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EDITORIAL

Sense and Sensitivity: Issues in Technology Assessment

Evaluation of a new imaging technology in oncology is usually based on determination of sensitivity and specificity by correlation of imaging results with histologic diagnosis. Meaningful estimation of sensitivity and specificity is possible when the study population is appropriate and when full histologic evaluation of the target lesion or tissue is feasible. Examples of such studies include assessments of imaging in axillary staging of breast cancer and mediastinal staging of lung cancer. In both instances, surgical sampling can be performed, and the accuracy of positive and negative imaging findings can be determined with acceptable precision.

In many diagnostic situations, such precision cannot be achieved. Validation of imaging for detection of hepatic metastasis is one example. Even if all study subjects undergo surgical evaluation after imaging, undetected lesions will be diagnosed only if they are sufficiently large and superficial to be apparent on inspection and palpation of the accessible portions of the liver. Smaller and deeper lesions, which have not been detected by imaging and are not found at surgery, will remain undiagnosed and will not be recog-

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nized as sites of false-negative findings. As a result, sensitivity will be overestimated.

Such inaccuracy is inevitable in many areas in which full histologic evaluation is not possible and is most striking in whole-body tumor imaging, in which validation of tumor in nonsymptomatic areas is entirely dependent on imaging results. There is no possibility of detecting asymptomatic tumor that is not associated with an imaging abnormality, since the site of a lesion must be suspected from clinical or imaging findings before biopsy can be undertaken. Thus, there is little opportunity to establish false-negative results. Values obtained in this circular fashion are commonly reported as "sensitivity."

Determination of specificity in such circumstances is also problematic, since metastatic lesions commonly occur at multiple sites, and it is neither practical nor ethically acceptable to confirm all positive findings histologically. In most cases, the largest and most intense imaging abnormality is selected for biopsy, and smaller and less intense abnormalities, which are more likely to represent false-positive findings, remain unvalidated. As a result, some false-positive findings are likely to remain unrecognized, thereby inflating the measured specificity as well.

When figures for sensitivity and specificity are subsequently quoted in other publications, methodologic details are usually not recorded. The reader cannot evaluate the reliability of the reported results without reviewing the original publication, and even this may not be sufficient. Often, the quoted figures are accepted at face value, and, with sufficient repetition, may become part of the imaging folklore. For example, in an editorial on imaging in colorectal cancer, the sensitivity of CT for hepatic metastasis was quoted as 87.5% (*1*). Review of the article that initially reported this value showed that the presence or absence of hepatic metastasis was established by visual and manual examination of the liver during surgery (*2*). There was no further confirmation of negative findings, certainly leading to underestimation of false-negative results and overestimation of sensitivity.

In oncology, the reliability of imaging technology evaluations can be increased by clinical and imaging follow-up of study subjects in cases where no histologic diagnosis is obtained. If a site of imaging abnormality remains clinically free of disease, the finding was almost certainly false. If clinical or imaging evidence of disease later becomes apparent at the site, the finding was probably true. However, such patient follow-up requires a significant commitment of resources and is commonly not performed in imaging studies. Even when follow-up is part of the validation process, some uncertainty persists, due to the separation in time of the imaging findings and the clinical confirmation.

These issues have arisen recently in evaluations of whole-body PET imaging, which is proving to be highly sensitive and specific for staging some tumors (*3–5*). When a new technology such as PET proves to be more sensitive than existing technologies, it may be difficult to detect false-negative results. If the denominator for calculation of sensitivity is established by biopsy or by other procedures that are initiated by the imaging findings, the calculated sensitivity will approach 100%. Very high values for sensitivity have been published in evaluations of PET in recurrent colorectal carcinoma and melanoma, where negative results by both PET and CT were accepted as true in some cases without follow-up confirmation (*4,5*). A similar situation existed with the introduction of whole-body CT, leading to reports of greater than 90% sensitivity for detection of distant metastasis and recurrent disease in some tumors (*6,7*).

It is preferable to present results in such cases as simple comparisons between modalities, instead of calculating sensitivity values that are based on underestimates of actual disease prevalence. In general, perfect sensitivity is not achievable in tumor imaging, since early, microscopic tumor deposits will defeat the resolution capability of any macroscopic imaging modality. Where no true gold standard exists, as is usually the case in whole-body imaging, accurate determination of sensitivity is not possible. This shortcoming should be accepted to discourage the generation of misleading figures. Presently, data are [illegible] to meet the perceived expectations of reviewers frequently leads to stretching of the concept of "gold standard" to great lengths, with the production of figures that obscure meaningful results, rather than clarifying them.

Another term such as "detected sensitivity" might be used instead of "sensitivity" in situations in which full histologic validation is not feasible, and it is apparent that the reference standard is imperfect. The use of such a term would avoid implying an unrealistic level of accuracy, while retaining usability for making quantitative comparisons. In any given case, a statement of detected sensitivity would require a description of the validation procedures that were used as well as the value that was obtained.

Knowledge of sensitivity and specificity is desirable, since it permits the calculation of post-test probabilities and comparison of modalities by receiver operating characteristics. However, clinical evaluation of a new diagnostic modality does not depend on this knowledge. What is required is a comparison of accuracy with existing modalities to determine how many additional lesions can be detected and how many false-positive results can be avoided by the new technique. Also, the positive predictive value should be estimated from biopsy and follow-up of positive findings. Since positive findings in oncology frequently trigger treatment change, a knowledge of the positive predictive value is needed for management decisions.

The percentage of cases where the new modality permits more accurate diagnosis needs to be determined, as does the percentage of cases in which a more accurate diagnosis leads to improved management and treatment outcome. From this, the significance of the new modality on the cost of patient management and the effect of change in treatment outcome on societal costs can be calculated, thereby permitting determination of cost-effectiveness. These are the issues of importance in the evaluation of new clinical tools, and a lack of knowledge of sensitivity and specificity does not hinder their appraisal.

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