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Editorial Commentary: Should “heterogeneous response” be considered as new category for assessing treatment response in patients with breast cancer?

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One of the most common clinical indications for [18 F] FDG PET/CT examinations is evaluation of response to therapy. Response to therapy on [18 F]FDG PET is often analyzed with PERCIST criteria, which define categories of complete metabolic response (CMD), partial metabolic response (PMD), stable metabolic disease (SMD), and progressive metabolic disease (PMD) [1]. In these criteria, any new [18 F]FDG-avid malignant lesions delegate to scan as PMD [1]. We would like to raise awareness of heterogeneous response in patients with breast cancer and suggest these patients may be better served by classifying them as heterogeneous responders, rather than by being classified as PMD.

Response heterogeneity describes the situation in which some tumour lesions respond well to treatment, while other lesions in the same patient do not [2, 3]. Its frequency is around 10% and its prognosis is more favourable than for progressive disease [4, 5]. Some authors referred that the time to progression was longer in patients with a heterogeneous metabolic response compared with those with homogeneous non-response [6]. Therefore, continuation of treatment should be considered in such patients [3, 4]. However, the effect of heterogeneity on clinical outcome remains unclear.

The concept has been often used when assessing treatment response to immunotherapy, but heterogeneous response can be observed with chemotherapy and targeted-therapy, however its frequency varies across treatment and primary cancer types [7]. It seems more common in cancers with heterogeneous tissue-specific tumour microenvironments, heterogeneous molecular profiles between metastases, and tumour dedifferentiation, such as breast cancer

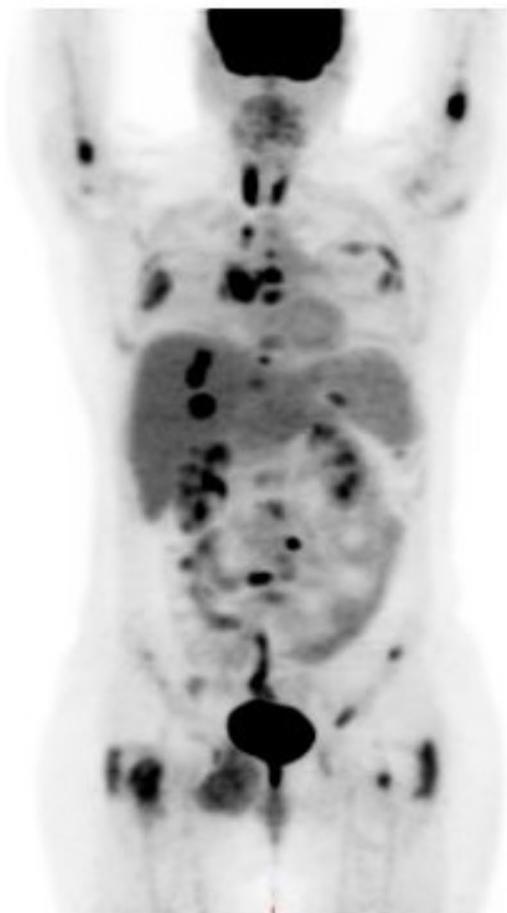
(Fig. 1) [7, 8]. Besides inherent inter-lesion heterogeneity, the existence of synchronous malignancies, or the treatment-induced emergence of resistant tumour clones may also justify heterogeneous response [9].

Although the progression of lesions, it is important to emphasize that heterogeneous response should not be immediately interpreted as non-response or progressive disease. One may think of it as oligoprogression, which is differently perceived from progressive disease, and aim to personalize individual lesion's treatment, when necessary, rather than treating all lesions in the same manner. To discontinue therapy, particularly targeted therapy or immunotherapy, may compromise treatment success, as there are lesions still responding positively. Patients presenting heterogeneous response may benefit from the addition of other complementary therapies for the non-responding lesions. The treatment of the oligoprogressive lesions may include local therapy (e.g. radio frequency ablation, stereotactic body radiation therapy or stereotactic ablative radiotherapy, interventional radiological procedures, metastasectomy or other surgery) or a combination with another systemic therapy [5, 9, 10]. Although some groups have tried to identify prognostic characteristics that may guide clinical decision in patients presenting heterogeneous response to therapy [6, 11, 12], no definitive findings or agreement have been reached yet, namely in breast cancer. Currently, in clinical practice, when dealing with heterogeneous response, the clinician should base the decision to keep or withdraw treatment according to the patient's clinical status and well-being.

In the recent EANM/SNMMI guidelines about the use of [18 F]FDG in no special type breast cancer, which was endorsed by the most relevant societies in the field, [18 F] FDG PET/CT may play a role in monitoring treatment response in metastatic breast cancer [13]. Some authors have demonstrated the superiority of [18 F]FDG PET/CT

