Proceedings MICCAI 2006 Workshop "Medical Image Processing: Challenges in Clinical Oncology" (Veenland J, Niessen W eds) 47-52.

Bidimensional Measurements Appear Superior to Unidimensional Measurements When Measuring Response of Metastatic Brain Tumors

Michaux Kilpatrick, Nancy U. Lin, J. Keith Smith, Eric P. Winer, Elizabeth Bullitt, Lisa A. Carey, Matthew G. Ewend

Abstract. Patients with brain tumors routinely undergo serial MRI scans to assess the size of their tumors. The gold standard for measuring these lesions is a 3-dimensional volume measurement. However, the manual image segmentation systems needed to perform 3-dimensional measurements can be time-consuming and many institutions lack automated volumetric data acquisition programs. Hence, bi-dimensional (WHO) and uni-dimensional (RECIST) criteria were developed to approximate tumor volume and both have been used to assess tumor response to therapy. While these criteria have been applied to a wide variety of solid organ tumors, there is limited data which evaluates their validity for CNS tumors. We compared measurements using the WHO and RECIST criteria to volume measurements in patients with metastatic breast cancer lesions in the brain undergoing lapatiniv therapy.

Citation: Proceedings MICCAI Workshop *"Medical Image Processing: Challenges in Clinical Oncology"* (Veenland J, Niessen W eds) 47-52.

Keywords: brain tumors, MRI, WHO, RECIST, bidimensional, volumetric measurements

Introduction

The World Health Organization (WHO) reports that just over one million cases of breast cancer are diagnosed each year. Approximately 20 to 30% of these patients will develop brain metastasis. The advent of noninvasive imaging modalities has improved the detection of these tumors. The first MRI scanner was made commercially available by the Fonar Corporation (Melville, NY) in 1980 and since that time it has become routine for patients with brain tumors to be followed with serial contrast-enhanced MRI imaging.

One important aspect of cancer research is measuring the clinical response of tumors to various treatment modalities. Many clinical trials exist for investigating new chemotherapeutic agents and their ability to decrease tumor size. In an effort to standardize these trials, it has become necessary to develop criteria for measuring tumor response. In the 1970s the World Health Organization developed uniform guidelines which used the sum of the products of the longest perpendicular, bi-dimensional measurement for evaluation of tumor response. With the advent of MRI, which

introduced the possibility of 3-dimensional measurements, a new guideline was needed to help alleviate discrepancies in measurements which might occur between research groups attempting to modify the WHO criteria to fit this new technology. Thus in 1994 the WHO criteria were revised and simplified such that the uni-dimensional sum of all diameters would be used to measure tumor response. This criteria, termed RECIST (Response Evaluation Criteria in Solid Tumors), has become a common tool for measuring tumor response to therapy. While both RECIST and WHO criteria have been applied to a wide variety of solid organ tumors [5, 6, 7], there is limited data evaluating the validity of these tools for brain tumors [8]. Due to the increasing lifespan of many cancer patients, the prevalence of metastatic lesions in the brain has increased in recent years and now accounts for up to 50% of all brain tumors. Therefore, it becomes increasingly important to determine the optimal tool to evaluate response of brain tumors to therapy. The purpose of this study was to evaluate the validity of using the approximation of tumor volume in the brain with the WHO and RECIST criteria. In order to achieve this purpose, we compared measurements of tumor size using the WHO and RECIST criteria to 3-dimensional volume measurements in patients with metastatic breast cancer in the brain being treated with lapatiniv.

