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Novel Texture-Based Radiomic Signatures for Non-Invasive Prediction of EGFR Mutation Status in Lung Nodules

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Abstract

Background. Accurate identification and analysis of lung nodules via computed tomography are pivotal for lung cancer diagnosis and the detection of genetic alterations, such as epidermal growth factor receptor (EGFR) mutations. While conventional radiomics has become a cornerstone of medical imaging, its predictive power for determining EGFR mutation status remains limited, necessitating innovative approaches to improve diagnostic reliability.

Objective: to enhance the accuracy of EGFR mutation status prediction in lung nodules by introducing and integrating novel texture-based radiomics features into conventional radiomics analysis.

Material and methods. Three novel radiomic features were developed: Adaptive Texture Contrast (ATC), Directional Texture Uniformity (DTU), and Co-occurrence of Texture Transitions (CTT). They were designed to capture complex texture patterns associated with EGFR mutations. Integrating these features, a classification model was employed to differentiate EGFR mutant from wild-type lung nodules.

Results. The incorporation of ATC, DTU, and CTT into the radiomics feature set improved the classification accuracy by 4%. The Minimum Redundancy Maximum Relevance (MRMR) feature selection method further validated the significance of these features, ranking them as the top contributors to the model's predictive performance.

Conclusion. The findings underscore the potential of advanced texture analysis in improving the diagnostic capabilities of radiomics for lung nodule classification. By enabling more accurate predictions of EGFR mutations, the study supports the advancement of personalized medicine and targeted treatment strategies in lung cancer, highlighting the importance of continuous innovation in feature engineering.

Keywords: lung nodule classification; EGFR mutation; radiomics; texture analysis; feature engineering; computational diagnostics; personalized medicine; machine learning; MRMR feature selection.

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Новые текстурные радиомические сигнатуры для неинвазивного прогнозирования статуса мутации EGFR в легочных узелках

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Резюме

Актуальность. Точная идентификация и анализ легочных узелков с помощью компьютерной томографии имеют решающее значение для диагностики рака легких и выявления генетических изменений, таких как мутации рецептора эпидермального фактора роста (epidermal growth factor receptor, EGFR). Хотя традиционная радиомика стала основой медицинской визуализации, ее прогностическая ценность для определения статуса мутации EGFR остается ограниченной, что требует инновационных подходов для повышения надежности диагностики.

Цель: повысить точность прогнозирования статуса мутации EGFR в легочных узелках путем внедрения и интеграции новых текстурных радиомических признаков в традиционный радиомический анализ.

Материал и методы. Разработаны три новых радиомических признака: адаптивный контраст текстуры (Adaptive Texture Contrast, ATC), направленная однородность текстуры (Directional Texture Uniformity, DTU) и совместная встречаемость переходов текстуры (Co-occurrence of Texture Transitions, CTT). Они предназначены для выявления сложных текстурных паттернов, связанных с мутациями EGFR. С использованием этих признаков применяется классификационная модель для различения легочных узелков с мутацией EGFR от узелков дикого типа.

Результаты. Включение ATC, DTU и CTT в набор радиомических признаков повысило точность классификации на 4%. Метод отбора признаков «минимум избыточности, максимум релевантности» (Minimum Redundancy Maximum Relevance, MRMR) дополнительно подтвердил значимость данных признаков, определив их основной вклад в прогностическую эффективность модели.

Заключение. Результаты исследования указывают на потенциал передового анализа текстур в улучшении диагностических возможностей радиомики для классификации легочных узелков. Полученные данные обеспечивают более точное прогнозирование мутаций EGFR, способствуют развитию персонализированной медицины и таргетных стратегий лечения рака легких, подчеркивая важность постоянных инноваций в инженерии признаков.

Ключевые слова: классификация легочных узелков; мутация EGFR; радиомика; анализ текстур; разработка признаков; вычислительная диагностика; персонализированная медицина; машинное обучение; отбор признаков MRMR.

