Editorial

Radiomic features of the lung: a promising marker to predict response to immune-checkpoint inhibitors in non-small lung cancer patients

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Comment on: Sun R, Limkin EJ, Vakalopoulou M, *et al.* A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol 2018;19:1180-91.

Received: 19 January 2019; Accepted: 24 January 2019; Published: 14 February 2019.

doi: 10.21037/pcm.2019.01.03

View this article at: http://dx.doi.org/10.21037/pcm.2019.01.03

First- or second-line immunotherapy administered to patients with advanced stage or metastatic (stage IIIB/IV) lung cancer give spectacular results in terms of overall survival but only for a limited number of patients. The objective now is to increase the percentage of patients who benefit from effective treatment but also to better select the patients receiving therapy and to propose, if required and without delay, an alternative therapy. It is within this context that biomarkers predictive of the response to immune-checkpoint inhibitors have been developed and then validated during clinical trials.

Among the biomarkers of response to immunotherapy, PD-L1 expression evaluated by immunohistochemistry (IHC), is the only test so far validated in association with first-line immunotherapy for stage IIIB/IV non-small cell lung cancer (NSCLC) (1). So patients with a tumor that expresses PD-L1 on more than 50% of tumor cells and that does not show genomic alterations in the *EGFR*, *ALK*, *ROS1* and *BRAF* genes, can immediately receive treatment with pembrolizumab. However, the validated PD-L1 biomarker is not perfect; patients without PD-L1 tumor expression may respond to immunotherapy while patients with over 50% PD-L1 expressing tumor cells may show no benefit from treatment. A second predictive biomarker, the tumor mutational burden (TMB), is being tested in clinical trials (2). It is noteworthy that this promising biomarker is independent of the predictive value of PD-L1 IHC. However, several issues still need to be validated before this biomarker is approved as a companion test of anti-PD1/PD-L1 molecules. In addition, different harmonizing studies are ongoing for the validation of the TMB and its use in clinical routine practice (3). Clinical trials using the genetic signature of tissues associated to T lymphocytes (T-cell—inflamed gene-expression profile or GEP) as a biomarker are also on going (4). In addition to these three biomarkers other potential factors predictive of the response to immunotherapy have been identified and may be tested in clinical trials (5). Among these biomarkers, the quantification of tumor infiltration by CD8 lymphocytes is envisaged in association with PD-L1 IHC to optimize the predictive value of PD-L1 IHC (6).

The study performed by Sun *et al.* used radiomic approaches to evaluate tumor infiltration by CD8 lymphocytes as well as the predictive value of the response to anti-PD1/anti-PD-L1 by patients with solid cancers of different organs and of different histological types (7). This work started with 135 patients included in the MOSCATO study and correlated the radiological images and results of RNA-seq analyses (7,8). The radiological images were studied according to a radiological approach following segmentation of the images (7). The segmented radiological images corresponding to the area of the biopsy was used to estimate the number of CD8 lymphocytes by RNA-seq. In particular, the transcriptomic signature of the *CD8B* gene

was used to estimate the abundance of CD8 lymphocytes infiltrating the tumor tissue. Three cohorts were then used to validate this signature (7). The first cohort of 119 patients comes from the cancer project gene atlas or TCGA (7). The number of CD8 lymphocytes in the tumor was estimated by radiomics developed from the available CT scan images in association with the RNA-seq and the histological data. The second cohort entitled the "immune-phenotype cohorte" was composed of 100 patients treated at the Institut Gustave Roussy (Villejuif, France). In this cohort the scan-nographic images were evaluated in comparison with the inflammatory or non-inflammatory character of the tumors observed by histology. Thus, the concordance between the radiomic signature and the immune-phenotype of the tumor could be studied. Finally, the third cohort of 137 patients of the Institut Gustave Roussy provided CT scan data and information concerning the treatment and response to the immunotherapy. This latter cohort analyzed the correlation between the radiomic data and prediction to response to immunotherapy (7). The data of the different cohorts (CT scan images, RNA-seq, histology, immune phenotype, treatment information and outcome of the patients) were studied using machine-learning integrating 84 variables including 78 radiomic parameters (7). Thus, for the first time this study demonstrated that radiomic predicted the degree of tissue infiltration by CD8 positive lymphocytes and correlated the response to immunotherapy by integrating CT scan images (7).

