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Phenotypic Heterogeneity of Circulating Tumor Cells in Lung Cancer Revealed by Immunocytochemical Profiling

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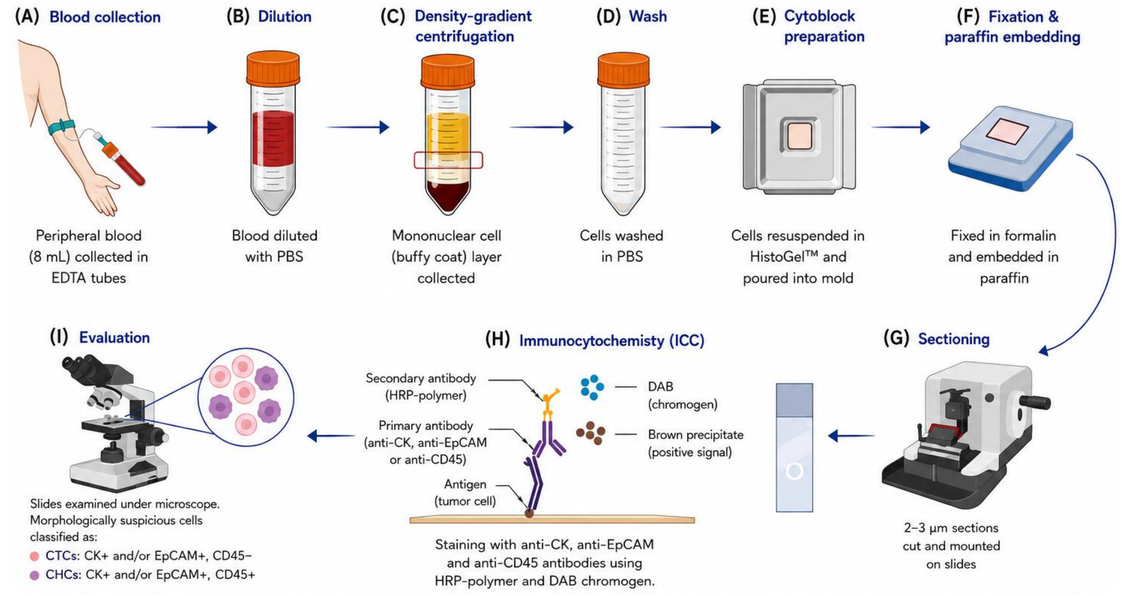
INTRODUCTION & AIM

Tumor heterogeneity is a major challenge in lung cancer, contributing to disease progression, metastatic dissemination, and therapeutic resistance [1]. Circulating tumor cells (CTCs) provide a minimally invasive opportunity to investigate this heterogeneity through liquid biopsy [2]. However, increasing evidence suggests that these cells extend beyond the classical epithelial CTC phenotype and may include transitional or hybrid populations that are not captured by epithelial marker-restricted approaches [3–5].

