A Practical Guide of the Southwest Oncology Group to Measure Malignant Pleural Mesothelioma Tumors by RECIST and Modified RECIST Criteria

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Abstract: Malignant pleural mesothelioma (MPM) is difficult to measure radiographically due to the nonradial and variable pattern of growth and response to therapy. Inaccurate and inconsistent tumor measurements often compromise results from clinical trials that are dependent on identifying response rate and progression-free survival. In this article, we sought to provide a practical guide through the Southwest Oncology Group on how to measure MPM by the updated RECIST version 1.1 and by modified RECIST. We hope that these steps will provide a simple means by which computed tomography measurements can be consistently performed, minimizing intra- and interobserver variability. With this consistency, we may be able to better estimate the prognosis and response to therapy. With greater utilization, we will be able to better understand the biology of MPM.

Key Words: Mesothelioma, RECIST, Modified RECIST, Measurement.

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Radiographically, malignant pleural mesothelioma (MPM) is difficult to measure given the nonradial and inconsistent pattern of growth and response to treatment. Clinical trials that use primary endpoints dependent on radiographic imaging, such as progression-free survival and response rate, may be compromised by inaccuracy of tumor measurements, inconsistency in measurement technique between clinicians, and a lack of experience in measuring pleural tumors, given the relative rarity of MPM. Currently, the measurement methods for MPM are either the RECIST[1,2] or the newer modified RECIST criteria.[3] Modified RECIST was developed based on speculation that RECIST did not address the unique shape of mesothelioma tumors with the pleural rind and thus led to inaccurate measurements.[4–6]

The summarized definitions of the two methods are as follows:

RECIST[1,2]: A measurable target lesion must be 2 cm or more when using cross-sectional imaging with a non-spiral computed tomopgraphy (CT) scan or MRI. If using a spiral CT scan, the measurements must be greater than 1 cm. Measure the long axis of the tumor to achieve the longest uni-dimensional measurement. With the updated RECIST criteria (version 1.1),[2] the number of target lesions required to assess clinical response has been reduced to a maximum of five measurements. Each involved organ site that has a measurable target lesion should be represented in this measurement. However, only 2 maximum measurements per organ are allowed. Therefore, only two pleural tumor uni-dimensional measurements for mesothelioma are required.

Tip for RECIST v1.1 reporting on pleural rind-like masses: Measure the longest diameter of the tumor along the chest wall.

Modified RECIST[3]: Uni-dimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum should be performed, measured in 2 sites at 3 different levels on CT scan. Transverse cuts used for measurement must be at least 1 cm apart, and related to anatomical landmarks in the thorax, preferably above the level of division of the main bronchi. At reassessment, pleural thickness must be measured at the same position and level. Nodal, subcutaneous, and other bi-dimensionally measurable lesions are measured uni-dimensionally as per the RECIST[2] criteria. Uni-dimensional measurements are added to produce the total tumor measurement.

The sum of 6 pleural thickness measurements = one univariate diameter.

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Although both methods define distinct rules of MPM measurements, these measurement techniques have been applied in a highly variable fashion by medical oncologists and radiologists, and obtaining accurate tumor measurements remains a dilemma for mesothelioma multicenter clinical trials. Ultimately, the future of mesothelioma clinical research may be dependent on volumetric measurements or fluorodeoxyglucose-positron emission tomography CT scans; these systems provide numerical values that should minimize interobserver variability and simplify the technique. To date, these volumetric methods are not validated and require further study before their implementation in large-scale clinical trials.[7–9] Educating clinicians in the proper application of the RECIST and modified RECIST systems and standardization of the manner in which the measurements are made is essential. There is no practical guideline to assist in the radiological assessment of pleural mesothelioma. We will attempt to provide detailed practical instructions on how to measure MPM by the updated RECIST version 1.1 and modified RECIST guidelines detailed earlier in the text.

HOW TO MAKE MEASUREMENTS OF MPM BY MODIFIED RECIST

Tips

- Larger lesions are easier and more accurate to measure. Choose the larger or thickest of the pleural disease to measure. Magnifying the image may enable an easier measurement.
- The short-axis diameter is defined as the shortestpathway from the tip of the tumor to the chest wall (Figure 1).
- Ensure that differentiation of normal chest wall from tumor is easy at the point of measurement (Figure 2).