Extended author information available on the last page of the article

Pre-treatment



Post-treatment

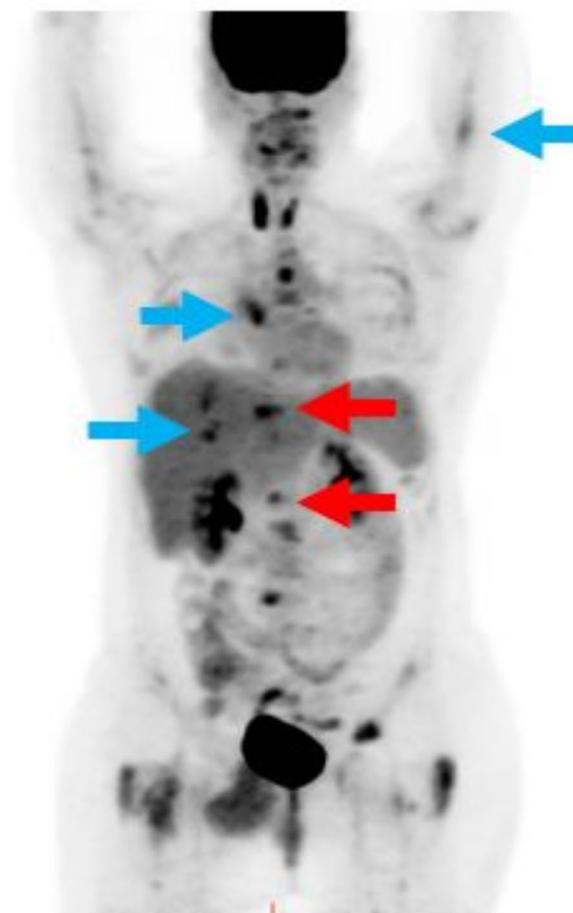


Fig. 1 Patient with breast cancer, not otherwise specified, before and after chemotherapy. Pre-treatment, the patient demonstrates osseous and hepatic malignancy. Post-treatment, some metastases are

decreased (blue arrows), while others have increased or are new (red arrows). This is a pattern of heterogeneous response

compared to CT, particularly to assess bone metastases and enable early response to treatment [14–16]. Overall, it is agreed that [18 F]FDG PET/CT improved patient management with survival benefit [17]. Because [18 F]FDG PET/CT can easily assess response on an individual lesion basis, and compare with baseline and/or previous examinations, heterogeneous response has been described in up to 48% of women treated for metastatic breast cancer [6, 7]. It is worth noting that heterogeneous response can be observed at any time during the imaging follow-up of patients treated with systemic therapy. Notwithstanding that most studies have described the occurrence of heterogeneous response during the first 2 or 3 months of treatment, it is currently unknown if it is more likely to be observed at early or late evaluation time points [7]. Furthermore, [18 F]FDG PET/CT can be helpful in identifying heterogeneous response by demonstrating persistent metabolic activity in residual masses that

are resistant to treatment, or the development of new lesions that are consistent with primary disease [9, 18].

Studying tumoral heterogeneity requires assessing the response of the whole baseline metastatic tumour load without limiting the number of lesions nor sites. Nevertheless, both morphological (RECIST and iRECIST) and metabolic (EORTC and PERCIST) response criteria only consider a limited number of operator-selected target lesions. Hence, the clinical scenario of a heterogeneous response has neither been integrated to morphological, nor to metabolic criteria of response yet [7]. Moreover, a proper, consensual nomenclature has not been given to this pattern yet [7]. Until now heterogeneous response was included in the “Progressive Disease” category of RECIST and PERCIST, based on the assumption that one progressive lesion is enough to define progression [1, 19]. However, one should notice that the paradigm evolved quickly with immune checkpoints inhibitors,

because it was demonstrated that heterogeneous response was associated with a favourable prognostic pattern in which the continuation of immunotherapy could provide a durable response [3, 7]. Furthermore, this is also becoming an important topic in the context of breast cancer due to the increased applications of PD-1/PD-L1 based immune checkpoints inhibitors in patients with triple negative breast cancer, and to the de-escalating projects focussing on reducing immunotherapy regimen administration, such as anti-dual HER2/TDM1 treatment, in patients with metastatic breast cancer [20–22]. According to the Joint EANM/SNMMI/ANZSNM practice guidelines/procedure standards on recommended use of [18 F]FDG PET/CT imaging during immunomodulatory treatments in patients with solid tumour, heterogeneous response definition should be inspired by PERCIST criteria and defined as a concomitant relative decrease $> 30\%$ in some tumour lesions metabolism (Δ SUV) and relative metabolic increase $> 30\%$ in others (and/or new hypermetabolic lesions) [5, 7]. We believe this definition could be used for establishing the criteria to report the new category of heterogeneous response by imaging modalities.

Considering that heterogeneous response to therapy has not been extensively explored in oncology, further studies addressing this specific topic are needed. It would be useful to assess the evolution and profile of heterogeneous response through sequential [18 F]FDG PET/CT scans. Moreover, it would be necessary to analyze the target lesions responsible for the heterogeneous response, and verify if there is any pattern in terms of lesions number or location (whether it affects several organs at the same time, or is more frequent in certain locations, such as bone). It would also be interesting to categorize the heterogeneous response according to the tumour subtypes and systemic treatments performed, to better assess its impact on the frequency and type of heterogeneous response.

The usefulness of using dedicated software to assess tumour heterogeneous response has been reported by several groups. Zheng et al. developed a novel metric for tumour response heterogeneity which demonstrated to be a powerful independent predictor of outcome in advanced lung adenocarcinoma [23]. To better assess intra-patient response heterogeneity, Lokre et al. developed new automated segmentation-based method, trained with features quantifying response heterogeneity in all individual lesion-ROI, for measuring treatment response, which showed superior prognostic power compared to traditional methods like RECIST and PERCIST [24].

Conclusion

Heterogeneous response is seen in patients with cancer, particularly metastatic breast cancer. As heterogeneous responses include increasing and/or new lesions, they would be classified as PMD on both RECIST and PERCIST. However, preliminary data suggests patients with heterogeneous response have better outcomes than patients with homogenous progression. We want to raise awareness of this phenomenon and suggest studies addressing the clinical impact of heterogeneous response to therapy are needed. If clinical outcomes are indeed unique between heterogeneous and homogenous progression, then a classification of heterogeneous response may be a valuable addition to defined response criteria.

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