Review

Imaging for oncologic staging and follow-up: review of current methods and novel approaches

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Abstract. *Purpose:* To review the current radiological methodologies and guidelines for staging and follow-up in oncology, and to give a perspective based on the available new technologies in oncologic radiology. *Materials and Methods:* The literature on cancer radiologic quantification in diagnostic phase and follow-up has been reviewed. The main concepts and guidelines (official and non-official) have been extracted taking into account the period of publication and the available technology. The current World Health Organization (WHO) and Response Evaluation Criteria In Solid Tumors (RECIST) guidelines have been critically evaluated on the basis of technical literature on quantitative radiology applied to oncology. Pitfalls of previous and current guidelines have been exploited on the basis of currently available techniques for quantification. *Results:* Errors due to operator, scanner, software, and measurement technique inconsistency are all together far more relevant than the recognized thresholds applied for detecting therapeutic response. For this reason the volumetric assessment of cancer disease should be introduced. *Conclusion:* Even though the technical constraints are still prominent in the clinical practice, the design of clinical trials should be planned taking into account these new volumetric quantitative techniques. (www.actabiomedica.it)

Key words: Tumor response, oncology, radiologic evaluation, criteria, guidelines, follow-up, staging

Introduction

"All men naturally have an impulse to get knowledge…" – "Clearly, then, wisdom is rational knowledge concerning certain basic factors and principles." (1). These assumptions, settled at the roots of western culture by Aristotle in his "Metafisica", still guide the man in his search of knowledge and truth.

Human cancer represents one of the main research topics of the last century. Recently it also became known as a dynamic living system rather than a circumscribed growing process. This multi-dimensional definition of cancer represents a new challenge in scientific methodology which can be summarized with the paradox of the hermeneutic circle (2): the theoretic prerequisite to know "the whole" to identify its constitutive parts and the necessity to proceed from the study of the parts to discern "the whole". The paradox becomes evident since the study and follow-up of cancer is currently performed using a few parameters (i.e. a few parts).

Theoretically, the biological follow-up in oncology is based on the assessment of the variation in the number of the neoplastic cells over time. However, no reliable estimation of the number of neoplastic cells can be performed in vivo. In fact the cellularity of a tumor is estimated through morphological and functional indicators. This indirect approach severely af-

fects the accuracy of the estimation since these indicators are neither linearly correlated nor exclusively dependent on the cellularity of the neoplasm.

The method for the selection, the sampling and the analysis of these indirect indicators are therefore crucial in order to avoid the collection of several errors from multiple sources. A few criteria could be identified as follows.

It seems reasonable to select multiple indicators with a high and well known dependence on the intrinsic factors of the tumor. Conversely these indicators should be independent from the extrinsic factors of the tumor.

The intra and inter-individual variability of the indicators should be well under the threshold above which the variation becomes clinically significant. This criterion is necessary in order to avoid intra and inter-individual fluctuations to simulate a significant variation of the indicator. As a consequence the variation of the indicator above which the clinical outcome becomes significant should be known. The clinical significance of the variation should also be defined.

A qualitative assessment through subjective judgments should be avoided. Theoretically, ordinal scales such as the TNM system should also be avoided. In fact in ordinal scales higher numbers represent higher stages. However, the intervals between stages are not necessarily equal or proportional. Moreover their correlation with the patient's outcome has been subsequently established.

Finally the intra and the inter-observer variability, the error of the measurement method should be under the threshold above which the variation becomes clinically significant for the same reasons already mentioned. Accuracy and reproducibility of the measurements are mandatory in order to overcome these drawbacks (3, 4).

In radiological practice, as well as in scientific research studies, tumor volume is assumed to be representative of the number of neoplastic cells. This criterion may be argued since a neoplastic lesion may be a mixture of cells, vessels, interstitium, necrosis, and fluid collections. However, an estimation of the lesion volume rouses controversy regarding the most appropriate method.

In this paper the current radiological methods and the guidelines for the assessment and follow-up of neoplastic diseases are reviewed.

Volume Estimation

The proceeding of volume estimation can be described in two main phases. The first one is represented by data acquisition. It is interesting that, in the various guidelines for tumor assessment and follow-up, little attention is given to the acquisition technique. In fact, several factors can affect the perception of the measured object, namely: the tissue contrast between the object and surrounding structures (5-10); intravenous contrast material (11-13); volume averaging (6, 7, 14); and window settings (14). The second phase is represented by the measurement itself which is performed with different methods.

