Tumor Response Assessment using CT and MRI: Current Clinical Practice

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The development of CT and MR using contrast enhancement have allowed radiologists to assess therapeutic response more accurately and reproducibly. Based on size measurements, radiologists can provide an objective response to therapy. Commonly used end-points in oncology trials, especially Phase II, are survival disease-free and progression-free survival, time to progression, and response rate (1). Imaging biomarkers used in the form of World Health Organization (WHO) and response evaluation criteria in solid tumors (RECIST 1.0 and 1.1), are based on lesion size and may be defined as standardized measurement techniques for converting visual imaging findings into quantitative measures for estimation of treatment response (2). It is important for radiologists to learn these criteria which are used by oncologists worldwide to assess response to therapy. They also need to understand their limitations as tumor assessment criteria need to evolve with newer oncologic treatments as size criteria may not be an accurate representation of response to therapy. Other features including necrosis need to be considered. Functional methods including perfusion and diffusion-weighted MR imaging and PET imaging have additional potential value in assessing response.

WHO and RECIST

Traditionally, measurement of response to therapy is based on size criteria. The WHO criteria was the first standardized approach for classification of treatment response of solid tumors on imaging studies according to estimation of change in tumor volume before and after treatment. The tumor volume estimation was determined by the use of target lesions to assess tumor response (3). The World Health Organization (WHO) criteria are based on bidimensional measurements of the two greatest perpendicular diameters of each lesion and sum of the products of these diameters. Subsequently the RECIST guidelines (response evaluation criteria for solid tumor) were introduced using unidimensional measurements in 2000 to simplify and standardize measurements and a revision RECIST 1.1 was published in January 2009 and addressed issues with earlier versions (4). Revised RECIST (version 1.1) includes reduction of the number of assessed lesions to determine tumor burden, incorporation of assessment of pathological lymph nodes, exemption of confirmation of response in randomized studies

and, inclusion of FDG-PET as an adjunct in detecting new lesions and determination of progression (5). RECIST 1.1 has included changes to avoid overcalling progressive disease including requiring an increase of at least 5 mm in the sum and at least a 20% increase in the sum of the target lesions to be progressive disease. In addition, it also assigns 5 mm as a default value for lesions that are "too small to measure". If the lesion disappears it is assigned a value of 0. When non-nodal lesions "fragment" on follow-up imaging the longest diameters of the fragmented portions should be added together and when they truly coalesce then the largest diameter of the coalesced lesion should be measured. RECIST 1.1 has incorporated the short axis of lymph nodes with those that are at least 15 mm considered target lesions, 10-15 mm as non-target lesions and less than 10 mm as normal. RECIST 1.0 did not include evaluation of lymph nodes.

Table Assessing Response based on RECIST criteria

Complete response (CR)   Tumors completely disappear

Partial response (PR)   Tumor shrink >30%

Stable disease (SD)   Tumors stable

Progressive disease (PD)   Tumors grow >20%

LIMITATIONS OF TRADITIONAL SIZE MEASUREMENTS

Significant limitations of size based tumor response criteria such as WHO criteria and RECIST (1.0 / 1.1) have come into focus in the wake of new treatments such as molecular targeted therapies or locoregional interventional procedures. These limitations primarily refer to inability of the traditional criteria to detect treatment response evidenced by changes other than change in size.

Imatinib mesylate (tyrosine kinase inhibitor) was the first biological targeted therapy to be used in the treatment of gastrointestinal stromal tumors (GIST) (6). Gastrointestinal stromal tumors treated with imatinib, are not effectively evaluated by RECIST criteria. Choi response criteria which incorporate smaller changes in size of 10% or more, or decrease of density of 15% or more on contrast enhanced CT, correlates well with good response by PET. The Choi response criteria were more predictive of time to tumor progression (TTP) than response by RECIST (7). This is also potentially applicable for other solid tumors as well which are treated with antiangiogenic agents or tyrosine kinase inhibitor treatments. However, it is not clear whether similar FDG-PET effects would occur with other agents that differ in mechanism of action from imatinib and if the changes will correlate with clinical benefit (8).