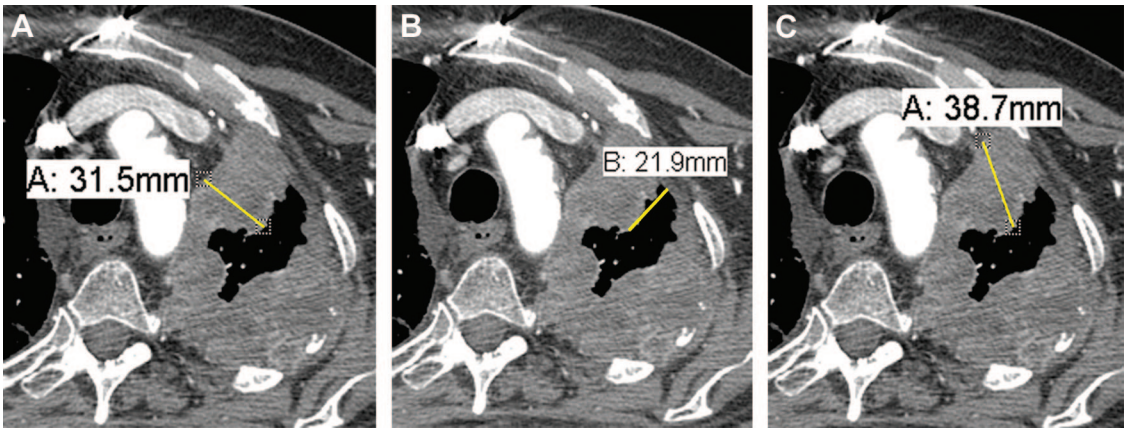

FIGURE 1. Example of well formulated and erroneous measurements using modified RECIST. *A*, Good measurement: the pleural disease has a short-axis measurement of 3.2 cm. The short axis is always measured perpendicular, or 90 degrees, to the chest wall or mediastinum and is the measurement between the point the pleural disease touches the chest wall/mediastinum and the point where the pleural disease touches normal lung. *B*, Malpositioned caliper: although this measurement takes a short path to the chest wall, perpendicular to the chest wall, it does not pass entirely through the tumor before meeting the chest wall and is therefore an erroneous measurement. *C*, Malpositioned caliper: although the measurement goes through tumor tissue, the path is not the shortest going to the chest wall, i.e., perpendicular. It forms an acute angle to the point where the pleural disease interfaces with the mediastinum and is therefore incorrect.

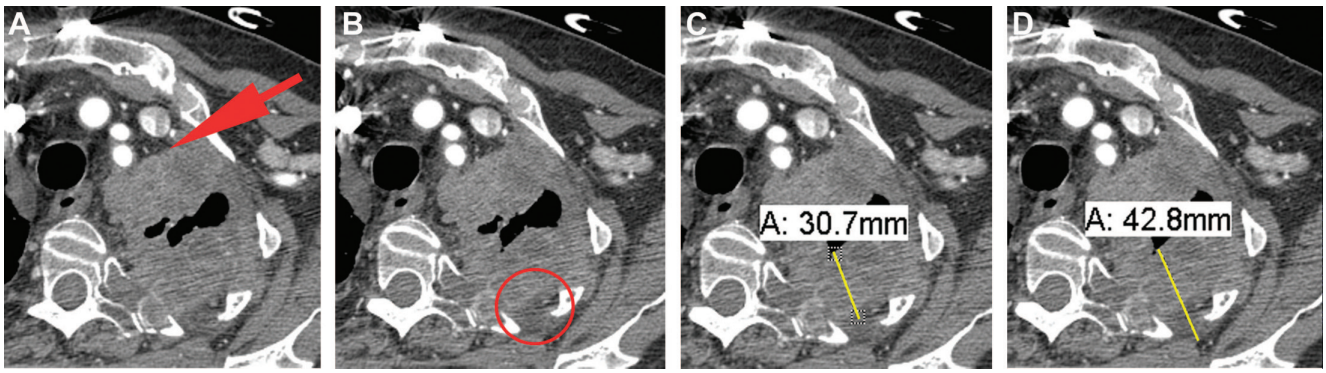

FIGURE 2. Examples of pleural disease interfaces with the chest wall or mediastinum. *A*, Example of a good interface to measure. There is a clear, well-marginated differentiation between the pleural tumor and the normal mediastinal fat (arrow). *B*, Example of a poor interface to measure. The border of the pleural tumor compared with normal tissues is not clear or distinct (circle). *C*, If choosing to measure the interface seen in *B*, measurements may erroneously underestimate tumor burden. *D*, If choosing to measure the interface seen in *B*, measurements may erroneously overestimate tumor burden.