Linear measurements

Linear measurements are the main method for the estimation of volume or the variation in size over time. The use of linear measurements for the follow-up of neoplastic lesions has been supported in the WHO guidelines by Miller et al. in 1981 (15), and in the RECIST guidelines by Therasse et al. in 2000 (16). These guidelines describe three aspects that should be considered in radiological follow-up, namely: the features required for a lesion to be measurable; how the measurements should be performed (WHO requires two perpendicular linear measurements along the main axis of the lesion, while RECIST requires a single linear measurement); and criteria for assessing therapeutic response. Complete or partial response, stable or progressive disease, are defined in terms of variation in volume percentage. Although easy to follow, these guidelines raise several objections that are set out below.

Defining the measurable lesion

According to these guidelines there is no indication on how to proceed for infiltrative or bulky neoplasms involving structures with complex cross-sec-

tional anatomy or hollow viscera. This is the reason why the evaluation of volume variation in these lesions (i.e., assessment of tumor response) is often reached by subjective assessment. In a phantom study by Tiitola et al. the subjective estimation of the size of several irregular volumes was correct in 51% of cases (17). The same authors concluded that the radiologist's volume estimation of irregular objects was suboptimal and should be replaced by computerized volume estimation. The radiologist's subjective estimation of regular structures also provides poor results (18).

Mathematical factors

From a strictly mathematical standpoint it is not correct to assess the variation in lesion volume using two-dimensional or one-dimensional criteria. If these techniques are adopted, the correlations are not linear, and consequently the response criteria will not be linear.

James et al. stated that one linear measurement shows a higher correlation with the cells killed by a standard dose of chemo-radiotherapy (19). On the contrary, Hilsenbeck and Von Hoff demonstrated that the correlation between tumor diameter and cell number is not linear (20): it is the logarithm of the diameter, and not the raw values, which is linearly related to the logarithm of the cell number.

Hilsenbeck and Von Hoff also noted that in studies supporting the use of linear measurements, these measurements were in some cases expressed as natural logarithms prior to analysis with high correlation values between the linear measurement and the volume (19, 21). As a result, the linear relationship between linear measurements and volume is derived from the difference in scale (20). In clinical practice, however, the use of logarithmic scales does not appear to be feasible.

Geometric factors

Without any scientific discussion it is clear that the assumption that it is possible to reliably assess a volume from linear measurements is not acceptable in biology. Therefore linear measurements can hardly be applied to estimate the volume of irregular solids (22). The assumption that focal lesions are spherical is methodologically erroneous since the spherical shape should be demonstrated (20). Linear measurements could be used for spherical and small lesions, but may therefore introduce an additional source of error. Although methodologically incorrect, it can be argued that such an error could be tolerated if it is well below the threshold above which the variation in volume is clinically significant. The problem is then defining what is clinically relevant. In many cases the variability of tumor shapes and volumes does not allow such calculations (23). Moreover, linear measurements critically depend on the level and orientation of the plane where they are performed. This determines poor reproducibility (23, 24). Finally, the longitudinal axis is not considered while lesion growth is not necessarily uniform (4).

Structural factors

As previously stated, a lesion is a mixture of cells, vessels, interstitium, necrosis and fluid collections. An increase in the volume of one of the non-cellular components (i.e., necrosis) may mask a decrease in cell numbers. As a result the tumor volume partially correlates with the cell number. This task could be better challenged for instance, with software tools that are able to quantify the amount of tumor with contrast enhancement. In our opinion, the response criteria should be adapted to the histology and natural history of the tumor. A 30% volume reduction may be a poor result in fast-growing tumors but it may also be considered a good outcome in slow-growing neoplasms.

Summing the areas

A method for estimating the volume from cross-sectional images which has been widely used prior to the development of more advanced technologies is the multiplication of the reconstruction interval with the result of the sum of the area of the lesion in each contiguous cross-sectional image (5, 9, 14, 17, 18, 25-30). Theoretically this method does not differ from more recent three-dimensional techniques. The latter

should be preferred because they are less time consuming and more accurate.

Three-dimensional techniques

Three-dimensional techniques achieved higher reproducibility when compared to conventional methods (12). The intrinsic error of these techniques have been assessed mostly in phantom studies. The error can be hardly validated in-vivo by measuring the true lesion volume of the pathological specimen. In fact in this instance, the spatial relationships between the lesion and its surrounding are lost, the intra- and extracellular fluids and the blood content are altered, and the true volume of the neoplasm cannot be evaluated (3, 11, 13).