With the advent of targeted molecular compounds, the reliance on response rate needs to be reconsidered because clinically significant survival advantages have been reported with only marginal tumor responses. Indeed, molecularly targeted compounds that produce objective response rates of less than 10% have resulted in improved survival in randomized control trials, including erlotinib in non – small cell lung cancer, temsirolimus in renal cancer, bevacizumab in metastatic colorectal cancer, and, more recently, sorafenib in liver cancer (1).

Tumors do not always decrease in size following therapy despite impressive response seen on PET scans. The presence of necrosis becomes a reliable feature of response which is not evaluated with the RECIST and other size criteria. Studies have found a poor correlation between the extent of tumor necrosis induced by new agents such as sorafenib or by interventional procedures such as chemoembolization and Yttrium microspheres and conventional methods of response assessment (1, 9, 10). Conventional criteria do not acknowledge that change in tumor viability may be the only sign of response as highlighted by locoregional treatment of hepatocellular carcinoma (HCC). Recently developed computer software, CT and MR advances in imaging technology now allows three dimensional volumetric assessment of tumor volume which together with exclusion of necrotic volume provides accurate evaluation of viable tumor volume. The hope is to have these techniques provide more reliable objective data but additional work is required to make these techniques time efficient to be used in everyday busy clinical practices.

RECIST guidelines describe tumor response for systemic treatments and provide minimal guidance for locoregional therapies, such as Yttrium 90 (Y-90) radioembolization and transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), and cannot be applied to most interventional oncology procedures (11). The RECIST guidelines cannot be used as effectively since locoregional therapies are administered at staged intervals, with different tumors being treated a variable number of times and at different time points (12). Locoregional therapies often lead to necrosis and associated hemorrhage may cause an increase in size of the lesions and be erroneously considered progressive disease using size criteria. Measurements of the density or signal intensity of the lesions on CT and MR may be of value to show lack of enhancement consistent with nonviable tumor. These challenges with RECIST have been recognized, and in their conclusions, the Barcelona–2000 European Association for the Study of the Liver (EASL) recommended that estimations of tumor response should account for necrosis, which can be estimated according to the size of the nonenhancing area on contrast-enhanced CT images (13). Papers have evaluated the role of EASL, RECIST and WHO alone or in

combination to assess therapy to hepatocellular carcinoma (11, 14). Papers have also examined whether assessing a primary index lesion is just as affective in the setting of transarterial chemoembolization for hepatocellular carcinoma(15).

In addition, although conventional criteria require the tumor to decrease in size, this does not always happen, especially early after therapy. Large lesions with lack of enhancement can be completely nonviable or dead at pathological examination consistent with a complete response (11). A thin rim of enhancement following Y-90 therapy may be seen which may be the result of inflammatory reaction and correlated well with histologic necrosis. A nodule of enhancement has different implications and may represent viable tumor with the use of RF ablation (15) and transarterial chemoembolization, but not represent tumor in the case of Y-90. Subtraction imaging techniques in which unenhanced images are electronically subtracted from contrast-enhanced images can be particularly useful.

RECIST has been found to be suboptimal in the evaluation of treatment response of malignant pleural mesothelioma (17), prostate cancer (18), pancreatic adenocarcinoma (19), and gastrointestinal stromal tumor (GIST) (20), to name a few. Evolution of new kind of anti-cancer therapy such as cytostatic agents which halt tumor progression rather than eliminating neoplastic cells, mean that conventional criteria are becoming less equipped to detect tumor response, as these new drugs don't always cause changes in size. Hence functional imaging markers based on tumor life-cycle have evolved in response (21).

[18]Fluorodeoxyglucose ([18]FDG) is the most widely employed functional imaging marker, however numerous other PET based markers have shown potential to evaluate other aspects of tumor physiology (22). PET Response Criteria in Solid Tumors (PERCIST) Version 1.0 guideline is an attempt to standardize and expand PET criteria for the evaluation of treatment response in solid tumors. Several aspects of PERCIST 1.0 are currently controversial and need further validation (23). The concept of therapeutic and diagnostic (theranostic) agents for targeted imaging and treatment is also evolving (24).

When evaluating lymph nodes, there are potential limitations especially in smaller nodes where there is higher likelihood of measurement error resulting in apparent significant changes. Lymph nodes do not typically disappear even when there is a complete response. In addition, the size of a lymph node is not always accurate in assessing malignancy with metastases being seen in normal sized nodes and absence of malignancy in enlarged nodes. RECIST 1.1 has recognized the use of short axis measurements of lymph nodes to assess response and that disappearance of lymph nodes is not

required but disappearance of all target lesions and reduction of pathologic lymph nodes to <10 mm in short axis diameter (16, 25).

