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## Perspectives on imaging and immunotherapy

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# Perspectives on imaging and immunotherapy: a review series

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In the latest version of Hallmarks of Cancer, avoiding immune destruction, which had originally been considered an ‘emerging hallmark’, is now clearly classified as a fundamental characteristic of cancer.<sup>1 2</sup> The relevance of this hallmark is becoming increasingly clear. Over the last decade, immunotherapy, especially with immune checkpoint inhibitors and chimeric antigen receptor (CAR) T cells, has played a prominent role in cancer therapy. This increased clinical experience with immune checkpoint inhibition has recently led investigators to identify unique clinical hallmarks for immune checkpoint inhibitor-based therapies. These clinical characteristics include long-term benefit with durable responses, depth of responses, treatment-free survival, efficacy in brain metastases, improved health-related quality of life, and unique safety profiles.<sup>3</sup>

Obtaining tumor-specific information with imaging is, for several of these clinical hallmarks, key to determining tumor response as well as response duration.

However, there are challenges with the interpretation of imaging studies, especially immediately after the initiation of immunotherapy. In the early days of immunotherapy, it was noticed that immune checkpoint inhibitors could induce pseudoprogression, defined as apparent anatomic growth in tumor size, due to T cell infiltration. This raised concerns that the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) criteria used for response measurements might no longer apply given the pseudoprogression seen. Therefore, a consensus guideline—iRECIST—was developed by the RECIST working group to use modified RECIST version 1.1 in cancer immunotherapy trials for the purpose of consistent design and data collection to facilitate the ongoing collection of trial data, and ultimately to allow for validation of the iRECIST guidelines.<sup>4</sup> In summary, the iRECIST guidelines enable continuing treatment (and collecting imaging data) initially when the disease ‘progresses’ on

anatomic imaging but while the patient is clinically stable.

Another critical aspect we will have to reconsider is the radiation burden induced by repeat CT imaging to determine response and disease-free and progression-free survival. There are increasing numbers of long-term survivors after immune checkpoint inhibition. For all immune checkpoint inhibitor trials that led to US Food and Drug Administration (FDA) approval up to July 29, 2019, the median calculated cumulative numbers of chest-abdomen CT scans after 1, 3, 5, and 10 years of study participation were 7, 16, 24, and 46, respectively. For ages 20–70 years at study entry, the average lifetime attributable cancer risk after 1 year of study participation ranged from 1.11% to 0.40% for men and from 1.87% to 0.46% for women.<sup>5</sup> At 10 years of study participation, this risk increased to a range of 5.91%–1.96% for men and 9.64%–2.32% for women. Therefore, some investigators have suggested adaptive imaging intervals and imaging termination rules for long-term survivors in immune checkpoint inhibition trials.

Regrettably not all patients benefit from immunotherapy. Therefore, biomarkers to select patients upfront or early during immunotherapy are needed. The development of these biomarkers, given the complexity of the immune response, is not easy. There is increasing awareness that a unique combination of tumor and patient characteristics results in treatment response determined in part by the immune system’s capacity. Numerous characteristics govern the anticancer immune response’s strength and timing as well as determine the cancer-immune setpoint.<sup>6</sup> This setpoint needs to be surpassed for a tumor response to immunotherapy. Several characteristics influence the setpoint. However, only two thus far, namely mutational load and microsatellite instability, serve across tumor types for personalized treatment decisions. Regrettably, neither predicts tumor response as accurately as we would like.



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The current practice of determining these characteristics with a single biopsy providing a snapshot insufficiently captures heterogeneity in space as well as in changing tumor dynamics during the course of treatment. As a result, the single ‘snapshot’ biopsy provides insight but does not give a complete overview of tumor dynamics. Using multimodal data inputs—including imaging and omics—serially before and during treatment may provide more of the changing overview needed. Such an approach may be critical to unravel tumor biology and provide the best tools for personalized treatment decisions. In this manner prudent use of innovative imaging approaches along with other omic techniques may be critical to enhancing the understanding and success of immunotherapy.

The purpose of this review series is to highlight the developments in imaging approaches to immunotherapy. We invited authors with diverse backgrounds to facilitate an understanding of the potential roles of imaging, comprising oncologists, radiologists, imaging scientists, nuclear medicine physicians, radiation oncologists and preclinical researchers. We focus on three areas. First, novel imaging strategies will be discussed. Information on molecular positron emission tomography (PET) imaging and optical imaging for immunotherapy and imaging to track T cells/CAR T cells is provided.

Next, new approaches to conventional imaging are provided. The role of validating imaging techniques for clinical use will be discussed, and an update will be given about the status of conventional imaging endpoints including iRECIST. Moreover, progress for immunotherapy imaging techniques using AI and radiomics from fundamentals to preliminary results and in MRI techniques will be described.

Finally, special considerations for radiotherapy, immunotherapy, and imaging are addressed.

We hope this series on imaging and immunotherapy is inspiring and illustrates the ongoing multidisciplinary efforts to implement imaging in a novel way for immunotherapy. We also hope that it will be a stimulus for the path of standardization of imaging procedures, collaboration, data sharing, and validation. We will need to explore

all these approaches to justify both scientifically and regulatorily the implementation of new imaging approaches in the end into daily care.

**Twitter** Elisabeth GE de Vries @VriesElisabeth

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