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Introduction / Введение

Lung cancer remains the leading cause of cancer mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for the majority of diagnoses. Among genetic alterations linked to NSCLC, mutations in the epidermal growth factor receptor (EGFR) gene have emerged as key biomarkers due to their critical role in guiding targeted therapies. Detecting EGFR mutations in lung nodules is pivotal for determining prognosis and tailoring treatment strategies, as these mutations significantly influence therapeutic response and patient survival [1].

The evolution of precision oncology has intensified demand for non-invasive tools capable of decoding tumor biology at the molecular level. Radiomics – a multidisciplinary approach combining medical imaging with advanced data analytics – addresses this need by translating standard medical images into quantitative descriptors. These descriptors, spanning shape, intensity, texture, and higher-order statistical metrics, enable a granular characterization of tumor heterogeneity and spatial complexity, surpassing conventional visual assessment [2–5].

The potential of radiomics extends beyond mere phenotypic characterization; it encompasses the predictive modeling of genetic mutations, such as those affecting the EGFR gene. This capability is particularly significant given the heterogeneous nature of lung

cancer, where tumors with identical histological classifications may exhibit divergent genetic profiles and, consequently, respond differently to targeted therapies. By correlating specific radiomic signatures with the presence of EGFR mutations, researchers aim to develop non-invasive biomarkers that can reliably predict mutation status. Such biomarkers would not only streamline the selection of appropriate therapeutic interventions but also eliminate the need for invasive biopsy procedures, thereby reducing patient discomfort and associated risks [2–4].

Furthermore, the integration of radiomics into clinical workflows holds the promise of transforming cancer care through personalized treatment strategies. By leveraging advanced machine learning algorithms to analyze the rich dataset provided by radiomic features, clinicians can gain unprecedented insights into the molecular underpinnings of each patient's tumor. This approach enables the tailoring of treatment plans to the individual's genetic profile, maximizing efficacy while minimizing unnecessary exposure to potentially ineffective therapies [6–8].

Despite the considerable progress made in the field of radiomics, its application in the context of EGFR mutation detection in NSCLC remains an area of active research. Challenges such as the standardization of image acquisition protocols, feature extraction methodologies, and the validation of predictive models across diverse patient populations are currently being addressed. As these obstacles are overcome, radiomics stands on the cusp of revolutionizing the paradigm of cancer diagnosis and treatment, heralding a new era of precision oncology that is guided by the intricate interplay between imaging phenotypes and genetic information.

This study introduces an innovative radiomics framework to improve the non-invasive prediction of EGFR mutation status in lung nodules by integrating three newly developed texture-based features engineered to quantify subtle textural and geometric signatures associated with genetic mutations, combining advanced mathematical models with state-of-the-art image processing techniques. By capturing previously underutilized patterns in computed tomography (CT) data, this approach seeks to enhance diagnostic precision, enabling clinicians to tailor targeted therapies and optimize patient outcomes through personalized oncological care.

Objective: to enhance the accuracy of EGFR mutation status prediction in lung nodules by introducing and integrating novel texture-based radiomics features into conventional radiomics analysis.

Material and methods / Материал и методы

Three novel texture-driven radiomic features – Adaptive Texture Contrast (ATC), Directional Texture Uniformity (DTU), and Co-occurrence of Texture Transitions (CTT) were designed to improve diagnostic precision in identifying EGFR mutations within lung nodules. These features integrate mathematical frameworks and cutting-edge image analysis techniques to quantify subtle textural and geometric signatures linked to genetic alterations. Figure 1 illustrates the radiomic feature extraction pipeline, which encompasses the conceptual foundation, computational workflows, and validation protocols for each feature.

The analysis leveraged a large-scale radiogenomic dataset [9, 10] comprising 211 patient cases, including high-resolution CT scans, clinical annotations of tumor regions, and genomic profiling data. This dataset enabled the systematic evaluation of feature performance in distinguishing EGFR mutation statuses while ensuring robustness across diverse clinical scenarios.