Other advanced imaging techniques include MRI based techniques such as dynamic contrast enhanced (DCE) imaging and its use in detecting tumor response to anti-angiogenic therapy (26).

Diffusion weighted imaging (DWI) can detect changes in tissue architecture and cellularity within tumors in response to treatment which may precede macroscopic changes in gross tumor size (27). Tumor may be seen as restricted diffusion and post-treatment necrosis as less restricted diffusion. Also, apparent diffusion coefficients may be higher in areas of necrosis than in areas of viable tumor (28-32). However, DWI is limited in organs subjected to respiratory motion or in areas of magnetic susceptibility, such as the air in the lungs (33).

Assessment of choline levels with hydrogen 1 MR spectroscopy is another method that can be used to assess tumor viability after an interventional oncology treatment. Choline is an essential component of cell membrane biosynthesis. In several tumors, elevated choline levels are associated with increased cell proliferation. Necrotic regions of treated tumors are believed to contain low amounts of choline, compared with regions of viable tumor (34). Dynamic contrast enhanced ultrasound as a functional imaging technique has been evaluated by limited number of studies (35).

CONCLUSION

The level of evidence required to formally and fully validate a new imaging marker as an appropriate end-point for the phase II trials is substantial. As the majority of the above mentioned novel imaging biomarkers currently lack standardization, RECIST Working Group at its last convention decided not to move from anatomic unidimensional assessment of tumor burden to either volumetric anatomical assessment or to functional assessment, although specific modifications such as inclusion of [18]FDG-PET as an adjunct in detecting new lesions and determination of progression of solid tumors have been made in RECIST version 1.1. Newer techniques including necrosis, diffusion and perfusion imaging will play a greater role in assessing response to therapy in the future.

References

1. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698-711.
2. Jaffe CC. Measures of response: RECIST, WHO, and new alternatives. J Clin Oncol. 2006;24(20):3245-51.
3. Suzuki C, Jacobsson H, Hatschek T, et al. Radiologic measurements of tumor response to treatment: practical approaches and limitations. Radiographics. 2008;28(2):329-44.
4. 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(3):205-16.
5. 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(2):228-47.
6. Linton KM, Taylor MB, Radford JA. Response evaluation in gastrointestinal stromal tumours treated with imatinib: misdiagnosis of disease progression on CT due to cystic change in liver metastases. Br J Radiol. 2006;79(944):e40-4.
7. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol. 2007;25(13):1753-9.
8. Sargent DJ, Rubinstein L, Schwartz L, et al. Validation of novel imaging methodologies for use as cancer clinical trial end-points. Eur J Cancer. 2009;45(2):290-9.
9. Mannelli L, Kim S, Hajdu CH, Babb JS, Clark TW, Taouli B. Assessment of tumor necrosis of hepatocellular carcinoma after chemoembolization: diffusion-weighted and contrast-enhanced MRI with histopathologic correlation of the explanted liver. AJR Am J Roentgenol. 2009;193(4):1044-52.
10. Miller FH, Keppke AL, Reddy D, et al. Response of liver metastases after treatment with yttrium-90 microspheres: role of size, necrosis, and PET. AJR Am J Roentgenol. 2007;188(3):776-83.
11. Riaz A, Memon K, Miller FH, et al. Role of EASL, RECIST and WHO Response Guidelines Alone or in Combination for Heptocellular Carcinoma: Radiologic-Pathologic Correlation. J Hepatol. 2010; In Press.
12. Lewandowski RJ, Mulcahy MF, Kulik LM, et al. Chemoembolization for hepatocellular carcinoma: comprehensive imaging and survival analysis in a 172-patient cohort. Radiology. 2010;255(3):955-65.
13. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35(3):421-30.
14. Duke E, Deng J, Ibrahim SM, et al. Agreement between competing imaging measures of response of hepatocellular carcinoma to yttrium-90 radioembolization. J Vasc Interv Radiol. 2010;21(4):515-21.
15. Riaz A, Miller FH, Kulik LM, et al. Imaging response in the primary index lesion and clinical outcomes following transarterial locoregional therapy for hepatocellular carcinoma. JAMA. 2010;303(11):1062-9.
16. Kim YS, Rhim H, Lim HK, et al. Completeness of treatment in hepatocellular carcinomas treated with image-guided tumor therapies: Evaluation of positive predictive value of contrast-enhanced CT with histopathologic correlation in the explanted liver specimen. J Comput Assist Tomogr. 2006;30(4):578-82.

