The Dutch Early-Stage Melanoma Study (D-ESMEL): a Discovery Set and Validation Cohort to Predict the Absolute Risk of Distant Metastases in Stage I/II Cutaneous Melanoma

Catherine Zhou [1], Antien L. Mooyaart [2], Thamila Kerkour [1], Marieke W.J. Louwman [3], Marlies Wakkee [1], Yunlei Li [4], Quirinus J.M. Voorham [5], Annette Bruggink [5], Tamar E.C. Nijsten [1], Loes M. Hollestein [1,3]*

[1] Department of Dermatology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
[2] Department of Pathology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
[3] Department of Research and Development, Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands
[4] Department of Pathology & Clinical Bioinformatics, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands
[5] Dutch Nationwide Pathology Databank (Palga), Houten, The Netherlands

Background Early-stage cutaneous melanoma patients generally have a favorable prognosis, yet a significant proportion of metastatic melanoma cases arise from this group, highlighting the need for improved risk stratification using novel prognostic biomarkers.
Aim The D-ESMEL study introduces a robust, population-based methodology to develop an absolute risk prediction model for stage I/II melanoma, incorporating clinical, imaging, and multi-omics data to identify patients at increased risk for distant metastases.
Methods Utilizing the Netherlands Cancer Registry (NCR) and Dutch Nationwide Pathology Databank (Palga), we obtained routinely collected data primary tumor formalin-fixed paraffin-embedded (FFPE) samples from early-stage melanoma patients both with and without distant metastases during follow-up. Our study design includes a discovery set of metastatic cases and matched controls to identify novel prognostic factors, followed by a validation cohort using a nested case-control design to validate these factors and to build a risk prediction model. Tissue sections underwent Hematoxylin & Eosin (H&E) staining, RNA sequencing (RNAseq), DNA sequencing (DNAseq), immunohistochemistry (IHC), and multiplex immunofluorescence (MxIF).
Results The discovery set included 442 primary melanoma samples (221 case-control sets), with 46% stage I and 54% stage II melanomas. The median time to distant metastasis was 3.4 years, while controls had a median follow-up time of 9.8 years. The validation cohort included 154 cases and 154 controls from a random population-based selection of 5,815 patients.
Conclusions Our approach enabled the collection of a large number of early-stage melanoma samples from population-based databases with extensive follow-up and a sufficient number of metastatic events. This methodology in prognostic cancer research holds the potential to impact clinical decision-making through absolute risk prediction.