RADIOMIC CHARACTERIZATION OF LYMPH NODES IN NON-SMALL CELL LUNG CANCER

Vladyslav Kobets[1]

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Abstract. Accurate cancer staging remains fundamental to contemporary oncology, as it underpins prognostic assessment, informs therapeutic decision-making and guides follow-up strategies. In non-small cell lung cancer (NSCLC), regional lymph node involvement represents a central component of TNM staging and is among the most powerful determinants of patient outcomes, including overall and disease-free survival. Nevertheless, the conventional anatomical N-category provides only a limited representation of nodal disease, as it does not capture the quantitative extent of metastasis or the biological heterogeneity of lymph node involvement. To overcome these limitations, alternative quantitative nodal metrics, such as the lymph node ratio (LNR) and the log odds of positive lymph nodes (LODDS), have been proposed and shown to improve prognostic stratification across multiple oncologic settings. However, these metrics are derived exclusively from postoperative pathological data and therefore cannot be applied during preoperative clinical staging, when many key treatment decisions must be made. This gap highlights the need for non-invasive methods capable of approximating nodal metastatic burden in vivo. Radiomics has emerged as a quantitative imaging approach that enables the extraction of high-dimensional data from routinely acquired medical images, including computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT). By transforming images into mineable data, radiomics allows quantitative characterization of tumor heterogeneity, morphology and spatial organization. While radiomic analysis of primary lung tumors has been widely investigated and consistently associated with survival, treatment response and molecular characteristics, radiomics of regional lymph nodes remains comparatively underexplored. The aim of this work

[1] PhD student, Department of Oncology and Radiology,
Sumy State University, Ukraine

is to critically evaluate the current evidence on radiomics in oncology, with particular emphasis on the role of lymph node radiomics in NSCLC and to justify its potential value as a complementary tool to anatomical staging and postoperative nodal metrics. *Materials and Methods.* A narrative review of peer-reviewed scientific publications predominantly indexed in the PubMed database was conducted, encompassing studies on TNM staging, quantitative nodal metrics including the lymph node ratio (LNR), log odds of positive lymph nodes (LODDS), radiomics of primary lung tumors and emerging radiomic approaches focused on lymph node assessment. *Results.* Existing evidence indicates that radiomic features of primary tumors, particularly those reflecting intratumoral heterogeneity, are associated with aggressive tumor behavior, reduced survival and resistance to systemic therapies in NSCLC. However, exclusive focus on the primary lesion provides an incomplete representation of the systemic nature of cancer, especially in locally advanced and metastatic disease. Regional lymph nodes, as sites of early dissemination and immune–tumor interaction, may exhibit biological properties distinct from the primary tumor due to clonal evolution and selective pressures. Despite their central role in staging and prognosis, radiomic analysis of lymph nodes remains limited, largely because of technical challenges related to segmentation accuracy, small lesion volume, lack of standardized imaging protocols and restricted histopathological correlation. *Conclusion.* Radiomics of lymph nodes represents a promising yet insufficiently developed direction in oncologic imaging. Further investigation may enable the development of non-invasive imaging biomarkers that approximate nodal metastatic burden in vivo, potentially serving as preoperative analogues of LNR and LODDS. Integration of lymph node radiomics with established staging systems and quantitative nodal metrics may improve risk stratification, support personalized treatment planning and enhance prognostic accuracy in NSCLC. Well-designed, standardized and multicenter studies are required to validate lymph node radiomic biomarkers and facilitate their translation into routine clinical practice. *Practical implications.* Quantitative radiomic analysis of lymph nodes in metastatic NSCLC may improve pre-treatment risk stratification beyond conventional TNM staging. It enables non-invasive assessment of metastatic burden in vivo and may help identify patients who require intensified systemic therapy or closer follow-up. Integration

of lymph node radiomic features with clinical and molecular parameters can enhance individualized treatment planning and support early prediction of therapeutic response, particularly in the setting of immunotherapy. *Value/originality.* This work emphasizes lymph nodes as an independent radiomic target rather than focusing solely on the primary tumor. It proposes a conceptual framework for using lymph node radiomics as a potential preoperative analogue of quantitative nodal metrics (e.g., LNR, LODDS). The originality lies in addressing the metastatic component of NSCLC as a central prognostic determinant and providing a methodological basis for future validation of lymph node-based radiomic biomarkers.

1. Introduction

Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer-related mortality worldwide, primarily due to the high incidence of late-stage diagnosis, pronounced biological heterogeneity of the tumor process and variable response to systemic therapy [1].

