Assessment of heterogeneous treatment response in patients with multiple solid tumors

Introduction: Imaging biomarkers such as those defined in RECIST¹ and PERCIST² are routinely used clinically to assess treatment response in patients with solid tumors. However, these measures are defined to evaluate individual tumors, and it remains unclear how they should be applied in patients with multiple lesions. This study assesses intra-patient heterogeneity in tumor response using common PET-based metrics in patients with multiple solid tumors.

Methods: Twelve patients with two or more solid tumors representing a variety of disease histologies were treated with a multi-targeted receptor tyrosine kinase inhibitor with anti-proliferative and anti-angiogenic effects. Patients were imaged using the cellular proliferation marker [¹⁸F]-3’-fluoro-3’-deoxy-L-thymidine (FLT)³ at baseline, peak drug exposure, and the end of the first drug holiday. Tumors were identified by a nuclear medicine physician and manually segmented. SUV_mean, SUV_max, SUV_peak, SUV_total, and PET-defined tumor volume were then calculated for each tumor. Response was defined as the percent change normalized to baseline, and response heterogeneity was quantified as the range of response across all tumors within a single patient.

Results: The heterogeneity results are plotted in Figures 1 and 2 below, grouped by response metric and scan, respectively.

Figure 1 Box and scatter plots of intra-patient response heterogeneity, grouped by response metric. For all metrics, substantial heterogeneity was observed. The highest mean heterogeneity was observed for both volume and SUV_total (45%), the lowest for SUV_mean (25%).

Figure 2 Scatter plot of response heterogeneity calculated using each metric, grouped by scan and patient. In 10% of cases, response heterogeneity greater than 75% was observed, and in 35% of cases response heterogeneity greater than 40% was observed.

Figures 1 and 2 demonstrate the magnitude of intra-patient response heterogeneity, but they do not capture the directionality of response with respect to baseline. Interestingly, in 18% of cases, tumors within the same patient exhibited opposite trends, with one increasing more than 20% and another decreasing more than 20% relative to baseline. The case presented in Figures 3 and 4 illustrates this circumstance:
By comparing tumors that are imaged during the same scanning session, many sources of uncertainty in PET quantification are either reduced or eliminated, including factors related to scanner performance and technical factors related to the injection. The greatest remaining source of uncertainty in treatment response quantification is ROI definition, to which volume and $SUV_{\text{total}}$ are the most sensitive.

Conclusions: In this study, heterogeneous treatment response was observed in nearly all patients with multiple tumors, and in some patients to a very large degree. Current treatment response metrics, which were developed for single-tumor evaluation, are therefore insufficient to fully characterize such patients’ response to therapy. Further investigation is necessary to assess how to apply imaging biomarkers of treatment response to patients with multiple tumors, as this study suggests that either new methods for interpretation or entirely new metrics are required for this population.