Assessing the Clinical Utility of Computed Tomography-Based Radiomics

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The tumor, node, metastasis (TNM) staging system is the universally accepted process that evaluates disease extent, guides prognosis, and leads to algorithms linked with treatment plans [1]. However, with the emergence of precision cancer medicine, there is increasing need for the development and implementation of integrated models beyond the TNM staging system that may aid clinicians in their decision making. This is particularly important in non-small cell lung cancer (NSCLC) with recent discoveries of actionable mutations in epidermal growth factor receptor (EGFR) mutations, translocations of echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase, and the *c-ros* oncogene 1 receptor tyrosine kinase, which can be used to guide biomarker-based treatment decisions. As tumors are spatially and temporally heterogeneous, techniques such as biopsies are limited in their ability to characterize tumors in their entirety and are subject to sampling error. Similarly, longitudinal biopsies aimed to assess resistance mechanisms or treatment response are expensive and often impractical or unacceptable to patients. In contrast, medical imaging is a noninvasive and readily repeatable investigation that may provide a more comprehensive understanding of tumor phenotype, allowing monitoring of treatment response and disease progression [2].

Historically, medical images have been described using limited metrics to characterize tumors typically related to size, density or qualitative aspects (e.g., necrotic or cystic change, ground glassing, spiculation). With advances in image acquisition, standardization, and analysis, objective quantitative descriptors or "radiomics" are being investigated to enable interrogation of medical images beyond the limits of visual inspection [2]. The conversion of these images to multidimensional histograms of image intensities can subsequently be mined using bioinformatics tools, measuring properties such as heterogeneity and guide models, which may increase diagnostic, prognostic, and predictive accuracy [3]. The overall hypothesis of this approach is that advanced analysis of standard imaging (such as computed tomography [CT]) can noninvasively augment clinical prognostic nomograms, correlate imaging phenotypes with genomic and proteomic expression, and therefore support clinical decision making.

The scope for using radiomics to guide clinicians in their decision process is considerable. Using this approach has demonstrated independent prognostic and predictive capacities in multiple tumor types, including head and neck, lung, glioblastoma, testicular, and hepatocellular carcinoma [2, 4–6]. Its capacity to quantify intratumoral heterogeneity assists with prognostication, as it is recognized that increased heterogeneity is associated with poorer outcomes and is a significant cause of treatment resistance [7–10]. For example, Aerts et al. demonstrated that a radiomic signature composed of limited features (tumor density, shape, and intratumoral heterogeneity) in NSCLC and head and neck cancers could improve TNM prognostic models [2]. Similarly, CT texture analysis of primary pulmonary lesions in a separate study in NSCLC provided a quantitative assessment of tumor heterogeneity that independently predicted overall survival [8].

Beyond refining prognostication, a radiomics approaches may also generate "imaging biomarkers" that assist in predicting responses to target-drug matching or immunotherapy, as the tumor microenvironment may exhibit distinct radiological features discernible by quantitative imaging metrics. In NSCLC, radiomic features have been used to predict responses to immune therapy as well as immune-related adverse events such as pneumonitis [11]. In addition, a radiomics approach may also help to assess responses to treatment by distinguishing between progression and treatment-related pseudo-progression. In glioblastoma, the use of RECIST criteria to determine treatment response can be challenging. Although specific radiological criteria such as the Response Assessment in Neuro-Oncology criteria have been developed to address this issue [12, 13], textural features on magnetic resonance imaging or positron emission tomography may also assist in discriminating between the two [14, 15].