Adaptive Texture Contrast (ATC)

The concept of ATC is developed from the empirical observation that pathological tissues exhibit distinctive texture patterns, which vary significantly in contrast across different scales. These patterns are crucial for distinguishing between normal and pathological tissue states and are particularly effective in identifying key genetic mutations, such as those associated with the EGFR.

The ATC computation is a detailed three-part process.

Fourier Transform

It is the first step in the ATC process involves transforming the region of interest (ROI) from the spa-

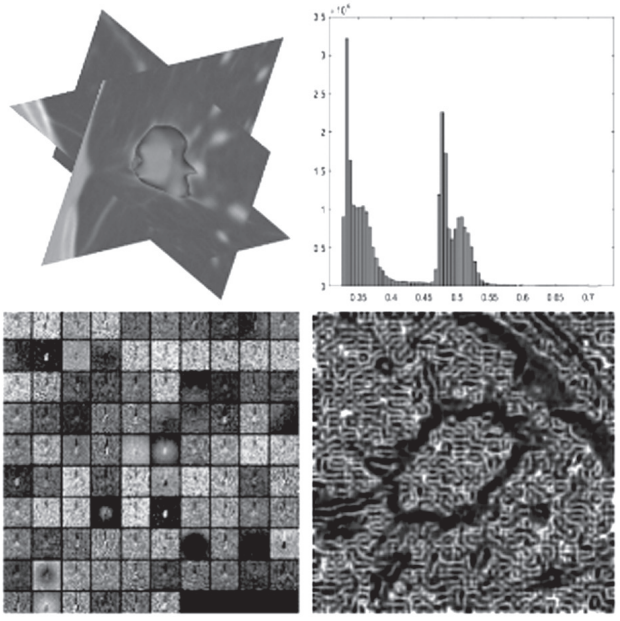

Fig. 1. Extracting features of radiomics

Рис. 1. Извлечение радиомических признаков

tial domain to the frequency domain using the Fourier Transform. This transformation is crucial as it allows us to analyze the frequency components of the image, facilitating the subsequent identification and isolation of dominant frequencies that are significant for textural analysis in the ROI).

Dominant Frequency Identification and Isolation

Following the transformation, the next step involves identifying and isolating dominant frequencies. This is achieved using a thresholding technique on the magnitude spectrum of the transformed data. A band-pass filter is applied to retain only those frequencies within a specific range set by a predefined threshold, effectively isolating the textures that are most relevant to the analysis.

Contrast Calculation

It is the final stage of the ATC workflow involves quantifying contrast levels within the isolated texture patterns. This is achieved through standardized metrics such as Michelson's contrast formula [11], expressed as:

$$C = \frac{L_{\max} - L_{\min}}{L_{\max} + L_{\min}}, \quad (1)$$

where, C denotes the contrast value, while L_{max} and L_{min} represent the maximum and minimum luminance values, respectively, within the ROI.

These luminance values are derived from the intensity levels highlighted by the band-pass filter, focusing on the texture patterns correlated with the dominant frequencies.

Directional Texture Uniformity (DTU)

DTU is engineered to evaluate the consistency of texture patterns across multiple orientations within a ROI. This metric is particularly vital for analyzing lung nodules, where pathological tissues often exhibit anisotropic (directionally dependent) textures – a hallmark of malignancy and genetic alterations like EGFR mutations. The degree of uniformity or spatial heterogeneity in these textures serves as a critical biomarker for distinguishing between benign and malignant transformations.

The DTU feature extraction process can be broken down into two main steps.