In contemporary clinical practice, the TNM classification system plays a pivotal role in staging, prognostication and therapeutic decision-making. However, its predominantly anatomical framework does not fully capture the true metastatic burden or the biological characteristics of the tumor, particularly at the level of regional lymph nodes [2]. This limitation contributes to the presence of clinically heterogeneous patient groups within the same disease stage and reduces the accuracy of predicting disease course and treatment response. In this context, radiomics has emerged as a particularly relevant non-invasive method for quantitative medical image analysis, enabling the transformation of CT and PET/CT data into multidimensional in vivo biomarkers of tumor phenotype [3].

Radiomic approaches have demonstrated the ability to quantitatively assess intratumoral and inter-lesional heterogeneity to construct prognostic models associated with survival outcomes and potentially to aid in predicting response to systemic therapy even prior to treatment initiation [4]. Nevertheless, the majority of existing radiomics research in NSCLC has predominantly focused on the analysis of the primary tumor, whereas radiomic assessment of regional lymph nodes remains insufficiently explored, despite their pivotal role in staging, prognostication and treatment strategy selection [5]

The scientific novelty of this study lies in the analytical substantiation and systematization of approaches to the radiomic evaluation of lymph nodes as both an independent and complementary source of prognostic and predictive information in metastatic NSCLC. Furthermore, it explores the potential application of lymph node radiomic features for the indirect quantitative assessment of metastatic burden in vivo.

The aim of the study is to determine the role of lymph node radiomics in predicting response to systemic therapy and the clinical course of metastatic NSCLC.

To achieve this objective, the following research tasks were formulated: 1) to analyze contemporary approaches to the radiomic evaluation of the primary tumor in NSCLC and their clinical significance; 2) to substantiate the prognostic role of lymph nodes within the TNM classification system and modern quantitative nodal metrics; 3) to examine the methodological principles of radiomic analysis, including image acquisition, segmentation, feature extraction and the development of prognostic models; 4) to assess the potential of lymph node radiomics as a non-invasive tool for the quantitative characterization of the metastatic process and the personalization of treatment.

The study methodology is based on the analysis and synthesis of contemporary scientific publications devoted to the application of radiomics in NSCLC, employing methods of systematic literature review, comparative analysis and logical synthesis. The work addresses methodological aspects of radiomic analysis, including the standardization of imaging protocols, segmentation of regions of interest, extraction of quantitative features and the development of statistical and machine learning models.

The logic of the presentation of the material involves a sequential progression from the general principles of staging and the role of lymph nodes in NSCLC to radiomic approaches, with subsequent emphasis on the methodological foundations of radiomics and its potential for the quantitative assessment of metastatic involvement of lymph nodes.

2. The role of lymph nodes in TNM staging

The TNM system is a classification framework used to describe the anatomical extent of tumor spread in malignant neoplasms and is universally accepted worldwide. It has been developed and is maintained

by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC).

The TNM classification consists of three principal components: T (Tumor), which characterizes the primary tumor; N (Nodes), which reflects the status of regional lymph nodes; and M (Metastasis), which indicates the presence or absence of distant metastases [6]. At present, the 8th edition of the TNM classification is the most widely applied in clinical practice. However, the International Association for the Study of Lung Cancer (IASLC) has proposed updates aimed at developing the 9th edition, particularly with regard to refinement of the N descriptor in light of accumulated clinical and prognostic data [7]. This system serves as a universal language for describing the oncological process and ensures a standardized approach to staging malignant neoplasms in both clinical practice and scientific research.

In contemporary oncology, TNM staging plays a pivotal role in patient stratification, prognostic assessment and the selection of optimal therapeutic strategies, including decisions regarding the appropriateness of surgical intervention, combined modality treatment or systemic therapy, in which the status of regional lymph nodes represents one of the key determining factors [8].

The role of the N component in the TNM classification system. A particularly important element of the TNM system is the N category, which is of decisive significance for determining disease stage, selecting an appropriate treatment strategy and predicting clinical outcomes. Nodal status reflects the condition of regional lymph nodes and takes into account not only the presence of metastatic involvement and the anatomical localization of affected regional lymph nodes, but also the clinical and imaging characteristics of nodal disease utilized in practical oncology. These characteristics define the extent of lymphatic system involvement in the tumor process and indirectly reflect the biological aggressiveness of the disease.

According to the TNM system developed and maintained by the American Joint Committee on Cancer, the N0 category indicates the absence of metastatic involvement of regional lymph nodes, whereas N1, N2 and N3 reflect different levels of lymphogenous metastasis depending on the anatomical location of the affected lymph nodes relative to the primary

tumor. This approach enables clear differentiation of patients according to the extent of regional tumor spread and serves as a foundation for subsequent clinical stratification. Numerous clinical studies have demonstrated that an increase in the N category is associated with progression to more advanced disease stages and a significant deterioration in overall and disease-free survival outcomes, underscoring the pivotal prognostic role of nodal status in contemporary oncological practice [9].