Within this context, in this issue of *The Oncologist*, Lee and colleagues sought to address whether radiomic features on preoperative CTs for 339 patients with pathological stage I–III lung adenocarcinoma could be prognostic in addition to baseline clinicopathological features [16]. Lung cancer is a particularly

interesting model to investigate with radiomics, as it is a heterogeneous disease entity with a high somatic mutational burden [17]. Outcomes are poor, particularly in those patients with locally advanced nodal involvement. Thus, there is considerable scope to improve outcomes through discovery of radiological features that may enable judicious selection of disease modifying agents complementary to conventional treatment modalities. The researchers' key finding was that the integration of 31 selected radiomic features led to better discriminative performance compared with standard TNM variables, with the C-index improving from 0.74 to 0.77. Two radiomic features were significant on multivariate analysis: maximum value of the outer third of the tumor (hazard ratio [HR], 1.001; $p = .017$), which is thought to represent the tumor microenvironment [18, 19], and size zone variance (HR, 0.998; $p = .038$), which is thought to measure intratumoral heterogeneity [7–10]. Although this technique is novel and gives unique insight into tumor biology using imaging phenotypes, many questions remain about its clinical translatability. Of note, the hazard ratios for both radiomic features were close to the null value, suggesting that neither was strongly prognostic for overall survival in comparison with conventional clinicopathological variables. This is reflected in the marginal improvement of the C-index of the combined nomogram compared with using standard TNM variables alone. In addition, in clinical practice, minimally invasive or radiological staging is commonly used to inform treatment selection. However, it is recognized that clinically node-negative NSCLC may be pathologically upstaged in 14%–19% of cases [20, 21]. Therefore, it is unclear whether the proposed decision-making model that was built on postoperative pathological findings would remain valid in the preoperative setting.

Although using radiomics is a promising approach, there are still several challenges limiting its routine implementation into clinical practice. First, there is a lack of standardization with regard to image acquisition, reconstruction, and annotation of volumes of interest. Harmonization of quantitative image generation and reporting is essential to ensure that future studies are reproducible and data can be shared efficiently between sites [22]. Furthermore, many of these processes, such as contouring volumes of interest, require skill and content expertise that take time to acquire, limiting the rate of uptake into routine practice. Although automated contouring may assist, it is of variable reproducibility depending on the degree of differentiation from neighboring structures such as vessels [23, 24]. Second, radiomics will produce a significant amount of data for each patient. Although correlations between quantitative features and prognosis or treatment outcomes may be able to be obtained statistically, it may be difficult to attribute causality to the radiomic features [3]. External validation of these correlations in independent, prospective, multicenter cohorts or radiomic substudies of ongoing clinical trials will be vital to ensure that models generated from retrospective studies remain robust in the broader population.

Further exploration of the correlation between radiomics features representing the interaction between the tumor and immune infiltrates and responses to immunotherapy is required. The challenges of programmed death-ligand 1 staining as a way of predicting response to immunotherapy in different tumor types have been well documented [25, 26]. Radiomics is well placed as an alternative method of holistically quantifying a tumor's interaction with immune infiltrates, although further work is required to define the relevant radiomic features. For example, the definition of the outer third of the tumor, and how this is delineated on contouring, remains ambiguous and possibly challenging to reproduce. Although efforts are underway to explore this in the context of metastatic NSCLC, similar techniques may hold promise in selecting patients for adjuvant immunotherapy after definitive chemoradiotherapy in locally advanced disease [27]. This may be particularly relevant as tissue confirmation prior to chemoradiation is typically via needle biopsy, which is prone to sampling error. Similarly, radiomics may also assist in the prediction of response to targeted therapies. Currently, biopsy samples are used to test EGFR mutation status in lung adenocarcinoma. However, variations in mutant DNA allele concentration and intratumoral heterogeneity may lead to false negative results [28–30]. Liu et al. demonstrated that the addition of radiomic features to a pre-existing clinical model resulted in significant improvement in the model's ability to predict for an EGFR mutation in lung adenocarcinoma [31].

Lastly, incentives are required to address the challenges of standardization, information sharing, and the management of "big data." This will require a multidisciplinary effort from information technology, radiologists, bioinformaticians, statisticians, and clinicians. In the future, it is envisaged that quantitative data will be routinely extracted from imaging and combined with clinicopathological information to improve the diagnostic accuracy and predictive power of clinical decision-making models. This will help expand radiomics beyond a boutique research area into a clinically useful translational technology.

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Editor's Note:

See the related article, "Comprehensive Computed Tomography Radiomics Analysis of Lung Adenocarcinoma for Prognostication," by Ho Yun Lee et al., on page 806 of this issue.