Applying Directional Filters

To effectively highlight specific texture orientations within the ROI, Gabor filters are employed, known for their efficacy in texture analysis. Gabor filters are particularly adept at isolating frequency content in precise orientations, making them ideal for distinguishing subtle textural differences in pathological tissues. The response of a Gabor filter applied to an image is mathematically defined as:

$$G(x, y; \lambda, \theta, \psi, \sigma, \gamma) = \exp\left(-\frac{x'^2 + \gamma^2 y'^2}{2\sigma^2}\right)\cos\left(2\pi\frac{x'}{\lambda} + \psi\right), \quad (2)$$

where,

$x' = x\cos\theta + y\sin\theta$;

$y' = -x\sin\theta + y\cos\theta$;

θ: Orientation angle of the filter's normal vector relative to the direction of parallel stripes, enabling directional sensitivity;

σ: Standard deviation of the Gaussian envelope (σ), dictating the spatial localization of the filter's response;

λ: Wavelength of the sinusoidal component, governing the periodicity of texture patterns captured;

ψ: Phase displacement, controlling the sinusoidal wave's alignment within the filter;

γ: Spatial aspect ratio, specifying the ellipticity of the filter's support region to accommodate anisotropic textures.

For this study, Gabor filters were configured to target specific frequencies and orientations based on preliminary analysis of lung CT images, which suggested enhanced detection of anomalous textures associated with EGFR mutations. The filter parameters were optimized through a series of experiments to maximize the detection accuracy of early-stage mutations.

Calculating the Uniformity

After filtering, uniformity of the emphasized textures is assessed, serving as a key indicator of tissue normalcy or pathology.

Entropy measures the randomness in the distribution of filtered image values, computed as:

$$H = -\sum_i p(i)\log_2 p(i), \quad (3)$$

where, H is the entropy, $p(i)$ is the probability of intensity level i in the filtered image.

High entropy values suggest significant texture variation, often correlating with pathological changes. Similarly, the dispersion of intensity values (variance) is analyzed to determine how widely texture intensities are spread about the mean, which assists in distinguishing pathological from normal textures. The specific methods and thresholds used for calculating these metrics are tailored to the unique characteristics of the lung nodule textures observed in the datasets. Variance provides a measure of how widely texture intensities are spread about the mean, further assisting in distinguishing pathological from normal textures.

Co-occurrence of Texture Transitions (CTT)

The feature represents an innovative texture-centric metric engineered to refine the precision of EGFR mutation status prediction in lung nodules. By systematically quantifying the spatial interplay among distinct textural configurations, CTT prioritizes transitions between these patterns within a defined ROI. Building on the framework of the gray-level co-occurrence matrix (GLCM) [12], CTT shifts analytical focus from basic pixel intensity variations to intricate textural pattern interactions, delivering a detailed perspective on tumor heterogeneity and architectural complexity.

CTT is designed to capture the evolution of texture within medical images, analyzing how different texture patterns interact spatially. This approach moves beyond the traditional GLCM, which primarily assesses gray-level spatial dependencies, to explore texture transitions that are indicative of underlying tissue architecture changes, such as those associated with pathological conditions like EGFR mutations.

The computation of CTT involves several key steps, each contributing to the extraction of this advanced feature.

Texture Pattern Identification

The process begins by distinguishing different texture patterns within the ROI. The process begins by distinguishing different texture patterns within the ROI. This categorization is achieved through unsupervised learning techniques that utilize rotation-invariant texture descriptors like Local Binary Patterns (LBP), which systematically group voxels with analogous textural properties.

The LBP operator is defined for each pixel by comparing it with its neighbors, computed as:

$$LBP(x_c, y_c) = \sum_{p=0}^{P-1} s(i_p - i_c) 2^p \quad (4)$$

where i_c is the intensity of the central pixel, i_p are the intensities of P surrounding pixels in a circular neighborhood, and s is the sign function:

$$s(x) = \begin{cases} 1 & x \geq 0 \\ 0 & otherwise \end{cases} \quad (5)$$

Techniques such as K-means are applied to the LBP values to systematically identify distinct texture patterns across the ROI.

Texture Transition Matrix (TTM) Generation

After identifying unique texture patterns, a Texture Transition Matrix (TTM) is constructed. This matrix is analogous to GLCM but focuses specifically on texture transitions rather than gray-level changes.

Statistical Analysis of TTM

Each element TTM(*i,j*) in the matrix quantifies the frequency of transitions between texture pattern ii and texture pattern j, considering a specified distance and direction, thus highlighting the spatial interplay of textures.

