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] | Uni-dimensional[8] | Volumetric[8] |
|----------|--------------------|--------------------|---------------|
|          | *Cross-product      | Diameter           | 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 tech-
niques 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[9]. 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 guide-
lines) 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 inac-
curate 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 (con-
ventional 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 re-
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 tu-
mor 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 prelim-
inary 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
formule 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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