset from the Central Malignant Melanoma Registry, and the link to German public health care registries responsible for documenting death and cause of death, allowing for the accuracy of the survival data. Given the

Table 3
5- and 10-year survival of histologic subtype lentigo maligna melanoma and acral lentiginous melanoma, stratified by CP-GEP. Relapse-free survival (RFS), distant metastasis-free survival (DMFS), melanoma specific survival (MSS) and overall survival (OS).

		5-year RFS		10-year RFS		5-year DMFS		10-year DMFS		5-year MSS		10-year MSS		5-year OS		10-year OS	
Stratification	**N**	**Events**	**(95 %CI)**	**Events**	**(95 %CI)**	**Events**	**(95 %CI)**	**Events**	**(95 %CI)**	**Events**	**(95 %CI)**	**Events**	**(95 %CI)**	**Events**	**(95 %CI)**	**Events**	**(95 %CI)**
Lentigo maligna melanoma	180	18	83.6 [75–89.5]	20	87.3 [80.8–91.7]	6	95.2 [89.5–97.8]	8	94.6 [89.3–97.3]	4	96.7 [91.3–98.8]	8	94.6 [89.3–97.3]	40	77.7 [70.9–83.1]	59	65.3 [57.6–72]
CP-GEPLow Risk	172	14	86.3 [77.7–91.8]	16	89.2 [82.8–93.3]	4	96.8 [91.5–98.8]	6	95.6 [90.3–98.1]	2	98.3 [93.5–99.6]	6	95.6 [90.3–98.1]	36	79 [72.1–84.4]	54	66.8 [58.9–73.5]
CP-GEPHigh Risk	8	4	33.3 [4.6–67.6]	4	42.9 [9.8–73.4]	2	62.5 [14.2–89.3]	2	68.6 [21.3–91.2]	2	62.5 [14.2–89.3]	2	68.6 [21.3–91.2]	4	50 [15.2–77.5]	5	33.3 [5.6–65.8]
Acral lentiginous melanoma	43	14	52.4 [32.1–69.2]	15	60.9 [43.5–74.5]	2	93 [74.6–98.2]	3	90.8 [73.5–97]	2	92.7[73.3–98.1]	2	94.4 [79.5–98.6]	13	69.8 [53.7–81.2]	16	62.5 [46.3–75.1]
CP-GEPLow Risk	33	8	67.1 [43.3–82.7]	9	71.2 [51.7–83.9]	0	100[100]	1	95.8 [73.9–99.4]	0	100[100]	0	100[100]	5	84.8 [67.4–93.4]	7	78.6 [60.2–89.2]
CP-GEPHigh Risk	10	6	0[100]	6	0[100]	2	60 [12.6–88.2]	2	66.7 [16–91.4]	2	60[12.6–88.2]	2	62.5 [14.2–89.3]	8	20 [3.1–47.5]	9	10 [0.6–35.8]

single center design of the study, its retrospective nature and the fact that only patients with a tissue sample available were analyzed, a bias cannot be excluded.

5. Conclusion

CP-GEP can risk stratify patients with early-stage melanoma based on their risk of recurrence, even in patients who did not undergo SLNB. CP-GEP may support better identification of patients at high risk for recurrence and death from melanoma, providing a more personalized approach beyond SLNB.

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CRediT authorship contribution statement