The final analytical phase involves calculating statistical measures on the TTM to derive meaningful features that reflect the texture transitions. The key statistics computed include:

– Contrast: Measures the intensity contrast between a pixel and its neighbor over the whole image:

$$Contrast = \sum_{i,j} (i-j)^2 TTM(i,j) \quad (6)$$

– Correlation: Evaluates how correlated a pixel is to its neighbor over the entire image:

$$Correlation = \sum_{i,j} \frac{(i-\mu_i)(j-\mu_j) TTM(i,j)}{\sigma_i \sigma_j} \quad (7)$$

– Energy: Sum of squared elements in the TTM, indicating texture uniformity:

$$Energy = \sum_{i,j} TTM(i,j)^2 \quad (8)$$

where, μ_i, μ_j are the means and σ_i, σ_j, the standard deviations of the row and column sums of the TTM, respectively. These statistics are crucial for understanding the spatial distribution and intensity variations of textures, providing insights that are directly relevant to diagnosing pathological changes associated with EGFR mutations.

Results / Результаты

The classification of pulmonary nodules into EGFR-mutant and wild-type subtypes was performed through quantitative analysis of standard radiomics biomarkers extracted from CT imaging. These biomarkers include morphometric parameters (e.g., spiculation index, lobulation degree), attenuation characteristics (e.g., histogram skewness, kurtosis), and spatial heterogeneity measures derived from second-order texture analysis, providing a multidimensional representation of nodule phenotype for molecular subtype discrimination.

For the study, the dataset was randomly divided into training and validation sets with an 70% training and 30% validation split. This resulted in 319 training samples and 173 validation samples for the EGFR mutant category. To achieve a more balanced dataset, the Wild-Type category was adjusted to include 578 training samples and 248 validation samples. Sev-

eral classification models were then trained and validated using this arrangement, achieving a baseline performance that serves as a reference for subsequent comparisons (Table 1). Table 2 highlights the reduction in false negatives and false positives, along with increases in true positives and true negatives for the EGFR mutant and wild-type categories.

The proposed features were meticulously designed to capture intricate texture patterns and variations within the lung nodules, potentially indicative of underlying genetic mutations. Upon incorporating these novel features into the existing set of radiomics features, a significant enhancement in classification performance was observed. Specifically, the addition of ATC, DTU, and CTT led to an average increase of about 4% in the accuracy of predicting the EGFR mutation status. This enhancement demonstrates the critical importance of advanced texture characterization in decoding tumor biology at the molecular scale, particularly for identifying genetic alterations that influence therapeutic response.

Discussion / Обсуждение

To objectively evaluate feature significance, the Minimum Redundancy Maximum Relevance (MRMR) algorithm [13] was implemented. This computationally efficient method identifies optimal feature subsets by maximizing statistical dependence on mutation status while minimizing inter-feature correlations, ensuring selection of maximally informative yet non-redundant biomarkers. Remarkably, the MRMR analysis, the results of which is provided in Table 3, revealed that ATC, DTU, and CTT emerged as the top-ranked features, indicating their paramount significance in the classification model. The MRMR results and classification performance metrics collectively validate the diagnostic value of these novel features, demonstrating their unique capacity to encode critical pathophysiological information directly relevant to EGFR mutation mechanisms.

The experimental results demonstrate that the proposed methodology achieves superior predictive performance compared to contemporary approaches in EGFR mutation detection. While recent investigations utilizing advanced deep architectures report notable accuracy benchmarks – Mut-SeResNet [14] attaining 88.3% accuracy through hybrid texture-morphological analysis and CT-based deep radiomics models [15] reaching 88% classification accuracy – our approach yields a 4% improvement in diagnostic precision (92% accuracy) (Table 4). This enhanced performance stems from the synergistic integration of:

– adaptive texture contrast quantification targeting mutation-specific spatial patterns;

Table 1

Comparison of classification methods' accuracy and precision before and after adding novel texture-based features, %