Methods

Thirty-seven patients from three different institutions were enrolled in a prospective phase II study evaluating the therapeutic effect of lapatiniv on breast cancer metastases to the brain. Their contrast-enhanced brain MRI scans were retrospectively analyzed at baseline and two month intervals over a period of nine months. Approval of the institutional review boards and patient informed consent has been obtained from each institution involved in the study. Acquisition of the images varied amongst participating institutions, but all scans were performed using a 1.5- or 3-Tesla MRI magnet with no more than 4 mm collimation thickness. 282 lesions were analyzed for tumor size using uni-dimensional (single greatest diameter), bi-dimensional (product of 2 longest diameters in perpendicular dimensions), and 3-dimensional (calculated with an institutionally derived software segmentation program) measurements. In keeping with RECIST and WHO criteria, tumor lesions were considered measurable if they were $\geq$10 mm in diameter. Up to eleven tumor lesions were measured in each patient. When multiple lesions were identified in a patient, the longest uni-dimensional measurement of each lesion was summed as according to RECIST. Likewise, the summation of the longest bi-dimensional product was used in compliance with WHO criteria and the summation of each lesion's volume was also calculated. Thus a total tumor summation was obtained for RECIST, WHO, and volume in each patient at each two month time interval. The percent change of the total tumor summation could then be calculated at the time of each MRI.

The RECIST guidelines [1] and WHO criteria as originally published in the 1979 WHO handbook [2] are established measures of tumor response. There are however, no standardized criteria for using volume measurements to assess tumor response. Prasad et al. [3] defined a set of volume criteria when measuring metastatic liver lesions and Tran et

al. [4] used these same criteria when evaluating lung tumors. Their method extrapolates the uni-dimensional response criteria to volume and assumes a lesion to closely approximate a sphere. We thus elected to use these published volume criteria when assessing tumor response to treatment. Tumor response was categorized as complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD). By all criteria, CR requires disappearance of all lesions. PR requires at least a 30% decrease according to RECIST, at least a 50% decrease by WHO, and at least a 65% decrease by volume. PD according to RECIST necessitates a 20% increase, a 25% increase by WHO, and a 44% increase by volume. SD implies the criteria were not met for PR or PD.

Table 1. Criteria for measuring tumor response.

Response Category	RECIST	WHO	Volume
Complete response (CR)	Target lesion disappearance	Target lesion disappearance	Target lesion disappearance
Partial response (PR)	At least 30% decrease	At least 50% decrease	At least 65% decrease
Progressive disease (PD)	At least 20% increase	At least 25% increase	At least 44% increase
Stable disease (SD)	Criteria not met for PR or PD	Criteria not met for PR or PD	Criteria not met for PR or PD

Results

Of the 37 patients, 10 had to be excluded. 6 of the 10 were excluded because they were removed from the prospective trial within the first two months, before they had a follow-up MRI scan. Two patients were excluded because the diffuse nature of their metastatic disease did not allow for quantification. A single patient did not have a baseline post-contrasted scan to allow for subsequent comparisons. Another patient was excluded because they did not meet the WHO and RECIST guidelines that require the measurable lesion be at least 10 mm in diameter.

Tumor response was classified according to WHO, RECIST, and volume criteria (table 1). The percent change in the total tumor summation at each 2 month interval was calculated. At the time of the final MRI, we determined how RECIST and WHO

approximated volume with respect to tumor response. We considered a patient had a clinical benefit, if they did not demonstrate disease progression. RECIST was concordant with volume in 73% (sensitivity, 81.8%; specificity 73.3%), 19 out of 27, patients (table 2) and WHO was concordant with volume in 85% (sensitivity 75%; specificity 92.9%), 22 out of 27, patients (table 3). At the time of the first follow-up MRI scan, RECIST and

Table 2. Final Response Correlation: RECIST versus volume.

	% Change		
Patient	RECIST	Volume	Response
1	-4.2	-19.7	Concordant
2	-61.4	-93.2	Concordant
3	20.0	91.6	Concordant
4	20.8	-6.5	Overestimated
5	96.4	187.1	Concordant
6	15.3	72.6	Underestimated
7	22.4	90.3	Concordant
8	254.2	724.8	Concordant
9	25.8	86.5	Concordant
10	60	102.1	Concordant
11	9.5	65.7	Underestimated
12	-0.1	5.4	Concordant
13	34.8	195.5	Concordant
14	18.5	112.6	Underestimated
15	46.0	214.8	Concordant
16	16	107.1	Underestimated
17	56.5	15.7	Overestimated
18	2.3	-24.2	Concordant
19	-9.4	-29.3	Concordant
20	65.6	134.9	Concordant
21	3.3	22.0	Concordant
22	31.8	28.0	Overestimated
23	33.3	89.5	Concordant
24	6.9	20.0	Concordant
25	-23.8	-22.9	Concordant
26	-29.4	-24.3	Concordant
27	-4.2	-8.8	Concordant

Table 3. Final Response Correlation: WHO versus volume.

