

Measure Once or Twice—Does It Really Matter?

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There is an old carpenter's dictum that one should measure twice (and cut once). Supposedly, this leads to fewer irreversible errors—with wood. The question is, do we have to measure a tumor twice in the practice of medical oncology?

In an article in this issue of the Journal, James et al. (1) conclude that a one-dimensional measurement of tumor maximum diameter (rather than a two-dimensional measurement) may be sufficient to assess the change in solid tumors following treatment. The authors are to be congratulated for taking a new look at the “conventional wisdom” of the way we measure tumors. The question one must ask is, are there any reasons for the general practice of oncology to adopt unidimensional measurement of tumors?

It is true, as pointed out by James et al. (1), that the process of measurement of tumors in two dimensions and the calculation of products and their sum is laborious. Anything that gives us more time to spend talking with our patients rather than measuring with calipers and calculating with a calculator is certainly welcome. However, one must remember that, to ascertain the maximum diameter of a tumor (since a tumor is frequently not exactly spherical), one usually takes more than one measurement to make sure one has the maximum diameter. Therefore, one may not save much time. On the positive side, requiring only unidimensionally measurable disease as an entry criterion (rather than the usually required bidimensionally measurable disease) may allow more patients to participate in clinical trials. However, allowing that there may be a savings of time by measuring each tumor in one dimension and having a larger percentage of patients able to participate in clinical trials, are there other reasons to adopt the unidimensional method?

The authors present a theoretical reason for using only one dimension for measurement of tumor response. They posit that changes in diameter relate more closely to the fixed properties of cells killed by a standard dose of chemotherapy than do changes

in the bidimensional product. However, we have some concerns about that reasoning. Assuming for the moment that we have a single, spherical tumor, then

$$\text{volume} = \frac{4}{3} \pi r^3 = \frac{\pi}{6} D^3,$$

where r = radius and D = diameter. If D is measured in centimeters, then

$$\begin{aligned} \text{cells} = D^3 \times 10^9 \quad \text{and} \quad \log_{10}(\text{cells}) &= \log_{10}(D^3) + 9 \\ &= \frac{3}{2} \log_{10}(D^2) + 9 \\ &= 3 \log_{10}(D) + 9. \end{aligned}$$

Clearly, it is the logarithms of D and D^2 , not the raw values, that are linearly related to the logarithm of the number of cells. In fact, it is not clear to us why a linear relationship between a measure of tumor size (i.e., D) and $\log_{10}(\text{cells})$ would be desirable. Such a relationship, carried to its logical conclusion, would imply that a 1-cm decrease in diameter, say from 5 cm to 4 cm or from 1 cm to 0 cm, would result in the same proportional reduction in the number of cells. The appearance of linearity in Fig. 1 of the article by James et al. (1) seems largely due to the difference in scales. A plot of the data from Table 1 of the article by James et al. (our Fig. 1) shows that, if anything, the product definition might provide a closer approximation of proportional changes in volume and, therefore, proportional changes in cell number.

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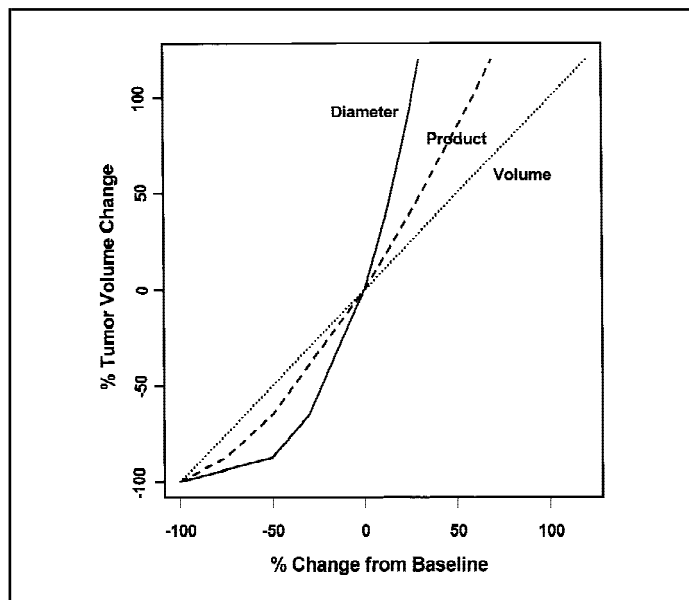