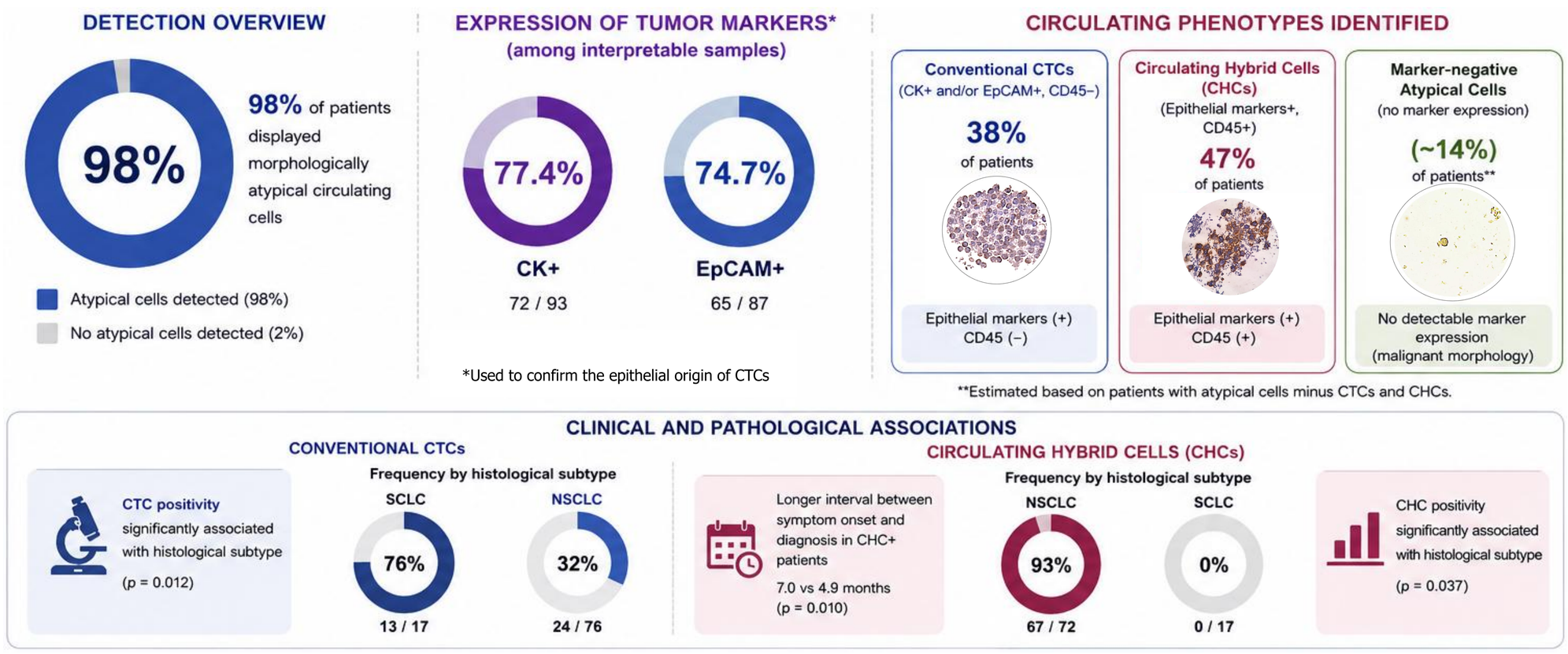
The present study aimed to characterize the phenotypic diversity of circulating tumor-associated cells in newly diagnosed lung cancer patients using a cytoblock-based enrichment protocol previously described by our team [6], combined with immunocytochemical profiling targeting epithelial and hematopoietic markers.

METHOD



RESULTS & DISCUSSION

The study population consisted of 100 newly diagnosed lung cancer patients (mean age: 64 years), predominantly male (83%), with a high prevalence of smoking history (80%). Most patients presented with advanced disease, with 94% diagnosed at stages III–IV. Representative morphological and immunocytochemical findings are shown below.



Our observations are consistent with previous reports describing phenotypic plasticity among circulating tumor-derived cells. Gast et al. demonstrated the existence of CHCs expressing both tumor and leukocyte markers, while Dietz et al. reported that such hybrid populations may exceed classical CTCs in frequency [3,4]. Likewise, studies investigating epithelial–mesenchymal transition have shown that some CTCs may lose epithelial marker expression while retaining metastatic potential [5].

CONCLUSIONS

Using a cytoblock-based approach combined with immunocytochemistry, we identified a broad spectrum of circulating tumor-associated cells in lung cancer patients. Three major phenotypic categories were observed: conventional epithelial CTCs, CHCs co-expressing epithelial and hematopoietic markers, and atypical marker-negative cells displaying malignant morphology.

The detection of CHCs (47%) and marker-negative atypical cells highlights the limitations of epithelial marker-restricted approaches and suggests that circulating tumor-associated cells encompass a broader phenotypic spectrum than conventional CTC definitions. We thus conclude that integrating morphological assessment with multiparametric immunocytochemical profiling provides a more comprehensive characterization of circulating tumor heterogeneity and may improve the biological relevance of liquid biopsy approaches in lung cancer.

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