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Radiomic Trajectory Quantifies Early Lung Adenocarcinoma Progression

Accurately determining progression in early-stage lung adenocarcinoma (esLUAD) is central to diagnosis, treatment selection and follow-up, yet conventional grading can miss important differences within the same category. Histopathology offers critical insights but is invasive, susceptible to sampling bias and affected by interobserver variability. Computed tomography (CT) captures whole-lesion characteristics, and radiomics has shown potential, though most approaches mirror discrete pathological grades rather than quantifying a continuous disease course. A deep learning framework called RadioTrace addresses this gap by integrating radiomic and pathological information to map tumours along a continuous trajectory and assign a pseudo-progression score (PPS). Evaluated across multi-institutional cohorts, RadioTrace aligns with established grades, associates with clinically relevant phenotypes and outcomes and reveals within-grade heterogeneity that current criteria do not capture.

Deep Learning Builds a Continuous Radiomic Trajectory

RadioTrace is constructed with a deep contrastive learning strategy that embeds 3D CT tumour regions using a convolutional neural network and weak supervision from pathological grades. The approach encourages embeddings of tumours with the same grade to cluster while separating those from different grades, enabling the model to learn features linked to evolutionary status rather than static labels. After training on a cohort from Guangdong Provincial People's Hospital, principal component analysis arranges tumour embeddings along a curve. Using an established trajectory inference method with adenocarcinoma in situ as the starting point, the framework defines a radiomic path from preinvasive to invasive disease and computes a PPS for each tumour. PPS increases consistently across atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinoma and invasive adenocarcinoma grades I–III, reflecting progressive biological change.

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Trajectory Aligns with Grades and Predicts Key Outcomes

Performance was assessed across four cohorts comprising 1,843 tumours from 1,827 patients, including internal validations and an external cohort from Shenzhen People's Hospital. Beyond mirroring grade order, PPS captured clinically relevant phenotypes. It was higher in tumours with spread through air spaces and in those with lymph node metastasis, indicating alignment with features linked to aggressiveness. Survival analyses support the prognostic value of the trajectory: across cohorts, PPS stratified disease-free survival and functioned as an independent prognostic factor, with a cohort-derived threshold validated externally. Importantly, RadioTrace exposed heterogeneity within the same pathological grade. In grade II invasive adenocarcinoma, PPS differed between tumours with and without spread through air spaces and between those with and without lymph node metastasis, and it separated disease-free survival within this single grade. Similar analyses in other grades did not show consistent differences, underscoring the particular variability within grade II tumours and the potential to refine stratification beyond current criteria.

Molecular Correlates and Longitudinal Tracking Support Utility

Associations between the trajectory and tumour biology were examined in a multiomics cohort. Tumours with higher PPS were enriched for alterations in TP53, LRP1B and SMAD4, genes previously linked to progression. Transcriptomic comparisons between high- and low-PPS groups showed enrichment of pathways associated with malignancy, including G2M checkpoint, E2F targets, mTORC1 signalling, epithelial–mesenchymal transition and glycolysis. Gene module analysis identified a transcriptomic signature that separated overall and disease-free survival in multiple external datasets, suggesting that the radiomic trajectory aligns with conserved biological programmes. RadioTrace also tracked temporal change in longitudinal cases. In one individual, steadily rising PPS preceded resection of a grade II lesion without adverse features. In another, persistently low PPS supported an indolent course consistent with minimally invasive adenocarcinoma at surgery. A third case showed progressive PPS increases over years, culminating in surgery complicated by nodal involvement and the need for more extensive resection and adjuvant therapy. Together these scenarios illustrate how a continuous radiomic measure can reflect evolving lesion status during surveillance and clarify when apparent stability or change is clinically meaningful.

RadioTrace offers a quantitative, interpretable trajectory of esLUAD progression that complements histopathology. By aligning with grades while revealing within-grade risk, associating with key phenotypes and outcomes, connecting to genomic and transcriptomic hallmarks and capturing longitudinal dynamics, it adds resolution to current assessment and may support more precise decisions on surveillance and intervention. Further work is needed to validate performance internationally, examine robustness across imaging protocols and delineation approaches and define intervention thresholds in prospective settings, but the present findings indicate that a continuous radiomic trajectory can strengthen diagnostic confidence and patient management in early lung adenocarcinoma.

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