This study holds a number of pitfalls, some of which were mentioned by the authors (7). First of all the cohorts of patients were composed of tumors of miscellaneous origin with at least 15 tumor sites and 15 different solid tumors, for example for the initial training cohort. This was the same for the three validation cohorts. This can have an impact on the statistic results knowing that a high number of variables were used by approaches of machine-learning. Another point of discussion concerns the RNA-seq approach that used the transcriptomic signature of the *CD8B* gene to quantify the CD8 positive lymphocytes in the tissue. In fact it is impossible with this analysis, in the absence of associated histological images, to identify the spatial organization of the cells of interest (intra-tumoral infiltration, exclusion of immune cells at the periphery of the tumor mass, mixed feature associating the two topographies). In fact, one of the predictive factors of response to immunotherapy is certainly the intra-tumoral infiltration by CD8 lymphocytes and this would be assess in this study. The evaluation of CD8 antigen expression by lymphocytes without the analysis of certain co-expressing antigens is certainly a simplified approach to the biology of cells and the analysis by RNA-seq should be able to quantify other associated biomarkers which should be taken into consideration too (9,10). The tumor heterogeneity is a point for discussion when considering the study of Sun *et al.* (7). In fact, it is not certain that the RNA-seq analysis was totally representative of the inflammatory status of the studied tumor. A large degree of variation can exist from one site to another of a tumor and between the different sites of the tumor of the same patient. So it would have been of strong interest to analyze by RNA-seq several biopsies from different locations of the tumor and compared it to the radiological analyzes. Finally, this study was performed on four different cohorts of patients and was retrospective. This raises a number of issues: (I) discordance regarding the quality of the approaches can exist, the information obtained and the techniques used according to the series, which can lead to difficulties concerning the homogeneity of the data, and, (II) it would be interesting to confirm the results of this first study by validation with a prospective cohort of patients including a large number of patients and by targeting only one or two pathologies.

The radiomic is a novel and extremely promising method that probably will soon be used in oncology to validate the efficacy of the radiological approach as a new diagnostic, prognostic or predictive marker of lung cancers (11-13). One of the present challenges is to be able to predict the hyperprogression behavior of some tumors treated by immunotherapy (14-16). Likewise, it seems important to be able to predict the response to immunotherapies of elderly patients knowing the high number of this population of patients in thoracic oncology (17).

It is necessary to compare the different biological and clinical parameters of the radiological images obtained from the same patients and to ensure the high quality of the data. Without this robustness in the data assessment there is a risk of transforming this incomplete or erroneous data into new uncontrolled data of poor quality. Several radiomic applications can already be envisaged in thoracic oncology, including prediction of adverse events on the lungs due to the immunotherapy, the development of radiogenomics to detect the presence of different genomic alterations based on imagery and, the possibility of distinguishing the benign or malignant character of lung nodules (18,19). We need now to know when and how the transfer of radiomic methods will be realize in routine practice, in particular within the context of thoracic oncology and immunotherapy (20).

The implementation of radiomics in the clinic must involve independent validation steps and studies with large cohorts of patients while ensuring that no inter observer variation occurs (21). The biological and clinical data (histology, IHC, genetics, transcriptomics, etc.) that can be associated to radiomic methods are presently inexhaustible, including the data obtained from liquid biopsies (22). In this context, the development of new tools using artificial intelligence should allow integration and exploitation of all the complex data (23). These approaches will not replace radiologists and pathologists but will provided rapid diagnostic aid and medical decisions for optimal care of patients with lung cancer.

Acknowledgments

Funding: The author wishes to thank the Canceropole PACA, the Ligue Départementale 06 de Lutte contre le Cancer and the Conseil Départemental 06 for their financial support.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Precision Cancer Medicine*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/pcm.2019.01.03). PH is a member of different industrial scientific advisory boards (Roche, AstraZeneca, Bristol-Myers Squibb, Pfizer, Novartis, Merck, MSD, Qiagen, Thermofischer, Biocartis) for which he receives honorarium. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pcm.2019.01.03
Cite this article as: Hofman P. Radiomic features of the lung: a promising marker to predict response to immune-checkpoint inhibitors in non-small lung cancer patients. Precis Cancer Med 2019;2:3.