Teresa Amaral: Study concept, Data Collection, Data analysis, Data interpretation, Writing, Final approval. **Eftychia Chatziioannou:** Study concept, Data Collection, Data analysis, Data interpretation, Writing, Final approval. **Alica Nuebling:** Data Collection, Data interpretation, Writing, Final approval. **Lena Nanz:** Data Collection, Data analysis, Data interpretation, Writing, Final approval. **Tobias Sinnberg:** Study concept, Data Collection, Data interpretation, Writing, Final approval. **Heike Niessner:** Study concept, Data Collection, Data interpretation, Writing, Final approval. **Tim Arentsen:** Study concept, Data Collection, Data analysis, Data interpretation, Writing, Final approval. **Romy Ruiter:** Data Collection, Data analysis, Data interpretation, Writing, Final approval. **Jvalini Dwarkasing:** Study concept, Data analysis, Data interpretation, Writing, Final approval. **Alexander M. Eggermont:** Study concept, Data analysis, Data interpretation, Writing, Final approval. **Ulrike Leiter:** Data Collection, Data analysis, Data interpretation, Writing, Final approval. **Lukas Flatz:** Data interpretation, Writing, Final approval. **Stephan Forchhammer:** Study concept, Data Collection, Data analysis, Data interpretation, Writing, Final approval.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TA reports personal fees for advisory board membership from Delcath and Philogen; personal fees as an invited speaker from Bristol Myers Squibb (BMS), Medscape, Neracare, Novartis and Pierre Fabre; personal fees for a writing engagement from CeCaVa and Medtrix; institutional fees as local principal investigator (PI) from Agenus Inc., AstraZeneca, BioNTech, BMS, HUYA Bioscience, Immunocore, IO Biotech, MSD, Pfizer, Philogen, Regeneron, Roche and University Hospital Essen; institutional fees as coordinating PI from Unicancer; institutional research grants from iFIT and Novartis; institutional funding from MNI - Naturwissenschaftliches und Medizinisches Institut, Neracare, Novartis, Pascoe, Sanofi and Skyline-Dx; non-remunerated membership of the American Society of Clinical Oncology (ASCO) and the Portuguese Society for Medical Oncology; a role as clinical expert in the area of medical oncology for Infarmed, and a role as an expert for SGA-Oncology at EMA. EC: No relationships to disclose. AL: No relationships to disclose. LN: No relationships to disclose. TS: reports institutional funding from Novartis and Pierre-Fabre outside the submitted work. HN: reports institutional funding from Novartis and Pierre-Fabre outside the submitted work. TA: reports stock and other ownership interests – SkylineDx B.V., Employment – SkylineDx B.V. RR: reports stock and other ownership interests – SkylineDx B.V., Employment – SkylineDx B.V. JD: reports stock and other ownership interests – SkylineDx B.V., Employment – SkylineDx B.V.; Leadership – SkylineDx B.V. and Honoraria – SciBase A.B. AE: reports stock and other ownership interests - IO Biotech, Sairopa B.V., SkylineDx B.V.; Honoraria Consulting or Scientific Advisory Role - Agenus, Boehringer Ingelheim GmbH, BioInvent, BioNTech, Brenus, CatalYm GmbH, Egle, Eurobio, ImmTech, IO Biotech, IQVIA, Merck KgA, Merck&Co, MSD, Oncolytics, Pierre Fabre, Sairopa BV, Secarna GmbH, SkylineDx B.V., Thermosome GmbH, Trained Immunity Therapeutics Discovery; Data safety monitoring board: BioNTech, IQVIA, Pfizer. UL: reports research support from MSD, consulting fees and honoraria from Sun Pharma, Sanofi (personal and institutional), MSD (personal and institutional), Novartis, Roche, Almirall Hermal, support for attending meeting from Sun Pharma and participation on a Data Safety Monitoring Board or Advisory Board from Sun Pharma, Sanofi, MSD, Novartis, Roche, Almirall Hermal, outside the submitted work. LF: reports Grants or contracts from Hookipa Pharma, SAKK / Immunophotonics, DFG Grant (Deutsche Forschungsgemeinschaft), Philogen and Mundipharma; consulting fees from Philogen, Sanofi, Novartis, BMS; participation on Data Safety Board University of Basel and stocks or stock options from Hookipa Pharma, outside the submitted work. SF: reports institutional funding from SkylineDx B.V. in relation with the submitted work; institutional grants from BioNTech and Neracare as well as personal honoraria for lectures from Recordati, Kyowa Kirin and Stemline Pharmaceutical, outside the submitted work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115372.

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