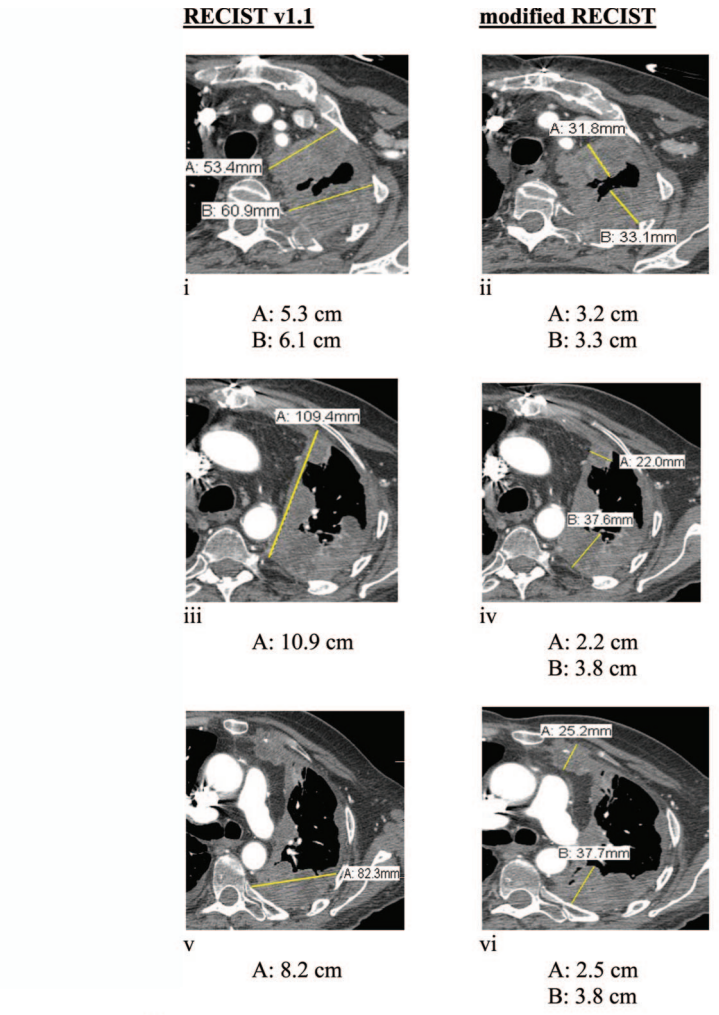

FIGURE 3. Comparison of tumor measurements using the updated RECIST criteria version 1.1 (i, iii, v) and the modified RECIST criteria (ii, iv, vi). *Although additional measurements were made of the pleural tumor in the patient example (see Figure 3i.); by RECIST version 1.1, only the 2 longest measurements of the pleural tumor are used in calculating the total RECIST v. 1.1 measurement. For the example, this patient had pleural tumor measurements of 5.3 cm, 6.1 cm, 10.9 cm, and 8.2 cm. The 2 longest measurements (10.9 cm, 8.2 cm) were chosen to be added together for the total RECIST v1.1 measurement (19.1 cm).

1. To ensure accuracy, all measurements must be performed electronically in the same window setting on consecutive studies. We recommend using the "soft tissue" setting (not lung windows), as it enables accurate pleural mass measurements with the electronic calipers and avoids the incorporation of chest wall or mediastinal fat within the calculations, which are not as easily identified when using lung windows.
2. CT scan slices up to 5 mm can be used, but for greater accuracy, thinner slices such as 2.5 mm are preferable. Ideally, all subsequent CT scans should use the same slice thickness.
3. To limit interobserver variability in measuring tumor response, it is preferred that the same clinician measure the tumors at baseline and on all subsequent CT scans.
4. The pleural disease to be measured should have a short-axis diameter of at least 1 cm, as lesions less than 1 cm are considered nonmeasurable.
5. To obtain the short axis of the disease, with electronic calipers, measure the distance between the point where the tumor abuts the chest or the mediastinal border and the point where the pleural disease touches normal lung (Figure 1*A*). The shortest route possible is the one perpendicular to the chest wall/mediastinum.
6. Avoid measuring regions where tumor infiltration obscures the interface of tumor to normal tissue. A good interface for measurement is usually one where the tumor abuts fat or an intact rib/vertebral body, as the density of the pleural tumor differs significantly from bone or fat and the difference can be easily observed. Avoid choosing an interface of tumor with muscle, as muscle and tumor have similar CT densities and are often difficult to distinguish when they abut one another (Figure 1).
7. Following the instructions in 5, choose three different axial slices, preferably above the level of the main bronchi and record two measurements per slice, thus resulting in six separate measurements (Figure 3).
8. If any additional nodal, subcutaneous or other bidimensionally measureable lesions are available, they should undergo unidimensional measurements *by RECIST* version 1.1 and be added to the total obtained from 7.

