Invited Commentary

Analysis of Routine Computed Tomographic Scans With Radiomics and Machine Learning
One Step Closer to Clinical Practice

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Response Evaluation Criteria in Solid Tumors (RECIST)[1] has been the standard approach to assess response and predict survival in oncology clinical trials for many years. In RECIST 1.1, the percentage change in the sum of the longest single dimension of up to 5 target lesions is used to classify response. Although many studies have supported the utility of this approach, other studies have shown that there is room for improvement. For example, volumetric changes in tumor size and radiomics signatures of image textural qualities have shown promise as tools to predict survival that are complementary to RECIST.

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In this issue of *JAMA Oncology*, Dercle et al[2] apply radiomics and machine learning to baseline and 3-month follow-up computed tomographic (CT) scans from 2 large clinical trials of immune checkpoint blockade in patients with advanced melanoma (KEYNOTE-002 [Study of Pembrolizumab (MK-3475) Versus Chemotherapy in Participants With Advanced Melanoma][3] and KEYNOTE-006 [Study to Evaluate the Safety and Efficacy of Two Different Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Participants With Advanced Melanoma][4]). Patients were divided into a training cohort (n = 252), which was used to build the radiomics signature, and a validation cohort (n = 287), which was used to test the signature. For each CT scan, all measurable lesions larger than 10 mm were segmented by a radiologist using a semiautomated algorithm, and 1126 quantitative imaging features were extracted. After reducing these features to 20 uncorrelated features using principal component analysis and adding 5 tumor burden features, a machine-learning algorithm was used to select the features that best estimated overall survival in the training cohort. Four features were selected for the radiomics signature: 2 features related to tumor burden (change in tumor volume from baseline to month 3 and tumor volume at baseline) and 2 radiomics features that characterized changes in tumor spatial heterogeneity and texture. When this radiomics signature was applied to the validation cohort, the signature outperformed RECIST for estimation of overall survival (OS).

This study addresses one of the major challenges in radiomics: development of a signature that is applicable across different medical centers. Prior studies summarized by Wang et al[5] have largely been performed at single institutions, so radiomics signatures that were validated at one site were not necessarily tested at other sites. Given that many radiomics features measure image heterogeneity and texture of tumor lesions, which can be affected by scanner model, acquisition parameters, and reconstruction algorithm, the successful application of a radiomics signature using data from large multicenter trials such as KEYNOTE-002 and KEYNOTE-006 is a notable advance. In addition, this work reinforces the importance of using multiple features in the radiomics model while avoiding an excess of features that could result in overfitting. Interestingly, and perhaps not surprisingly, change in tumor volume is ranked as the highest in importance relative to other imaging features, supporting the biological basis for a decrease in tumor size as a metric for response assessment. This suggests that there is value in moving to a volumetric standard for comparison of lesion size and that there is value in adding radiomics measures to the response assessment.

Are the results of this study generalizable to other patient populations? The radiomics signature used by the authors was developed using data from patients with melanoma treated with ipilimumab or pembrolizumab and was validated in patients with melanoma who were treated with pembrolizumab; the authors also confirmed that the signature was generalizable to smaller cohorts of patients with melanoma who were treated with ipilimumab (n = 36) and chemotherapy (n = 93). In addition, 3 of the 4 features identified in this study were also identified in an ancillary study in patients with colorectal cancer.[6] Thus, it is possible that this signature will apply more broadly to patients with other cancers treated with immunotherapy, perhaps even across tumor types and treatment regimens. On the other hand, different disease sites may have distinct imaging features, suggesting a need for further study to determine how broadly the 2 radiomics features used in this study will apply to other treatments and disease sites. Nevertheless, this study serves as an important proof of concept in which measures of tumor burden and radiomics measures are combined to better predict survival compared with the current standard, RECIST.

The results from this study suggest that the translation of the radiomics signature to routine clinical practice will likely have the largest effect on patients with stable disease and progressive disease identified by RECIST. Patients with an objective RECIST response (complete response or partial response) were found to have uniformly favorable OS predicted by the radiomics signature. In contrast, patients with stable disease and progressive disease had heterogeneous signatures that appeared to provide information distinct from tumor volume changes that contributed predictive value for OS. Patients with stable disease could be divided into a large cohort with favorable OS, and a much smaller cohort with poor OS, whereas patients with progressive disease were fairly evenly divided between favorable and poor OS. This study also confirmed that pseudoprogression in patients with melanoma treated with immune checkpoint blockade is rare, occurring in only 2.8% of patients. Of note, 9 of 11 patients whose

tumors were categorized as pseudoprogression were correctly classified by their radiomics signature as likely to have a favorable outcome. In all the above cases, identification of patients with favorable and poor predicted OS could help to guide management with regard to the timing of follow-up, the need for alternative treatments, and discussions on goals of care.

Despite these results, several obstacles to the clinical translation of a radiomics signature remain. First, the need for manual lesion segmentation will limit the consistency and clinical application of the signature until an automated segmentation tool becomes available for clinical use, reducing analysis time and interreader variability. Second, software that performs the radiomics analysis, while currently publicly available, will need to be packaged in a manner that allows it to be easily and consistently applied in a variety of clinical settings. Third, guidelines for image acquisition and processing parameters that are compatible with a radiomics analysis will need to be established.

One of the advantages of this study is the application of radiomics and machine learning to routine CT scans performed at baseline and after 3 months of treatment, supporting widespread application of this approach. It is important to acknowledge, however, that a radiomics signature can only be calculated for patients with measurable disease, so alternative approaches to response assessment will be needed for nonmeasurable sites such as bone.[7] A number of other approaches that may provide complementary information are being explored to assess immunotherapy response at even earlier points, including approaches that measure $CD8^+$ T cells and immune activation, such as CD8 positron emission tomography (PET)/CT[8] and granzyme B PET/CT,[9] and measures of microenvironmental immune and tumor glucose metabolism by fluorine 18–labeled deoxyglucose PET/CT as early as 1 week after treatment.[10]

In summary, this well-designed trial by Dercle et al[2] represents an exciting milestone in the application of radiomics to routine CT scans from multicenter clinical trials. Although there are a few hurdles to overcome before this approach becomes part of routine clinical practice, it is only a matter of time before those tools are developed. As a first step, tools that enable automatic lesion segmentation and change in volume would be a welcome addition to radiology clinical practice. Once these tools are established, it will be fairly straightforward to add radiomics to the analysis with improved prediction of survival for patients with cancer who are treated with immune checkpoint blockade.

ARTICLE INFORMATION

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