Combining PALGA and IKNL data to create a representative cohort for validating *LY75* promoter methylation as a predictor of stage I–III melanoma patients at high risk of disease recurrence

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Background and objective:

Accurately predicting recurrence risk in stage I–III primary melanoma is essential to prevent under- and overtreatment. Current predictors are suboptimal, with up to 28% of high-risk patients undetected and 35% of sentinel lymph node biopsy-eligible patients declining the procedure. Previously, *LY75* promoter methylation has been identified as an independent predictor of melanoma recurrence across three independent cohorts. The aim of this study is to perform a large-scale validation of *LY75* methylation as a predictor for recurrence risk in stage I–III melanoma patients. Creating a representative and adequately powered cohort is a crucial step in achieving this goal.

Methods:

Data from the Pathological Anatomical National Automated Archive (PALGA) and the Netherlands Comprehensive Cancer Organisation (IKNL) were combined. All primary stage I-III melanoma patients diagnosed between 2003 and 2017 were identified, along with corresponding disease recurrence data. Based on power calculations, 142 events (recurrence or metastasis) were required for stage I, 324 for stage II, and 411 for stage III. The cohort was created by randomly selecting melanoma patients within each stage until the required number of events was met, ensuring representativeness while minimizing selection bias.

Results:

The final cohort consisted of 5568 patients: 3187 (57.2%) stage I, 1503 (27.0%) stage II, and 878 (15.8%) stage III. Tumor subtypes included 3920 (70.4%) superficial spreading melanomas, 933 (16.8%) nodular melanomas, and 680 (12.2%) unspecified melanomas. Disease recurrence occurred in 218 (6.8%) stage I, 477 (31.7%) stage II, and 590 (67.2%) stage III patients. Formalin-fixed paraffin-embedded tumor samples have been requested to assess *LY75* methylation status.

Conclusions:

Integrating PALGA and IKNL data, we established a representative cohort of 5568 primary stage I-III melanoma patients, sufficiently powered for robust validation of *LY75* methylation as a predictor of recurrence risk. This minimally biased approach enables clinically meaningful insights into recurrence prediction.