



## Invited Commentary | Imaging

# Peritumoral Radiomics and Predicting Treatment Response

Ruijiang Li, PhD

Esophageal cancer is a common malignant neoplasm with a poor prognosis, causing more than 400 000 deaths worldwide every year. Neoadjuvant chemoradiotherapy (neoadjuvant CRT) followed by surgical treatment has been associated with an overall survival benefit compared with surgical treatment alone and has become a standard treatment for locally advanced esophageal cancer. Overall, approximately one-quarter to one-half of patients with esophageal cancer who receive neoadjuvant CRT will achieve pathological complete response after treatment. However, on an individual level, tumor response to neoadjuvant CRT is highly heterogeneous. It has been challenging to predict the likelihood of pathological complete response for a given patient prior to treatment initiation.

To address this unmet need, the study by Hu et al<sup>1</sup> used a radiomics approach to develop an imaging signature for predicting response to neoadjuvant CRT of esophageal cancer in a multi-institutional study. Hu and colleagues extracted radiomics features from intratumoral and peritumoral regions on baseline computed tomography scans and then examined a combination of these features to compare several different machine learning models. The models based on intratumoral or peritumoral features alone had similar performance for predicting pathological complete response, with results for area under the curve of 0.730 (95% CI, 0.609-0.850) for intratumoral and 0.734 (95% CI, 0.613-0.854) for peritumoral, while the combined model, consisting of 7 intratumoral and 6 peritumoral features, achieved a significantly better accuracy of 0.852 (95% CI, 0.753-0.951) in an independent test set. Hu and colleagues further showed that the discriminative power of the radiomics model was independent of several clinical parameters, including sex, smoking and drinking history, and tumor stage and grade.

Radiomics has been used extensively in oncology to discover novel prognostic and predictive imaging signatures for various cancers.<sup>2</sup> The term *radiomics* refers to the extraction of quantitative features from regions of interest in medical images, which can then be used for classification and prediction. Traditionally, this approach has been focused on the bulk analysis of the primary tumor. Because invasion is a hallmark of cancer, it is conceivable that regions surrounding the tumor (ie, peritumoral regions) contain complementary and useful information about the disease. Several recent studies have successfully demonstrated the proof of principle for using peritumoral radiomics to predict treatment response in breast<sup>3</sup> and cervical<sup>4</sup> cancers. The study by Hu et al<sup>1</sup> provides additional evidence for the value of peritumoral radiomics, specifically in the context of response prediction in esophageal cancer.

The advent of big data and deep learning suggests that these handcrafted features, which rely heavily on domain expertise and prior knowledge, could be automated, and initial results are encouraging. A 2020 study that used a class activation map for visualization of deep learning networks<sup>5</sup> identified regions surrounding the primary tumor as important areas for prediction of prognosis in gastric cancer. This suggests that deep learning could recapitulate the findings of radiomics studies and provide further support for the utility of peritumoral evaluation.

Another notable aspect of the study by Hu et al<sup>1</sup> is that the researchers integrated imaging and gene expression data to perform a radiogenomics analysis; this analysis may provide important insight into the biological underpinnings of the radiomics model. They found that the imaging signature was associated with adaptive immunity, such as lymphocyte infiltration and interferon signaling in the tumor. This finding is consistent with a 2017 study<sup>6</sup> demonstrating the critical role of a tumor's immune microenvironment in determining therapy response and outcomes. Interestingly,

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a recently developed radiomic signature combines features of intratumoral and peritumoral regions, allowing the noninvasive evaluation of the immune microenvironment in gastric cancer and predicting prognosis and chemotherapy response.<sup>7</sup>

The study by Hu et al<sup>1</sup> used high-quality rigorous radiomics research. In addition to the use of intratumoral and peritumoral features and integrative radiogenomics analysis, a strength of this work is its multi-institution cohort study design, with independent validation of the radiomics model (albeit with a relatively small number of patients for validation). The study used a test-retest strategy to avoid feature redundancy and minimize interobserver variability. Method details were provided for feature harmonization, selection, and evaluation to ensure a robust prediction model. These are important attributes of reproducible radiomics research that may help move the field forward.

The ability to reliably predict treatment response may improve the selection of patients who are most likely to benefit from neoadjuvant CRT while sparing others from the toxic effects associated with the treatment. The radiomic signature developed by Hu et al<sup>1</sup> provides a promising direction to follow in pursuing this goal.

However, before the practical implementation of this method can occur, several issues and questions need to be addressed. First, the generalizability of the imaging signature across different computed tomography scanners and imaging protocols should be rigorously assessed. Second, because the study investigated multiple machine learning classifiers with varying levels of accuracy, it will be important to choose a final model, which will be locked before it is ready for further validation in prospective studies. Third, the patient population in this study comes from 1 geographic region in southern China, where most esophageal cancers are squamous cell carcinomas. In Western countries, this pattern is reversed, and most esophageal cancers are adenocarcinomas. Given the different response rates to neoadjuvant CRT of these 2 histological subtypes, it will be interesting to test how this signature works for adenocarcinomas. Despite the need for further validation, the study by Hu et al<sup>1</sup> represents a step forward toward an individualized approach to the treatment of esophageal cancer.

## ARTICLE INFORMATION

**Published:** September 10, 2020. doi:[10.1001/jamanetworkopen.2020.16125](https://doi.org/10.1001/jamanetworkopen.2020.16125)

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**Corresponding Author:** Ruijiang Li, PhD, Department of Radiation Oncology, Stanford University School of Medicine, 1070 Arastradero Rd, Palo Alto, CA 94304 ([rlr2@stanford.edu](mailto:rlr2@stanford.edu)).

**Author Affiliation:** Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California.

**Conflict of Interest Disclosures:** Dr Li reported receiving grants from the US National Institutes of Health outside the submitted work.

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