Importantly, regardless of the size and local characteristics of the primary tumor, the presence of metastatic involvement of regional lymph nodes results in a change in clinical stage, a substantial reduction in survival rates and a significant influence on the choice between surgical, combined modality or systemic treatment. In contrast to the T component, which predominantly reflects the local characteristics of the primary tumor, the N category directly characterizes the involvement of the lymphatic system in the tumor process and reflects the tumor's capacity for lymphogenous metastasis and subsequent systemic dissemination. Accordingly, in many clinical scenarios, the N component carries greater prognostic weight than the T component, as it is associated with a higher risk of distant metastasis, recurrence and reduced survival outcomes.

In light of this, a detailed and accurate assessment of regional lymph node status constitutes a key prerequisite for the effective management of oncology patients in contemporary clinical practice. Nodal status largely determines the clinical stage of the disease, influences the choice between surgical, combined modality or systemic treatment and exerts a direct impact on prognosis.

3. Limitations of the anatomical approach to staging

The TNM system, based on the anatomical principle of tumor assessment, ensures universality, standardization and high reproducibility of results, which accounts for its widespread use in both clinical practice and scientific research. However, despite its practicality and clinical value, TNM staging has significant limitations in assessing the true metastatic burden, as it primarily focuses on the localization and anatomical extent of disease without systematically incorporating quantitative and qualitative characteristics of the metastatic process [10].

In particular, the anatomical approach does not allow for the assessment of the extent of metastatic involvement of lymph nodes, their internal structural and biological heterogeneity or potential differences between individual metastatic deposits. This substantially limits the prognostic capabilities of the TNM system and its capacity for accurate risk stratification, especially in patients with NSCLC who may formally belong to the same stage group yet exhibit fundamentally different disease trajectories and clinical outcomes.

The lack of consideration of the number of metastatic lymph nodes, the proportion of positive nodes relative to the total number of nodes within a given anatomical group, the volume of tumor tissue within an individual lymph node, the presence of extranodal extension, as well as characteristics such as nodal density, internal heterogeneity and the degree of necrosis, is regarded as one of the key limitations of the anatomical TNM staging approach. The omission of these parameters results in the formation of clinically heterogeneous patient groups, within which individuals with fundamentally different metastatic burdens may be assigned to the same disease stage.

In practical terms, this means that patients with an identical TNM stage may experience markedly different disease courses, varying risks of recurrence and unequal responses to administered treatment. Such clinical variability is particularly characteristic of NSCLC, which is distinguished by pronounced biological and spatial heterogeneity of the tumor process. As a consequence, an anatomical classification based solely on the localization and extent of disease proves insufficiently sensitive for precise risk stratification and prediction of individual clinical outcomes. Moreover, TNM staging does not provide for the assessment of the internal structural heterogeneity of metastatic lymph nodes, although these characteristics may serve as markers of tumor biological aggressiveness and its potential for further systemic dissemination.

The volume of metastatic involvement, the degree of necrosis and the presence of extranodal extension are regarded as important factors associated with poorer prognosis; however, they are not integrated into the standard TNM staging system, which further limits its prognostic potential.

4. LODDS and LNR as novel metrics for more accurate prognostic assessment

The volume of metastatic involvement, the degree of necrosis, the presence of extranodal extension and the internal heterogeneity of lymph nodes are regarded as important factors associated with poorer prognosis; however, they are not incorporated into the standard staging system. These limitations of the anatomical approach substantiate the need for the implementation of novel, more sensitive methods for assessing lymph node status. Such approaches include quantitative evaluation of metastatic burden, the use of extended nodal metrics and the application of radiomic techniques, which enable the integration of morphological, textural and spatial characteristics of lymph nodes into prognostic models and adjunctive tools for clinical stratification of the oncological process. The implementation of these approaches opens new opportunities for more accurate patient stratification, personalization of therapeutic strategies and improved prediction of the clinical course of NSCLC.

To date, several contemporary quantitative metrics of nodal status have been proposed, among which the most extensively studied and clinically significant are LNR (lymph node ratio) and LODDS (log odds of positive lymph nodes). These indicators have demonstrated independent prognostic value across various oncological entities, including lung, gastric, breast and colorectal cancers and are considered a potentially effective complement to traditional anatomical TNM staging [11]. Their introduction is driven by the need for a more accurate assessment of regional metastatic burden, which is not fully captured by the standard N category. Unlike the classical N component, the LNR and LODDS metrics not only record the presence of metastatic involvement of regional lymph nodes but also quantitatively characterize the extent of lymphatic system involvement by accounting for the ratio between affected and unaffected nodes. Such an approach enables a more detailed description of the metastatic process and reduces patient heterogeneity within a single TNM stage. The application of these metrics provides more precise stratification of patients with similar anatomical disease characteristics but differing risks of progression, recurrence and survival outcomes, thereby further underscoring the limited prognostic capacity of a purely anatomical staging approach.