Таблица 1

Сравнение аккуратности и точности методов классификации до и после добавления новых текстурных признаков, %

Method / Метод	Accuracy / Аккуратность		Precision / Точность	
	Before / До	After / После	Before / До	After / После
Support Vector Machine (SVM) / Метод опорных векторов	85	89	87	91
Random Forest (RF) / Случайный лес	88	92	90	93
Neural Network (NN) / Нейронная сеть	86	90	88	92
Gradient Boosting (GB) / Градиентный бустинг	87	91	89	94

Table 2

Comparison of confusion matrix parameters before and after adding novel texture-based features for Random Forest

Таблица 2

Сравнение параметров матрицы неточностей до и после добавления новых текстурных признаков для метода «Случайный лес»

Category / Категория	Predicted EGFR mutant / Предсказанная мутация EGFR		Predicted EGFR wild-type / Предсказанный EGFR дикого типа	
	Before / До	After / После	Before / До	After / После
Actual EGFR mutant / Предсказанная мутация EGFR	TP=155	TP=161	FN=33	FN=18
Actual EGFR wild-type / Предсказанный EGFR дикого типа	FP=18	FP=12	TN=215	TN=230

Note. EGFR – epidermal growth factor receptor; TP – true positives; TN – true negatives; FP – false positives; FN – false negatives.

Примечание. EGFR (epidermal growth factor receptor) – рецептор эпидермального фактора роста; TP (true positives) – истинно-положительные результаты; TN (true negatives) – истинно-отрицательные результаты; FP (false positives) – ложноположительные результаты; FN (false negatives) – ложноотрицательные результаты.

Table 3

Minimum Redundancy Maximum Relevance analysis results

Таблица 3

Результаты анализа «минимум избыточности, максимум релевантности»

Feature / Признак	Importance score / Оценка важности
ATC	0.80
DTU	0.79
Contrast / Контраст	0.77
Eccentricity / Эксцентриситет	0.76
Entropy / Энтропия	0.75
CTT	0.74
Homogeneity / Однородность	0.72
Energy / Энергия	0.71
Uniformity / Единообразие	0.70
Correlation / Корреляция	0.69
Sphericity / Сферичность	0.68
Volume / Объем	0.67
Surface area / Площадь поверхности	0.65
Compactness / Компактность	0.64
Kurtosis / Эксцесс	0.63

Note. ATC – Adaptive Texture Contrast; DTU – Directional Texture Uniformity; CTT – Co-occurrence of Texture Transitions.

Примечание. ATC (Adaptive Texture Contrast) – адаптивный контраст текстуры; DTU (Directional Texture Uniformity) – направленная однородность текстуры; CTT (Co-occurrence of Texture Transitions) – совместная встречаемость переходов текстуры.

– directional uniformity analysis capturing genotypic anisotropy;

– dynamic texture transition modeling through co-occurrence relationships.

Table 4

Comparison with other studies

Таблица 4

Сравнение с другими исследованиями

Research / Исследование	Mutation type / Тип мутации	Accuracy, % / Аккуратность, %
This research / Наше исследование	EGFR	92
Mut-SeResNet [14]	EGFR	88
Prediction model [15] / Модель прогнозирования [15]	EGFR	87

The accuracy differential underscores the critical advantage of specialized feature engineering over conventional deep learning pipelines in decoding subtle phenotypic manifestations of genetic alterations. These findings validate the clinical potential of dedicated texture analysis frameworks while highlighting the necessity for continued innovation in radiomic biomarker development.

This study has leveraged explainable artificial intelligence techniques to elucidate the mechanisms behind machine learning models used in classifying EGFR mutant from wild-type lung nodules which is shown in Figure 2. Insights from these methods have revealed that the current models predominantly focus on the edges of nodules to make their classifications. This observation suggests that the edges of nodules carry significant discriminatory features that are crucial for accurate differentiation.

