学位論文の要約

Usefulness of Quantitative Imaging Markers for Precision Diagnosis and Outcome Prediction

（定量画像指標を用いた精密診断および予後予測の有用性に関する研究）

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Traditional imaging assessment relies on radiologists' subjective judgment, leading to inter-observer variability and inconsistent diagnoses. Quantitative imaging biomarkers (QIBs) address these limitations by extracting objective, reproducible features from imaging data. QIBs are measurable characteristics derived from medical images that indicate normal biological processes, pathogenic processes, or therapeutic responses. Unlike qualitative assessment, QIBs enable early detection of subtle pathological changes and provide robust tools for treatment monitoring.

Modern oncology requires sophisticated imaging solutions for accurate tumor characterization. Traditional methods struggle with distinguishing malignant from benign lesions, characterizing tumor heterogeneity, and assessing microscopic invasion patterns. With advancing treatments and improved survival rates, treatment-related complications have become significant concerns, requiring early detection of subtle physiological changes.

QIB development has benefited from three technological advances: multimodal imaging techniques incorporating functional and physiological capabilities, novel biophysical parameter measurements, and computational image analysis methodologies including radiomics. This research demonstrates QIB approaches addressing key oncological questions through three studies.

Chapter 1: The potential usefulness of MRI-derived electrical conductivity values in diagnosing thoracic lesions

[Background and Objectives]

The feasibility and diagnostic potential of electrical conductivity (σ), derived from phase-based electric properties tomography (EPT), in thoracic lesions remains unexplored. Varying correlations between σ and apparent diffusion coefficient (ADC) were found in tissues except thoracic lesions.

[Materials and methods]

Twenty-three patients with focal lung and mediastinal lesions underwent DWI (2D-SE-EPI, TR/TE = 5656.3/65.7 ms) and phase-based MR-EPT (2D-SSFP, TR/TE = 16/4 ms) between June 2018 and January 2020. Histogram and texture features of the ADC and

σ were calculated and compared between benign and malignant lesions. The relationship between σ and ADC was examined using Pearson correlation coefficient. Feature reduction and index establishment was performed by the least absolute shrinkage and selection operator logistic regression.

[Results]

Histogram metrics of σ showed no significant differences between benign and malignant lesions, while ADC metrics were significantly lower in malignant lesions. In malignant lesions, the 90^{th} percentile and maximum of σ showed significant positive correlations with ADC metrics (r range: 0.533-0.661, $P < 0.05$). Kurtosis, gray level co-occurrence matrix (GLCM)-Joint energy, and GLCM-Maximum probability of σ were positively correlated with malignancy, while GLCM-Joint entropy and GLCM-Sum entropy were negatively correlated. The ADC- and σ-based indices showed similar diagnostic performance (AUC = 0.893 for both), while the composite index achieved a higher AUC of 0.964.

[Discussion]

This pilot study represents the first application of phase-based EPT for σ mapping in thoracic lesions. Unlike histogram metrics, texture features of σ showed significant correlations with malignancy, suggesting that spatial heterogeneity patterns rather than absolute conductivity values provide diagnostic value in thoracic pathology. The positive σ-ADC correlation in malignant lesions may reflect complex tissue microarchitecture relationships.

[Conclusion]

Phase-based EPT demonstrated feasibility for thoracic lesion assessment, with σ providing complementary diagnostic information to ADC for malignancy differentiation. A positive correlation between σ and ADC has been observed in thoracic lesions, with variations influenced by multiple factors including lesion solidity, malignancy status, histological subtypes, and tissue heterogeneity.

Chapter 2: Prediction of HCC histological characteristics using CT radiomic features

[Background and Objectives]

Hepatocellular carcinoma (HCC) represents one of the most prevalent primary liver malignancies with highly heterogeneous biological behavior influenced by various pathological features including tumor grade, microvascular invasion (MVI), hepatic steatosis, inflammatory activity, and fibrosis stage. Current evaluation relies on invasive procedures subject to sampling errors. This study aimed to develop computed tomography (CT)-based radiomics approaches for predicting multiple HCC pathological features from tumor, liver parenchyma, and spleen, while investigating whether correlation-aware algorithms can enhance predictive performance.

[Materials and methods]

192 HCC patients were divided into training (n=156) and validation (n=36) cohorts. Radiomic features were extracted from tumor, non-tumoral liver, and spleen across three enhancement phases. Two analytical approaches were employed: (1) traditional machine learning with 15 algorithms after recursive feature elimination (RFE), (2) Module network combining Bayesian network learning with hierarchical clustering. Feature importance analysis was performed to identify tissue/phase-specific contributions.

[Results]

3135 (41.4%) features showed high reproducibility. Tumor features demonstrated the highest reproducibility (56.6%), followed by liver (47.4%) and spleen (19.9%). Tree-based ensemble methods demonstrated superior cross-validation performance, with inflammatory activity showing the highest predictive accuracy (random forest [RF]: AUC=0.721, Bagged classification and regression trees [CART]: AUC=0.724), while tumor grading was most challenging (best AUC=0.644). In validation, C5.0 achieved excellent performance for inflammatory activity (AUC=0.859). Feature importance analysis revealed distinct patterns: delayed phase tumor features dominated grading and MVI prediction, portal venous phase features were crucial for steatosis, inflammatory activity showed multi-tissue involvement with prominent splenic contributions, and fibrosis relied primarily on arterial phase tumor features. Module Network showed limited success.

