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The effect of baseline morphology and its change during treatment on the accuracy of Response Evaluation Criteria in Solid Tumours in assessment of liver metastases

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Abstract ***Purpose:*** Tumour response assessment to therapy is crucial in oncology. We analysed the morphology of liver metastases (LM) in gastrointestinal stromal tumour (GIST) patients to determine whether uni-dimensional measurement of lesions by Response Evaluation Criteria in Solid Tumours (RECIST), accurately reflects lesion volume.

Materials and methods: The volumes of LM ($n = 139$) from a GIST patient cohort were measured using computed tomography (CT) at baseline, 3, 6 and 12 months after commencement of imatinib therapy. Baseline measurements were obtained by two independent investigators and inter-observer agreement assessed using Bland–Altman plots. Actual lesion volumes (V_{ACTUAL}) were measured and compared with volumes based on the RECIST measure (V_{RECIST}), and with volumes based on three orthogonal measures ($V_{ELLIPSOID}$) at several time-points.

Results: At baseline, the inter-observer bias for V_{ACTUAL} was just 1.8%. V_{RECIST} and $V_{ELLIPSOID}$ overestimated V_{ACTUAL} by a mean of 35% and only 9% respectively ($P < 0.0001$ for both). At baseline, 44% (61/139) of LM were classified as spheroidal and 56% (78/139) as ellipsoidal. During treatment, only 42% of LM retained their original morphology. The remainder demonstrated significant changes in morphology (from spheroidal to ellipsoidal and *vice versa*) over time, while the RECIST measure did not reflect such changes.

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Conclusions: The morphology of LM in GIST is rarely spherical (an underlying assumption for RECIST) and can change considerably during imatinib therapy. In this setting, measurements using RECIST do not reflect changes in size and morphology. Additionally, whilst $V_{ELLIPSOID}$ is a more suitable surrogate for volume estimation, it is still somewhat limited by the morphology and orientation of such lesions. Studies are warranted to further explore the clinical impact of these findings.

1. Introduction

Response assessment to anti-cancer therapies is a key decision-making instrument used by oncologists to guide systemic treatment changes for virtually all agents that we use in oncology, as well as to assess the efficacy of novel agents in early phase clinical trials. The gold standard criteria of response assessment, RECIST 1.1 (Response Evaluation Criteria in Solid Tumours), are based on uni-dimensional (1D) measurements (the sum of the longest diameter of up to two target lesions per organ) and their percentage change during therapy [1–3].

According to RECIST, a response is classified as a 'partial response' (PR) if a reduction of at least 30% of a lesion's maximum trans-axial diameter (MTD) (or, more precisely, the baseline sum diameters of the target lesions) is observed after a given treatment. More importantly, as this will change treatment, a response is classified as 'progressive disease' (PD) if the sum diameters increase by at least 20% compared to the smallest sum diameters reached during therapy (or with the appearance of new lesions).

These cut-offs are derived directly from the World Health Organization (WHO, 1979) criteria – the first response criteria to therapy created for solid tumours – which used the product of perpendicular cross-sectional diameters (bi-dimensional; 2D) [4].

In the late 1990s, RECIST replaced WHO criteria because they were easier to use in daily clinical practice and were thought to be accurate enough to assess response in solid tumours [2,3]. They are now used by academic institutions and industry for trials with objective response or progression as primary end-points and regulatory agencies have accepted this as the standard in response assessment for clinical trials in most countries [1,3]. Moreover, they were revised in 2009 to form RECIST 1.1 [1]. Of note, to translate the cut-offs from WHO to RECIST (from 2D to 1D), the assumption that lesions are spheres was made [2].

Although several limitations (e.g. irregular or confluent lesions, errors due to discrepant scan planes and patient positioning, intra-/inter-observer variability, lesions with cranio-caudal diameter (CCD) longer than the MTD) of RECIST criteria are widely recognised, no alternative assessment of tumour burden has been validated on large sets of patients [5–7]. During the last decade, an increasing awareness of the importance of the clinical implications of tumour response assessment criteria is evident, especially in the era of tumour heterogeneity and use of targeted therapies. Finally, despite a limit on the number of target lesions measured being considered acceptable and validated [1], concerns have been raised that RECIST is suboptimal, not being an actual assessment of tumour burden [7,8].

With advances in radiology and digital imaging analysis technology, more and more publications are reporting three-dimensional (3D) measurements being more advantageous than 1D measurements in the identification of size change. This is based on studies using artificial models (silicon or sponge objects as phantoms) as well as studies of primary and secondary lesions during systemic treatments [6,9,10]. Moreover, semi-automated techniques have been demonstrated to overcome the limitations of manual assessments in terms of time required and intra-/inter-observer variability, making large numbers of volumetric quantifications feasible [11–13].

Therefore, several proposals were made to shift from 1D to 3D criteria, mainly by translating 1D cut-offs into 3D cut-offs assuming tumours to be spherical [2]. However, solid metastases can be better described by ellipsoidal than spherical volumes [14]. Recently, it was also demonstrated that pancreatic cystic masses are not spherical and their longest trans-axial dimension is not an accurate surrogate for the actual volume [15]. Moreover, in our previous study where 1D and volumetric measurements of liver metastases (LM) from gastrointestinal stromal tumour (GIST) during imatinib treatment were compared [16], uncorrected volume measures detected a size change of $\geqslant$20% more frequently than RECIST, confirming previous findings on lung lesions [17]. When volume criteria, especially those derived by assuming metastases to be ellipsoidal volumes (see Fig. 1B), were used instead of RECIST, more patients were classified as imatinib-responders. Furthermore, despite a higher sensitivity for detecting early treatment response (PR), the threshold for progressive disease (PD) remained unaffected. The validity of this approach was borne out by better correlation with overall survival (than RECIST) in the studied cohorts [16]. Volume measures have a wider dynamic range such that smaller alterations can be detected