Fig. 1. Plot of data in Table 1 of James et al. (1). Diameter refers to the tumor's largest diameter (i.e., unidimensional measurement); product refers to the multiplication of the tumor's largest diameter by its perpendicular (i.e., bidimensional measurement).

As the authors point out, it is possible to define equivalent criteria for response, stable disease, and progression using either the sum of diameters or the sum of bidimensional products. This applies even when there are multiple lesions, the lesions are NOT spherical, and the lesions are not all the same shape. Theoretically, if all measurable lesions are at least approximately ellipsoidal and the semi-axes of all lesions change by the same proportion, then patients will be classified identically by both criteria. If some tumors change less than others, the results are less predictable. In general, both sets of criteria will tend to underestimate the new volume (i.e., progressive disease by volumetric measures might be called stable disease by sum of the diameters or products, and stable disease might be called a partial response). It is interesting that the degree of underestimate seems to be slightly less for the sum of the products than for the sum of the diameters, although, for equivalently defined criteria, measurement variability probably outweighs this effect. This is confirmed in the study by James et al., where concordance between classifications was very high and discrepancies were random.

The points the authors make about definition of disease progression are good ones. In 1980, Lavin and Flowerdew (2) clearly demonstrated that use of a 25% increase in the product of the maximum perpendicular diameter did have a one in four chance of declaring that progression had occurred when, in fact, the tumor was unchanged. The change proposed by James et al. to use a 30% increase in the largest diameter as a definition of progression does mean that the patient's tumor has grown substantially more (120% increase in volume versus a 40% increase in volume as measured by current methods) before a change in therapy is made. That may not make a difference if one does not have effective second-line therapy. However, with second-line therapy now causing a substantial increase in survival (3), one wonders if we might be waiting too long before we make a change in therapy if we use the proposed criterion. The retrospective data presented by James et al. do not address that issue. It can be addressed only via a prospective randomized clinical trial.

In reviewing the results of the comparison of the response data using the unidimensional versus the bidimensional method, we are concerned about some of the studies utilized. No details are given as to why the particular studies were selected. What were the selection criteria? Studies such as the brain tumor study, where tumor measurements on scans are so difficult to assess, clearly complicate the conclusion that there are no differences in the response rates using the two methods (unidimensional versus bidimensional).

Other important questions include the following: (a) Were the responses audited? (b) Why were phase II and III studies utilized? (c) Why were only four studies used to generate the progression, decrease, or stable disease data?

Overall, while this retrospective study is of interest, one wonders whether the theoretical and practical reasons the authors give for adopting the new criterion are sufficient to warrant changing what has become quite an accepted method for evaluating the efficacy, or lack of efficacy, of antitumor agents. Without a prospective evaluation of their criteria, particularly the criteria for tumor progression, to determine whether or not harm could be done, it is probably not yet time to adopt the unidimensional measurement system. This is particularly true because, with many of our new clinical trials, even with cytotoxic agents, the measurement of the percent of patients with progression at a point in time (4,5) or the presence of a "state of non-progression" (6) is becoming an accepted end point.

Finally, there are some innovative methods for making tumor measurements easier for clinical investigators. For example, a device called the tumorimeter (a hand-held device with a sliding loop to measure ellipsoid tumors circumferentially) has been shown to enhance the speed and accuracy of tumor measurement (7).

In summary, it is clear that any methods to make clinical trials technically easier are welcome. However, we would all probably agree that the real problem is that we need more things to shrink tumors regardless of how many ways we devise to measure that shrinkage.

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