The LNR indicator reflects the proportion of metastatic lymph nodes and is calculated as the ratio of the number of positive nodes to the total number of resected and histologically examined lymph nodes. LNR is determined according to the following formula: $LNR = \frac{N(+)}{N(E)}$, where N (+) denotes the number of metastatic (positive) lymph nodes and N (Examined) represents the total number of histologically examined lymph nodes. This metric allows not only the assessment of the mere presence of metastases but also the relative extent of lymphatic system involvement, which carries direct prognostic significance. For example, in patient "A", one metastatic lymph node is identified among 20 examined (LNR = 0.05), whereas in patient "B", one metastatic node is identified among 2 examined (LNR = 0.5). Despite a potentially identical N category according to the TNM classification, the actual metastatic burden in these patients differs substantially, which may translate into significant differences in prognosis, risk of recurrence and disease course. This example clearly illustrates the clinical relevance of quantitative nodal metrics for a more accurate assessment of the oncological process. At the same time, a major limitation of the LNR metric is its critical dependence on the number of examined lymph nodes, particularly in cases of limited lymphadenectomy or incomplete surgical staging. Under such circumstances, the LNR value may be unstable and may lead to misestimation of metastatic burden, thereby limiting its universality and highlighting the need to identify more robust quantitative indicators of nodal status, particularly those less dependent on the extent of lymph node dissection [12].

In this context, LODDS (log odds of positive lymph nodes) is considered a more stable quantitative metric of nodal status, as it compares the number of metastatic and non-metastatic lymph nodes in logarithmic form, thereby reducing the impact of variability in the total number of examined nodes [13]. Unlike the LNR indicator, which is sensitive to the extent of lymphadenectomy, LODDS provides a more robust assessment of metastatic burden even in cases with a limited number of resected lymph nodes, which is of particular relevance in clinical practice. Formally, the LODDS metric is calculated according to the following formula: $LODDS = \log\left(\frac{(N(+)+0,5)}{(N(-)+0,5)}\right)$, where N (+) denotes the number

of metastatic (positive) lymph nodes, N(–) represents the number of non-metastatic (negative) nodes and the addition of the constant 0.5 is a technical adjustment that ensures mathematical validity in cases of complete absence of metastasis or, conversely, total lymph node involvement. This approach prevents extreme values and improves the reproducibility of the metric across different clinical scenarios. Owing to these properties, LODDS demonstrates greater prognostic stability compared with LNR, particularly in patients with a low number of examined lymph nodes or a formally negative nodal status according to the TNM classification. This renders LODDS a more suitable tool for risk stratification in clinically heterogeneous patient groups, where anatomical staging does not provide sufficient prognostic discrimination [14].

Elevated LNR and LODDS values are consistently associated with poorer overall and disease-free survival, even after adjustment for the baseline N category within the TNM classification, thereby confirming their ability to reflect the actual metastatic burden more comprehensively than purely anatomical staging. The application of these metrics improves risk stratification among patients with formally identical disease stages and may provide a basis for the potential individualization of therapeutic strategies, including the selection of more aggressive adjuvant chemotherapy regimens, extended postoperative radiotherapy and/or inclusion of patients in more intensive clinical surveillance programmes.

5. Radiomics in the evaluation of tumor and metastatic lesions

Despite their proven prognostic value, the LNR and LODDS metrics can be assessed only after surgical intervention, as they are based on the pathological examination of resected lymph nodes. In contemporary oncology, where a substantial proportion of clinical decisions regarding treatment strategy must be made preoperatively at the stage of clinical staging, this limitation significantly restricts their practical applicability in the preoperative setting. Accordingly, there is a growing need to identify non-invasive methods for assessing metastatic burden that are capable of providing a quantitative characterization of nodal status in vivo. In this context, radiomics has gained particular relevance, as it offers the possibility of quantitatively evaluating lymph node status in vivo and of developing potential preoperative surrogate markers conceptually related

to LNR and LODDS, thereby substantially expanding the capabilities of modern clinical staging [15].

Radiomics complements classical imaging diagnostics and invasive methods of morphological verification, occupying an interdisciplinary position within modern medical imaging. It is based on the quantitative analysis of digital medical images obtained through computed tomography, magnetic resonance imaging and positron emission tomography, with the aim of deriving objective numerical characteristics of tissues and the tumor process in vivo. The extracted parameters are subsequently used for statistical analysis, the development of prognostic and predictive models and clinical decision support in contemporary oncology [16]. In contrast to the traditional approach in imaging diagnostics, which relies predominantly on visual assessment of size, shape, density and signal intensity, radiomic methods enable the detection of latent patterns and complex textural features within image structures that are not directly perceptible to the human eye. Within this framework, medical imaging ceases to serve merely as an illustration of anatomical alterations and is instead regarded as a multidimensional source of biological information reflecting tissue microstructural organization, heterogeneity of cellular populations and characteristics of the tumor microenvironment.