17.   Ceresoli GL, Chiti A, Zucali PA, et al. Assessment of tumor response in malignant pleural mesothelioma. Cancer Treat Rev. 2007;33(6):533-41.

18.   Scher HI, Morris MJ, Kelly WK, Schwartz LH, Heller G. Prostate cancer clinical trial end points: "RECIST"ing a step backwards. Clin Cancer Res. 2005;11(14):5223-32.

19.   Rezai P, Mulcahy MF, Tochetto SM, Berggruen S, Yaghmai V. Morphological analysis of pancreatic adenocarcinoma on multidetector row computed tomography: implications for treatment response evaluation. Pancreas. 2009;38(7):799-803.

20.   Choi H, Charnsangavej C, de Castro Faria S, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol. 2004;183(6):1619-28.

21.   Curran SD, Muellner AU, Schwartz LH. Imaging response assessment in oncology. Cancer Imaging. 2006;6:S126-30.

22.   Mankoff DA, Shields AF, Krohn KA. PET imaging of cellular proliferation. Radiol Clin North Am. 2005;43(1):153-67.

23.   Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50 Suppl 1:122S-50S.

24.   Kwekkeboom DJ, Bakker WH, Kam BL, et al. Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0),Tyr3]octreotate. Eur J Nucl Med Mol Imaging. 2003;30(3):417-22.

25.   Schwartz LH, Bogaerts J, Ford R, et al. Evaluation of lymph nodes with RECIST 1.1. Eur J Cancer. 2009;45(2):261-7.

26.   Hayes C, Padhani AR, Leach MO. Assessing changes in tumour vascular function using dynamic contrast-enhanced magnetic resonance imaging. NMR Biomed. 2002;15(2):154-63.

27.   Moffat BA, Chenevert TL, Meyer CR, et al. The functional diffusion map: an imaging biomarker for the early prediction of cancer treatment outcome. Neoplasia. 2006;8(4):259-67.

28.   Kamel IR, Bluemke DA, Eng J, et al. The role of functional MR imaging in the assessment of tumor response after chemoembolization in patients with hepatocellular carcinoma. J Vasc Interv Radiol. 2006;17(3):505-12.

29.   Kamel IR, Bluemke DA, Ramsey D, et al. Role of diffusion-weighted imaging in estimating tumor necrosis after chemoembolization of hepatocellular carcinoma. AJR Am J Roentgenol. 2003;181(3):708-10.

30.   Deng J, Miller FH, Rhee TK, et al. Diffusion-weighted MR imaging for determination of hepatocellular carcinoma response to yttrium-90 radioembolization. J Vasc Interv Radiol. 2006;17(7):1195-200.

31.   Rhee TK, Naik NK, Deng J, et al. Tumor response after yttrium-90 radioembolization for hepatocellular carcinoma: comparison of diffusion-weighted functional MR imaging with anatomic MR imaging. J Vasc Interv Radiol. 2008;19(8):1180-6.

32.   Liapi E, Geschwind JF, Vossen JA, et al. Functional MRI evaluation of tumor response in patients with neuroendocrine hepatic metastasis treated with transcatheter arterial chemoembolization. AJR Am J Roentgenol. 2008;190(1):67-73.

33.   Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol. 2007;188(6):1622-35.

34.   Chen CY, Li CW, Kuo YT, et al. Early response of hepatocellular carcinoma to transcatheter arterial chemoembolization: choline levels and MR diffusion constants--initial experience. Radiology. 2006;239(2):448-56.

35.   Choi D, Lim HK, Kim SH, et al. Hepatocellular carcinoma treated with percutaneous radio-frequency ablation: usefulness of power Doppler US with a microbubble contrast agent in evaluating therapeutic response-preliminary results. Radiology. 2000;217(2):558-63.