Artificial intelligence-based pRb subtyping of pulmonary large cell neuroendocrine carcinoma on small haematoxylin and eosin-stained specimens

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Background

Molecular subtyping of pulmonary large cell neuroendocrine carcinoma (LCNEC) based on retinoblastoma protein (pRb) expression may influence systemic treatment decisions. Current histomorphological assessments of haematoxylin and eosin (H&E)-stained tissue samples cannot reliably differentiate these molecular subtypes. Alternatively, artificial intelligence (AI) may help.

Objective

This study investigated the potential of AI to identify histological patterns distinguishing the pRb-based subtypes of LCNEC, aiming to uncover cytonuclear biomarkers for diagnosis.

Methods

An AI pipeline, utilizing a custom-made convolutional neural network, was designed to classify the binary expression of pRb in small H&E-stained tissue samples from panel-reviewed LCNEC patients. All data for this retrospective population-based study were retrieved from the Dutch pathology registry (PALGA, lzv2020-48_def_C-/_U-). Our model was trained, cross-validated, and tested on tissue micro-array (TMA) cores from 143 resection specimens and biopsies from 21 additional patients, with corresponding immunohistochemical pRb status.

Results

The best-performing AI model achieved a patient-wise balanced accuracy (BA) of 0.76 and an area under the receiver operating characteristic curve (AUC) of 0.80. On biopsy samples alone the model demonstrated a patient BA of 0.75 and an AUC of 0.77, significantly outperforming the H&E-based subtype classification by expert lung pathologists who recorded an average BA of 0.52 and AUC of 0.53. Explainable AI techniques highlighted pleomorphic cells with coarse chromatin patterns and prominent nucleoli as distinguishing features for pRb positive status. Meanwhile, pRb negative cases appeared to be typified by limited cytoplasm and morphological similarities with small cell lung cancer.

Conclusion

This study proposes an AI pipeline to enable the sub-classification of LCNEC based on the pRb expression status using only small H&E-stained tissue specimens. These findings suggest that AI analysis of histopathology samples could replace immunohistochemical pRb testing, upon further development. Such a prediction, applied on biopsy specimens, may assist in guiding chemotherapy decisions, particularly in metastatic cases.