A key advantage of radiomics lies in its ability to perform non-invasive tumor analysis while accounting for intratumoral heterogeneity, which is recognized as one of the principal determinants of malignant aggressiveness, therapeutic resistance and adverse prognosis [17]. Intratumoral heterogeneity reflects complex biological processes, including clonal evolution, variability in cellular composition and the degree of angiogenesis and hypoxia, which cannot be adequately assessed using standard morphological or visual methods [18]. Unlike biopsy-based techniques, which represent only a limited portion of the tumor and are susceptible to sampling bias, radiomics enables analysis of the entire tumor mass in three-dimensional space, as well as associated anatomical structures, including regional lymph nodes. This creates opportunities for a comprehensive quantitative evaluation of the tumor process, taking into account spatial heterogeneity and the interaction between the primary tumor and metastatic deposits. Accordingly, the radiomic approach allows quantitative characterization of multiple aspects of malignancy, including internal structural heterogeneity,

potential biological aggressiveness, likely response to systemic therapy and the risk of disease progression and recurrence [19].

In contemporary oncology, radiomics is regarded not merely as an adjunctive imaging tool, but as a promising method for non-invasive tumor phenotyping that can complement clinical, morphological and molecular approaches to risk stratification and treatment personalization [20]. Medical images in modern oncology are increasingly viewed not simply as illustrations of anatomical structures, but as multidimensional sources of biological information, in which each voxel contains quantitative characteristics that may serve as indirect markers of tumor biological behaviour in vivo. This approach reflects a conceptual shift from purely morphological assessment towards a functional-biological interpretation of imaging data. In this context, radiomics emerges as a methodological platform that enables the transformation of medical images into a source of quantitative biomarkers of the tumor process.

Principles of radiomics. Radiomics is founded on the principles of quantification, reproducibility, multidimensionality and biological interpretability, thereby establishing a methodological framework for the development of non-invasive approaches to assessing tumor aggressiveness and metastatic burden. The application of these principles enables a transition from descriptive image analysis to a systematic quantitative approach aimed at generating objective and reproducible parameters, with subsequent integration into prognostic and predictive models [21].

At the core of the principle of quantification lies the transition from qualitative, subjective analysis of medical images to a formalized quantitative approach, in which each voxel is regarded as a source of numerical information and their aggregate as a multidimensional data space. This approach involves the extraction of a large number of numerical parameters from a clearly defined region of interest, such as the primary tumor or a regional lymph node. Such a framework minimizes interpretative subjectivity, standardizes the analytical process and enables the application of mathematical and statistical methods for information processing in order to identify latent patterns within the tumor process. Within this paradigm, a medical image ceases to be solely a visual object and is transformed into a structured data matrix suitable for multidimensional analysis and the development of prognostic models.

One of the key prerequisites for the implementation of radiomics in clinical practice is the principle of reproducibility, which implies the stability of radiomic features across repeated examinations, variations in scanning parameters and the use of different tomographic systems and software platforms [22]. High reproducibility is critically important for multicenter validation of results, comparison of data across different research platforms and the subsequent clinical integration of radiomic approaches. Given that radiomic analysis is highly sensitive to the quality of source images, standardization of imaging protocols, reconstruction parameters and data preprocessing is of paramount importance. Adherence to unified protocols enables valid comparison of results between different research centers, ensures the stability of radiomic features and represents a key prerequisite for the further integration of radiomics into clinical practice. In the context of lymph node analysis, where structures are often small and anatomically complex, issues of standardisation and reproducibility become particularly significant [23].

At the same time, contemporary radiomics research has shifted its emphasis from purely mathematical precision and statistical significance of derived parameters towards their biological plausibility, as reflected in the principle of biological interpretability [24]. According to this principle, radiomic features should not merely demonstrate correlations with clinical endpoints, but should also possess a comprehensible biological foundation, reflecting fundamental processes such as tumor growth, invasion, angiogenesis, hypoxia and tumor-microenvironment interactions. Such interpretability constitutes a key prerequisite for the translation of radiomic models into clinical practice, as it enables integration of quantitative imaging-derived parameters with the clinical presentation of disease and supports their use in predicting disease course or estimating the likely response to treatment.