Three-dimensional volume estimation techniques prevent several problems encountered with the methods previously described , since the volume is obtained directly by counting the number of voxels composing the lesion. Tumor follow-up using this method takes the three dimensions into account, and the technique is unaffected by the geometrical factors. No studies nor clinical literature have been performed yet applying these techniques. Therefore new criteria should be identified. Other parameters should be probably considered in the identification of those criteria, such as the histological type, tumor location, and inner tumoral structure.

Lesion margins and tumor structure may be identified through the use of advanced segmentation and texture analysis techniques. The lesion can be defined either manually or using semi-automated or automated techniques (3, 11, 31, 32). While the former method still relies on the operator's subjective perception, the latter may be based on analytic, morphological and knowledge-based operations (33, 34). Both methods can allow, through thresholding for instance, a more precise analysis of the lesion components.

Tumor Structure

Some authors evidenced the usefulness of the assessment of structural changes in oncologic follow-up (35-37). These changes can be grouped in three categories according to their underlying etio-pathogenetic mechanisms: acute and chronic inflammation, reparative or amorphous structures, and tumor genesis.

Although these criteria can provide useful keys in directing the evaluation, they are often not adequate in establishing and particularly in quantifying tumor response. No quantitative studies have been performed to assess their reliability. Finally the differential diagnosis between tumor, inflammatory, reparative or degenerative changes is often challenging.

Discussion

This review of the methods that have been tested for volume estimation and for oncologic follow-up suggests the rejection of linear measurements since they are unreliable if not misleading. Accuracy and reproducibility are particularly important if the consistency of a clinical trial or a scientific study depends partly or completely on measurements. The measurement of lung nodule diameters by means of chest X-rays (CXR) demonstrated an inter-observer variability of 25% (38). In studies based on cross-sectional imaging with segmentation techniques, intra- and inter-observer variability was respectively assessed at 3% and 3.76% (24). Despite these apparently encouraging results, several patients (ranging from 17.7% to 26%) can be reclassified in a different category of oncologic response depending on the measurement method (i.e. linear measurement vs. three-dimensional segmentation technique) (23, 39). The impact of this observation on lower stages of disease is evident.

Three-dimensional techniques are still time consuming and not widely available (3, 4, 40). These facts lead radiologists and oncologists not to use them and on the contrary to prefer linear measurements. Although this can be understood in the clinical practice (quick and easy approach), it should not be tolerated in clinical trials. In other words, while the assessment of therapeutic response may be sub-optimal in the clinical practice due to the limitation of the resources, the efficacy of a therapy must be assessed with accurate and repeatable techniques (41, 42).

The point can be resumed in two questions: 1) Is the volume adequate as a radiological parameter for tumor assessment and follow-up? If the appropriate method to obtain the volume is used the answer may be "yes". 2) Is volumetric assessment the only current available radiologic parameter for oncologic follow-up? The development of new technologies such as functional and molecular imaging with MRI and PET will soon introduce new parameters that should be considered in oncology.

Some of these techniques are based on the volumetric approach which in fact means to overcome the discretization of the analysis that occurs with linear measurements. The mentioned guidelines gave little attention on the acquisition technique. This is understandable since the voxel size does not significantly influence linear measurements. Yet the acquisition technique is rather a critical aspect for three-dimensional 3D imaging and more advanced techniques.

These technologies will be of inestimable value for the assessment of the efficacy of anti-tumoral therapy, even though not for wide-spread clinical use. An additional aspect of these new techniques is that they facilitate to consider the cancer as a systemic disease due to their increased sensitivity and accurate quantification.

The impelling results achieved with these experimental technologies emphasize the requirement to build a common language which could be defined as the concept of "mathesis universalis" from the great mathematician and philosopher Leibniz (43).

Such a common language should include not only the methodological aspect, but also the conception itself of the neoplastic disease.

The methodological aspect should enclose the standardization of measurement units for some elementary characteristics.

With reference to the conception of neoplastic disease, the theoretical requirement to isolate the problem (the tumor) entails the loss of its multidimensionality and its definition as distinct entity from the organism. From a thermodynamic standpoint, there is the tendency to consider as "closed" a living and "open" system, which is part of a living system.

The methodological option is then to obtain few results of a limited entity or to collect more "points of view" on the complete "man-system". In this last case the validation of a system of measurement, for instance, should be performed through its correlation with the prognosis of the patient. This represents the only practicable way if a comparison with other systems of measurement is not possible or if the entity is of multi-factorial nature.

In conclusion a closer collaboration between radiologists and oncologists is recommended. New methods and new criteria should be established for radiological assessment of tumor response considering the new incoming technologies and, above all a common language is needed.

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