Building on this finding, future research should concentrate on developing and refining features that specifically enhance the visibility and analytical emphasis on the edges of lung nodules. Such efforts could involve engineering new image processing algorithms or adapting existing ones that more effectively capture

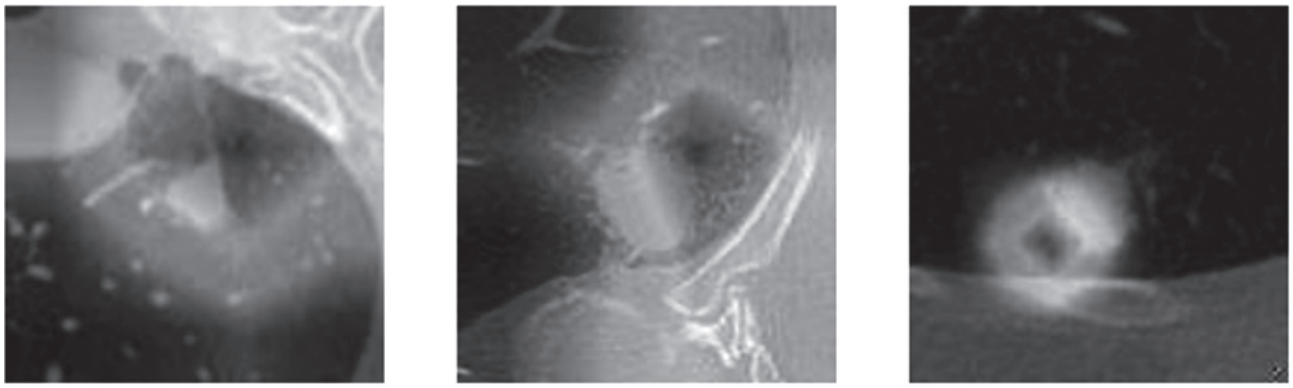

Fig. 2. Explainable artificial intelligence analysis of Residual Neural Network (ResNet) for classifying EGFR mutant and wild-type lung nodules

Рис. 2. Объяснимый анализ остаточной нейронной сети (ResNet) с помощью искусственного интеллекта для классификации мутантных и диких типов легочных узелков EGFR

edge-related features, which may include sharpness, texture gradients, or specific morphological markers.

Moreover, incorporating these edge-focused features into machine learning models could potentially improve the sensitivity and specificity of diagnostic tools, thereby facilitating earlier and more accurate detection of EGFR mutations. This line of research will not only push the boundaries of what is currently achievable with medical imaging analysis but also contribute to the personalized medicine approach by providing more tailored diagnostic insights based on subtle imaging cues.

Conclusion / Заключение

This study embarked on the quest to enhance the diagnostic precision of CT-based lung nodule classification by incorporating novel texture-based radiomics features, specifically aimed at distinguishing between EGFR mutant and wild-type statuses. The conventional radiomics feature set, while comprehensive, was augmented with three innovative texture descriptors: ATC, DTU, and CTT. These features were meticulously designed to capture subtle yet discriminative texture patterns within the nodules, potentially indicative of underlying genetic mutations.

The integration of ATC, DTU, and CTT into the radiomics framework resulted in a notable improvement in classification performance, with a 4% increase in accuracy. This enhancement underscores the critical role of texture analysis in the non-invasive assessment of lung nodules, offering a deeper insight into their genetic underpinnings. Furthermore, the significance of these novel features was affirmed by the MRMR feature selection method, where they were identified as the most impactful variables in the predictive model.

The findings of this research underscore the potential of advanced feature engineering in the realm of medical imaging, particularly in the context of lung cancer diagnostics. By providing a more detailed and nuanced analysis of lung nodules, the proposed texture-based features contribute to the broader goal of personalized medicine, enabling targeted therapies tailored to the genetic profile of tumors.

In conclusion, this study not only highlights the value of integrating novel radiomics features for the classification of lung nodules but also paves the way for future investigations into the development of more sophisticated diagnostic tools. As the field of radiomics continues to evolve, the pursuit of innovative features that can capture the complex biological characteristics of tumors will remain paramount in enhancing the accuracy of cancer detection and characterization.

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