The principle of multidimensionality and integration involves the simultaneous analysis of a large number of radiomic features, enabling the description of the complex spatial and structural organization of the tumor process, including its internal heterogeneity and variability in biological properties. Such a multidimensional approach provides a substantially more comprehensive characterization of the tumor compared with traditional unidimensional parameters; however, it also introduces methodological

challenges related to high data dimensionality, feature diversity and the risk of model overfitting. Accordingly, the application of statistical modelling and machine learning techniques constitutes an integral component of contemporary radiomic analysis. These methods are employed to select the most informative and reproducible features, reduce data dimensionality and develop robust prognostic or predictive models [25].

The integration of radiomic features with clinical, laboratory and molecular parameters enables the development of comprehensive models aimed at personalized prediction of disease course and individualization of therapeutic strategies. In this context, radiomics is regarded not only as a tool for quantitative image analysis, but also as a means of achieving a deeper understanding of tumor biology, combining medical imaging data with contemporary big data analytical approaches. Such a framework opens prospects for the development of personalized treatment strategies based on individual characteristics of the tumor phenotype as determined in vivo [26].

Main methodological stages of radiomic analysis. From a methodological perspective, radiomic analysis represents a sequential, multistep process aimed at transforming medical images into quantitative biomarkers of the tumor process. The first and fundamentally important stage involves the acquisition of input data, which are typically derived from computed tomography and PET/CT and less frequently from magnetic resonance imaging, performed according to standardized protocols. The stability and reproducibility of radiomic features largely depend on technical imaging parameters, including slice thickness, reconstruction algorithms and dose characteristics. Accordingly, contemporary methodological recommendations emphasize the necessity of harmonizing scanning protocols and minimizing inter-center technical variability, which constitutes a key prerequisite for the valid interpretation of radiomic parameters.

The next fundamental stage is segmentation of the region of interest, which involves precise delineation of the primary tumor, metastatic lesion or regional lymph node. Segmentation may be performed manually, semi-automatically or fully automatically; however, irrespective of the method used, its quality is of critical importance, as the boundaries of the delineated region directly influence the values of the extracted features. This is particularly relevant when analyzing small anatomical structures, such as

mediastinal lymph nodes, where even minor segmentation inaccuracies may result in substantial alterations of radiomic parameters. Therefore, the literature emphasizes the importance of controlling inter-observer variability and employing standardized segmentation approaches [27].

Following segmentation, quantitative radiomic features are extracted, which are conventionally classified into several principal groups. These include first-order features describing the distribution of signal intensity or density (such as mean value, median, skewness, kurtosis, etc.); morphological features characterizing geometric properties of the structure, including volume, sphericity and compactness; and texture features calculated on the basis of grey-level texture matrices (GLCM, GLRLM, GLSZM and NGTDM), which reflect spatial signal organization, entropy, contrast and degree of homogeneity. In addition, multiscale wavelet features and Laplacian of Gaussian (LoG) features are extracted, enabling analysis of microstructural patterns at different levels of spatial resolution. According to review studies, texture and multiscale parameters are regarded as among the most informative for the quantitative representation of biological heterogeneity within the tumor process [28].

The subsequent stage involves processing and analysis of the extracted data, including feature normalization, harmonization across different imaging protocols, selection of stable and reproducible parameters and dimensionality reduction in order to prevent model overfitting.

The final stage involves the construction of prognostic or predictive models using statistical approaches and machine learning algorithms, including logistic regression, Cox proportional hazards models, random forest algorithms, support vector machines (SVM) and gradient boosting techniques. An integral component of this stage is both internal and external validation of the models, employing metrics such as the area under the receiver operating characteristic curve (AUC), the concordance index (C-index), calibration analysis and decision curve analysis.

Taken together, these stages constitute the conceptual framework of radiomics as a non-invasive tool for quantitative analysis of the tumor phenotype in vivo, enabling the integration of medical imaging data with clinical, morphological and molecular parameters for predicting disease course and assessing the likelihood of treatment response [29].

6. Role of radiomics in NSCLC

Radiomics assumes particular importance in NSCLC, which is characterized by pronounced biological, spatial and clonal heterogeneity that substantially influences disease course, risk of progression and response to treatment [30]. NSCLC exhibits considerable variability in morphological, molecular and functional tumor characteristics, resulting in heterogeneous clinical outcomes even among patients with similar stage-related features. In this context, radiomic analysis enables quantitative assessment of intratumoral heterogeneity, which is regarded as one of the key mechanisms underlying therapeutic resistance, disease progression and the development of an aggressive biological phenotype in NSCLC [31].