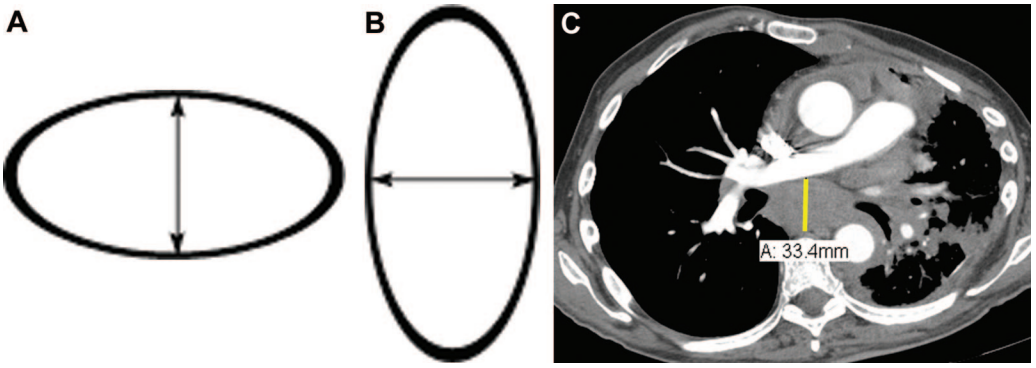

FIGURE 4. Lymph node measurements. Schematic representation of a horizontally oriented (*A*) or vertically oriented (*B*) lymph node and an enlarged subcarinal lymph node on contrast enhanced chest computed tomography (CT) at the level of the right pulmonary artery (*C*). Arrow denotes the short axis of the lymph nodes in *A* and *B*, and in the caliper measurements of the short axis of the 33.4 mm subcarinal lymph node seen in *C*. As an example, the measurements of the lymph node in *C* would be added to the pleural measurements obtained in Figure 3. RECIST method v1.1: total measurement = pleura (10.9 + 8.2 = 19.1 cm) + lymph node (3.3 cm) = 22.4 cm. Modified RECIST: total measurement = pleura (3.2 + 3.3 + 2.2 + 3.8 + 2.5 + 3.8 = 18.8 cm) + lymph node (3.3 cm) = 22.1 cm.

Tips on Lymph Node Measurements

Lymph nodes are considered as a separate organ to measure, and up to two lymph nodes can be measured per patient by RECIST version 1.1.[2] For unidimensional lymph node measurements,[10] use the short axis of the lymph node at baseline and then at every follow-up scan (Figure 4). To be considered as pathologically enlarged and measurable at baseline, the lymph node short-axis diameter should be ≥15 mm.

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REFERENCES

1. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247.
3. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol* 2004;15:257–260.
4. van Klaveren RJ, Aerts JG, de Bruin H, et al. Inadequacy of the RECIST criteria for response evaluation in patients with malignant pleural mesothelioma. *Lung Cancer* 2004;43:63–69.
5. Nowak AK. CT, RECIST, and malignant pleural mesothelioma. *Lung Cancer* 2005;49(Suppl 1):S37–S40.
6. Plathow C, Klopp M, Thieke C, et al. Therapy response in malignant pleural mesothelioma-role of MRI using RECIST, modified RECIST and volumetric approaches in comparison with CT. *Eur Radiol* 2008; 18:1635–1643.
7. Ak G, Metintas M, Metintas S, et al. Three-dimensional evaluation of chemotherapy response in malignant pleural mesothelioma. *Eur J Radiol* 74:130–135.
8. Ceresoli GL, Chiti A, Zucali PA, et al. Assessment of tumor response in malignant pleural mesothelioma. *Cancer Treat Rev* 2007;33:533–541.
9. Liu F, Zhao B, Krug LM, et al. Assessment of therapy responses and prediction of survival in malignant pleural mesothelioma through computer-aided volumetric measurement on computed tomography scans. *J Thorac Oncol* 2010;5:879–884.
10. Schwartz LH, Bogaerts J, Ford R, et al. Evaluation of lymph nodes with RECIST 1.1. *Eur J Cancer* 2009;45:261–267.

