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EDITORIAL

Radiological evaluation of oncologic treatment response: current update

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During pharmaceutical trials, clinical, laboratory and imaging methods are frequently used as surrogate endpoints that serve as early indicators of clinical endpoints and to reliably predict clinical outcomes. In cancer patients, objective tumor burden evaluation is commonly accomplished by radiological methods. Radiological monitoring of tumor burden is accurate, easily reproducible and provides an objective evidence of treatment response.

During oncology clinical drug trials, change in tumor size has long been considered as a surrogate marker of therapeutic efficacy that provides objective evidence about the drug efficacy and supplements subjective clinical endpoints such as quality of life[1,2]. Drug regulating agencies such as the US Food and Drug Administration (FDA) provide expedited approval of drugs for debilitating and life-threatening illnesses based on radiological evidence of tumor shrinkage[3]. Indeed, the FDA approved capecitabine following a phase-II trial based in part on reduction of tumor burden on CT scans[4].

Since the early 1980s, World Health Organization (WHO) guidelines based on bi-dimensional measurement of tumors have been followed for evaluation of treatment response[5,6]. According to these guidelines, individual tumor size is determined by a 'cross-product' obtained by multiplying the longest diameter in the axial plane by its largest perpendicular diameter (Table 1). Baseline and post-treatment measurements are then compared to categorise a patient's response to treatment into one of four categories described below. These consist of complete response (CR) indicating tumor disappearance, partial response (PR) indicating >50% decrease in cross-product, disease progression (DP) indicating >25% increase in cross-product, or stable disease (SD) representing <50% reduction to <25% increase in cross-product. For patients with multiple lesions, the cross-

Table 1 Treatment response categories and tumor measurement techniques

Category	Bi-dimensional[5,6] *Cross-product	Uni-dimensional[8] Diameter	Volumetric[8] **Volume
CR	Tumor disappearance	Tumor disappearance	Tumor disappearance
PR	>50% reduction in cross-product	>30% reduction in diameter	>65% reduction in volume
SD	Size intermediate to that for partial response and that for progressive disease		
DP	>25% increase in cross-product	>20% increase in diameter	>73% increase in volume

*Cross-product: the largest diameter and its maximum perpendicular diameter are multiplied to obtain cross-product. The individual cross-products are summed in patients with multiple lesions.
**Volume: volumetric measurement is obtained by multiplying the sum of areas from each slice with the reconstruction interval.

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product of several 'target' lesions is simply added to categorise the patient's response.

Lavin and Flowerdew concluded that due to variability in measurements, there was a one in four chance of declaring that DP had occurred if one considers the WHO criteria for DP[7]. Also, the measurements and mathematics involved to categorise patient response according to WHO criteria were cumbersome and time-consuming. In addition, assuming that most tumors grow as spheres, a single linear measurement would suffice to measure changes in tumor size.

In an effort to standardise tumor measurement techniques to achieve greater rigor in response and endpoint definitions, the European Organization for Research and Treatment in Oncology, National Cancer Institute of the United States and the National Cancer Institute of Canada Clinical Trials Group set up a task force in 1994. Based on retrospective statistical evaluation of measurements obtained in more than 4000 patients in 14 different trials, a uniform set of criteria for reporting treatment outcomes called the 'response evaluation criteria in solid tumors (RECIST)' guidelines were formulated in 1999 (Table 1). RECIST guidelines are more specific than the WHO criteria in the measurement of baseline tumor burden, the number of lesions that need to be measured on serial studies and the way the tumors are measured.

RECIST guidelines advocated that uni-dimensional measurement alone (largest diameter in the axial plane) be used for quantifying tumor burden[8]. Also, lesions are to be categorised as measurable or non-measurable. Measurable lesions consist of those that measure $\geq$20 mm using conventional imaging techniques (including incremental CT) or $\geq$10 mm using helical CT equipment. Non-measurable lesions are those with smaller dimensions. Furthermore, measurements are limited to an arbitrary five measurable lesions per organ (also called 'target' lesions) and up to 10 per patient with tumors in multiple organs[8]. These target lesions are selected based on size and suitability for reproducible measurements. For the uni-dimensional measurement approach, the criteria for treatment response categorisation were also modified with PR being defined as $>$30% decrease in tumor diameter, SD being $<$30% reduction to $<$20% increase in diameter and DP being $>$20% increase in tumor diameter[8]. A 20% increase in diameter (criteria for DP by RECIST guidelines) corresponds to an approximately 73% increase in tumor volume while a 25% increase in cross-product (criteria for DP by WHO guidelines) corresponds to an approximately 40% increase in tumor volume. Thus, according to RECIST criteria, the threshold for classifying patients as having DP has been increased. The criterion for CR was identical to that of the WHO criteria comprising of total tumor disappearance.

However, there are several drawbacks with the RECIST criteria. RECIST criteria do not specify toxicity criteria, a key component of other treatment response criteria[9]. In addition, uni-dimensional measurements may be inaccurate when measuring tumors of variable morphology; specifically when the lesion length exceeds twice its width[10]. Measurement errors in estimating change in the size of small lesions can thus result in misclassification of response. According to RECIST criteria, lesions measuring less than 1 cm (helical CT) and 2 cm (conventional CT) are not considered as target lesions; hence treatment response in patients with subcentimetre lesions cannot be adequately evaluated[11]. RECIST criteria also exclude cystic or necrotic lesions when evaluating response. In addition, since the edges of irregular, confluent or infiltrating lesions are often difficult to define, it may be better to obtain volumetric tumor burden.

Accurate estimation of change in tumor burden is of importance since even small differences in response rate could affect the conduct of phase I and II trials. Assuming spherical growth of tumors, there is a predictable mathematical relationship between the diameter, cross-sectional area and volume of a sphere for estimating tumor size. Recent advances in CT technology, specifically volumetric data acquisition and image processing, permit volumetric tumor burden quantification[12]. However, the value of volumetric tumor measurements has not been definitively established in clinical practice. Some preliminary studies have supported the use of three-dimensional measurement techniques for assessing tumor size[13,14]. Other studies have not found significant added benefit of volumetric tumor measurement for evaluating therapeutic response when compared to linear measurements[15,16]. However the results of a study by Hopper *et al.* showed considerable inter-observer variation among radiologists in CT linear tumor measurement, especially for ill defined and irregular lesions[17]. In a recent study involving patients with breast metastases to liver, the volumetric assessment produced different results in one-third of patients when compared with linear measurement techniques. Discordance between volumetric and linear measurements occurred in patients with considerable tumor burden or tumors that show asymmetric changes in tumor size[18].

An important theoretical advantage of volumetric measurements is that simply estimating overall tumor burden in an organ can eliminate the limitation of measuring five target lesions per organ (RECIST criteria). In addition, volumetric measurement might be a better method to measure size changes of lesions that are confluent. However, tracing individual tumor margins is a time-consuming process and special software for volume estimations may be required. In addition, different formulae for volume estimation need to be applied when considering non-spherical tumors. However, with advances in image processing and automation, volumetric tumor burden estimation may become simpler[19].

In conclusion, radiology plays a central role in quantifying disease burden and accurately evaluating response to treatment. With advances in cancer drug treatments, and our ability to accurately assess changes in

tumor size, it is imperative to develop consistent criteria to evaluate treatment response on a global scale.

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