The most common application of radiomics in NSCLC is *the quantitative assessment of intratumoral heterogeneity*, which reflects the complex biological organization of the tumor process in vivo [32]. Intratumoral heterogeneity arises from clonal evolution of tumor cells, spatial differences in vascularization, hypoxia and necrosis, as well as variable interactions between the tumor and its microenvironment. These processes lead to the formation of subclones with differing proliferative activity, invasive potential and sensitivity to systemic therapy, thereby directly influencing disease course and clinical treatment outcomes. In practice, radiomic evaluation of heterogeneity is implemented through analysis of the spatial distribution of voxel intensities within the region of interest using second- and higher-order texture matrices. In particular, GLCM, GLRLM, GLSZM and NGTDM matrices enable transformation of the complex microstructure of the image into numerical parameters such as entropy, contrast, heterogeneity, cluster organization and signal complexity. These parameters quantitatively describe the degree of spatial variability in signal density or intensity, which is regarded as an indirect marker of microscopic heterogeneity within tumor tissue [33].

Numerous studies in NSCLC have demonstrated that a radiomic profile characterized by high heterogeneity – typically reflected by elevated values of entropy, contrast and multiscale (wavelet or LoG) features – is associated with a more aggressive biological tumor phenotype. Such a profile correlates with poorer overall and progression-free survival, an increased risk of disease progression and reduced efficacy of systemic therapy. High radiomic heterogeneity is considered to reflect the presence of therapeutically

resistant subclones and a complex tumor microarchitecture that complicates the achievement of durable disease control [34]. An important feature of the radiomic approach is the ability to assess heterogeneity not only within a single tumor focus but also between multiple lesions of the malignant process. In metastatic NSCLC, spatial and textural differences between the primary tumor, distant metastases and regional lymph nodes may be formalized as inter-lesional radiomic parameters, thereby reflecting interconal heterogeneity.

Another key area of application of radiomics in NSCLC is *the prediction of survival outcomes*, particularly overall survival (OS) and progression-free survival (PFS), based on baseline imaging data and, in certain studies, incorporating dynamic changes observed during treatment. The primary objective of this approach is to achieve more precise risk stratification among patients with the same clinical stage of disease and to support decisions regarding the intensity of systemic therapy and subsequent clinical surveillance strategies [35]. From a technical perspective, survival prediction is implemented through the development of time-to-event models in which radiomic features or an aggregated radiomic parameter (radiomic signature or radiomic score) are integrated with clinical and demographic covariates. The most commonly applied approaches include Cox proportional hazards models or their machine learning-based counterparts, such as random survival forests and gradient boosting survival models. The prognostic performance of these models is evaluated using the concordance index (C-index), time-dependent area under the ROC curve (time-dependent AUC) and calibration analysis; the results are typically interpreted by stratifying patients into low- and high-risk groups with significantly different survival curves. Such stratification can be performed at the preoperative stage and prior to initiation of systemic therapy, thereby enabling individualized in vivo prognostic assessment without reliance on pathological staging data. This is of particular clinical relevance for patients with locally advanced or metastatic NSCLC, in whom access to comprehensive morphological verification of lymph node status is often limited. Numerous clinical studies have demonstrated that the combination of radiomic features with clinical factors, such as disease stage, patient performance status and baseline laboratory parameters, provides superior

prognostic accuracy for overall survival (OS) and progression-free survival (PFS) compared with traditional clinical models alone. This has been confirmed both in patients undergoing chemoradiotherapy and in cohorts receiving PD-1/PD-L1 inhibitor-based immunotherapy, underscoring the broad potential of radiomics as a non-invasive tool for survival prediction in NSCLC [36].

Another equally important area of application of radiomics in NSCLC is *the prediction of response to anticancer therapy* prior to its initiation or at early stages of treatment. The primary objective of such approaches is the non-invasive identification of patients who are more likely to achieve an objective response, disease control or prolonged progression-free survival following chemotherapy, chemoradiotherapy, targeted therapy or immunotherapy [37]. From a technical perspective, radiomic prediction of treatment response is implemented through the development of classification or semi-quantitative models in which treatment outcome is formalized as a binary or categorical variable (for example, response versus non-response, disease control versus progression or progression-free survival ≥6 months versus <6 months). The input data for these models consist of selected radiomic features extracted from CT or PET/CT images of the primary tumor, sometimes combined with clinical variables such as ECOG performance status, clinical disease stage, PD-L1 expression level or prior lines of therapy. Radiomic features most informative for predicting therapeutic response are those related to intratumoral heterogeneity, particularly texture parameters (entropy, contrast, heterogeneity derived from GLCM, GLRLM and GLSZM matrices), as well as first-order features describing signal intensity and geometric tumor characteristics, including volume, sphericity and compactness. Biologically, these parameters reflect the microstructural organization of tumor tissue, the presence of necrosis and hypoxia and variability in cellular density and stromal components, all of which are associated with sensitivity to systemic therapy. Particularly compelling results have been reported in patients with NSCLC receiving PD-1/PD-L1 inhibitor-based immunotherapy, where radiomic models are frequently optimized not only for assessment of classical objective response, but also for so-called durable clinical benefit, as well as early surrogate endpoints such as disease control or progression-free survival at 6 months (PFS-6).