[Discussion]

Evaluation of 15 machine learning algorithms demonstrated that non-linear ensemble methods consistently outperformed linear methods in handling high-dimensional radiomic feature spaces. The multi-tissue approach incorporating tumor, non-tumoral liver, and splenic features provided valuable complementary information, validating that HCC pathogenesis involves both local tumor characteristics and systemic changes. Feature importance analysis revealed that splenic features' prominence in inflammatory activity prediction reflects the spleen's role in chronic liver inflammation, while different enhancement phases provided complementary information for different pathological features. Traditional machine learning showed limitations in modeling complex relationships. The correlation structures in radiomics data are inherently different, involving spatial autocorrelations within imaging regions and temporal correlations across contrast phases that may not conform to the hierarchical clustering assumptions underlying module network methodology. Inflammatory activity emerged as the most predictable feature across all approaches, suggesting systemic inflammatory processes manifest as distinctive imaging patterns with clinical implications for disease progression and treatment response.

[Conclusion]

Non-linear machine learning algorithms effectively predicted HCC pathological features, with inflammatory activity being most accurate and tumor grading most challenging. Multi-tissue radiomics provided complementary diagnostic information.

Chapter 3: The potential of diffusion tensor imaging-derived quantitative features in early prediction of radiation-induced cognitive decline

[Background and Objectives]

Brain radiotherapy can impair cognitive function in patients with brain metastasis. This study investigated relationships between white matter microstructural changes after radiotherapy and cognitive performance using diffusion tensor imaging (DTI) histogram and texture analysis.

[Materials and methods]

Nineteen patients underwent DTI before and after radiotherapy. Histogram and texture features from whole-brain white matter were extracted, and delta features calculated. Cognitive function was assessed four months post-radiotherapy. Relationships were analyzed using multiple linear regression with FDR correction.

[Results]

Four DTI features showed significant changes post-radiotherapy: mean of axial diffusivity (AD_{mean}), skewness of axial diffusivity ($AD_{skewness}$), kurtosis of mean diffusivity ($MD_{kurtosis}$), and kurtosis of radial diffusivity ($RD_{kurtosis}$). Changes in AD_{mean} (ΔAD_{mean}) was significantly associated with poorer semantic fluency performance ($\beta = -3.303 \times 10^4$, $P = 0.002$), while changes in $AD_{skewness}$ ($\Delta AD_{skewness}$) showed positive correlation ($\beta = 4.642$, $P = 0.006$). After FDR correction, only the relationship between ΔAD_{mean} and semantic fluency remained significant ($P = 0.036$).

[Discussion]

Predominantly negative ΔAD_{mean} likely reflect acute-phase radiation responses including axonal swelling rather than permanent damage. The strong association between ΔAD_{mean} and semantic fluency suggests early axonal alterations impact cognitive networks requiring distributed white matter connections. Changes in $\Delta AD_{skewness}$ indicate heterogeneous radiation effects on white matter, with differential regional vulnerability potentially explaining varying cognitive network sensitivity. Semantic fluency showed particular sensitivity to white matter changes, likely due to its dependence on fronto-temporal pathways.

[Conclusion]

White matter microstructural changes, particularly increased axonal damage (ΔAD_{mean}) and heterogeneous damage distribution ($\Delta AD_{skewness}$), significantly correlate with post-radiotherapy cognitive performance. DTI histogram and texture analysis offers potential as an early biomarker for radiation-induced cognitive vulnerability.

This thesis systematically examined QIBs across three distinct oncological applications. First, the feasibility of phase-based EPT for thoracic lesion assessment was confirmed, with σ providing diagnostic information that complemented diffusion metrics. A

positive correlation between σ and ADC was observed in malignant lesions with variations influenced by lesion solidity, malignancy status, histological subtypes, and tissue heterogeneity. Second, in HCC, the application of non-linear machine learning algorithms to radiomic features demonstrated clear advantages over linear methods in predicting multiple histopathological characteristics. Importantly, the use of a multi-tissue radiomics framework that incorporated tumor, liver parenchyma, and splenic features produced complementary insights beyond tumor-only analysis, underscoring the systemic nature of HCC pathogenesis. Third, diffusion tensor imaging revealed that radiation-induced alterations in white matter microstructure, particularly changes in axonal integrity and the distribution of damage, were significantly associated with post-treatment cognitive performance. These findings established that histogram- and texture-based analyses of DTI can serve as early indicators of cognitive decline, offering potential for proactive patient management.

Taken together, the three studies demonstrate that QIBs can provide clinically relevant information across multiple anatomical sites, imaging modalities, and stages of disease. These findings support the view that quantitative imaging has a central role to play in the future of precision oncology, where objective, reproducible, and biologically meaningful metrics will help refine patient stratification and improve outcomes.