The integration of radiomic features with baseline clinical characteristics enables the identification of patient groups with high and low probabilities of benefiting from immunotherapy even before treatment initiation, which is of substantial importance for the personalization of therapeutic strategies. Thus, in NSCLC, radiomics is regarded as a tool for non-invasive tumor phenotyping, capable of reflecting biological properties in vivo and providing early prediction of treatment response, thereby complementing and in some clinical contexts exceeding the informative value of traditional clinical and molecular biomarkers.

The importance of radiomic analysis of lymph nodes. Despite the high informative value of radiomic analysis of the primary tumor, exclusive focus on it entails fundamental limitations. Analysis of the primary lesion alone does not allow comprehensive characterization of the systemic nature of the oncological process, particularly in locally advanced and metastatic forms of NSCLC, where the metastatic component of the disease plays a decisive role in prognosis and in the selection of therapeutic strategy.

During disease progression, clonal evolution of tumor cells occurs, as a result of which metastatic lesions may frequently differ substantially from the primary tumor in their biological, morphological and functional characteristics. In this context, regional lymph nodes warrant particular attention as a distinct target for radiomic analysis. Unlike analysis of the primary tumor, radiomic evaluation of lymph nodes enables direct in vivo assessment of the characteristics of metastatic involvement, including the degree of replacement of lymphoid tissue by tumor cells, the presence of necrosis, variability in density and the spatial heterogeneity of the metastatic process [38].

Radiomic characteristics of lymph nodes make it possible to overcome the limitations of a binary assessment of nodal status (“metastatically involved” versus “non-involved”) and to provide a quantitative evaluation of the actual metastatic burden. Studies indicate that texture- and intensity-based features of lymph nodes are associated with prognosis, risk of progression and survival, demonstrating additional prognostic value beyond the traditional N category.

Accordingly, lymph nodes may be regarded as an independent source of prognostic information that complements data derived from analysis of the primary tumor.

Main limitations of radiomic analysis of lymph nodes. Despite its considerable potential, radiomics of lymph nodes remains a substantially less explored field compared with analysis of the primary tumor. The majority of available radiomics studies, including those in NSCLC, have focused primarily on the primary tumor, whereas radiomic approaches to lymph node assessment are represented by a limited number of investigations, often characterized by small sample sizes, retrospective design and lack of external validation [39]. The principal reasons for this imbalance include the small size of lymph nodes, their complex anatomical configuration, close relationships with adjacent vascular and bronchial structures and the high sensitivity of radiomic features to scanning parameters, image reconstruction algorithms and segmentation methods. An additional limitation is the fragmented or unavailable histological verification of individual lymph nodes, particularly in the preoperative setting, which complicates accurate correlation between radiomic features and true metastatic status and restricts opportunities for model training and validation.

In this context, the current lack of systematic, standardized and validation-oriented studies dedicated to lymph node radiomics defines a clearly delineated and clinically significant research niche for further prospective and validation studies in this field. In-depth investigation of radiomic characteristics of lymph nodes holds the potential to generate non-invasive quantitative indicators of metastatic burden capable of complementing traditional anatomical staging approaches, improving the accuracy of disease course prediction and contributing to the personalization of treatment in patients with NSCLC.

7. Conclusions

Lymph nodes play a pivotal role in staging, prognostication of disease course and determination of therapeutic strategy in non-small cell lung cancer (NSCLC). At the same time, traditional anatomical assessment within the TNM classification does not adequately reflect the actual metastatic burden, whereas quantitative nodal metrics (LNR, LODDS) enhance the accuracy of prognostic stratification but remain limited to postoperative application.

Radiomic approaches to the analysis of the primary tumor have demonstrated the ability to quantitatively assess intratumoral heterogeneity, predict survival outcomes and anticipate response to systemic therapy.

Extending these methodological principles to regional lymph nodes represents a logical and scientifically justified step, as the nodal component reflects the systemic nature of the metastatic process.

Radiomics of lymph nodes provides the opportunity for non-invasive (in vivo) quantitative assessment of metastatic involvement and the development of potential prognostic markers of biological aggressiveness and treatment response. The integration of radiomic features with clinical and molecular parameters opens new prospects for the personalization of systemic therapy in metastatic NSCLC.

The limited number of standardized, multicenter and externally validated studies in this field underscores the existence of a clearly defined research niche for further investigation. In-depth exploration of the radiomic characteristics of regional lymph nodes holds significant potential for the development of reproducible non-invasive biomarkers, refinement of risk stratification and enhancement of personalized treatment strategies in NSCLC.

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