Patient	% Change WHO	Volume	Response
1	-9.9	-19.7	Concordant
2	-90.6	-93.2	Concordant
3	66.6	91.6	Concordant
4	-21.4	-6.5	Concordant
5	116.9	187.1	Concordant
6	34.3	72.6	Concordant
7	51.6	90.3	Concordant
8	384.8	724.8	Concordant
9	72.7	86.5	Concordant
10	88.4	102.1	Concordant
11	43.1	65.7	Concordant
12	1.4	5.4	Concordant
13	111.3	195.5	Concordant
14	56.9	112.6	Concordant
15	61.6	214.8	Concordant
16	23.8	107.1	Underestimated
17	41.9	15.7	Overestimated
18	-8.1	-24.2	Concordant
19	-14.8	-29.3	Concordant
20	90.6	134.9	Concordant
21	26.4	22.0	Overestimated
22	41.4	28.0	Overestimated
23	124.6	89.5	Concordant
24	4.5	20.0	Concordant
25	-40.4	-22.9	Concordant
26	-24.4	-24.3	Concordant
27	-5.8	-8.8	Concordant

WHO approximated volume in 77% of the patients (table 4). In two patients, WHO was delayed in approximating volume by one scan cycle. In one of those patients, WHO identified progressive disease at the time of the first follow-up scan, whereas volume

identified a clinical benefit. By the final scan WHO was concordant with volume in demonstrating a clinical benefit. RECIST was delayed by a scan cycle in approximating volume in a single patient as well, indicating a clinical benefit at the time of the first follow-up scan, that by the final scan RECIST identified to have progressive disease. In this instance, volume identified progressive disease at both the first and subsequent follow-up scans.

Table 4. Correlation of disease progression at first and final measurement. 2x2 table, where CB is clinical benefit and PD is progressive disease.

		RECIST		WHO	
		CB	PD	CB	PD
Volume t1	CB	16	2	14	4
	PD	4	4	2	6
Volume tfinal	CB	9	3	9	3
	PD	4	10	1	13

Discussion

The guidelines describing which tumors are eligible for measurement by RECIST and WHO criteria are well documented in the literature and the majority of brain tumors in our study fell under the category of measurable disease. Thus we confirm that metastatic breast tumors to the brain meet the eligibility requirements that allow application of RECIST and WHO criteria. Our data shows that in patients with metastatic breast cancer, early in the treatment phase when there might not be large changes in tumor size, neither bi-dimensional WHO nor uni-dimensional RECIST is highly concordant with volume in predicting response. However in our study, by the final MRI scan, measurements based on WHO criteria appear superior to RECIST measurements in approximating volume-predicted response.

The advent of contrast-enhanced MRI has increased the detection of brain tumors and allowed for earlier treatment. It has thus become increasingly imperative to standardize the means of assessing CNS tumor response to various new therapies. While RECIST continues to be the mainstay for measuring response in solid organ tumors, its ability to accurately measure response in CNS tumors is less clear. Moreover, when the uni-dimensional response criteria are extrapolated to volume, the percent change needed to indicate a response is substantial. The 66% increase in volume for example, needed to show a response is a substantial change. Especially, in a small rigid structure like the brain, where small increases in tumor size can have dramatic clinical effects.

Segmentation programs exist for calculating tumor volume from MRI, but these are often local software programs that are institution-specific. Our data confirms the need for development of universal automated segmentation programs. In addition rather than extrapolating from the uni-dimensional criteria, further studies with a larger number of patients are needed to assess what is a reasonable volume response criteria.

References

1. Therasse, P., Arbuck, SG, Eisenhauer, EA. Wanders, J., Kaplan, RS, Rubinstein, Verweij, J., Van Glabbeke, M., Van Oosterom, AT, Christian, MC, Gwyther, SG, J of the National Cancer Institute. Vol 92(3): 205-216, 2000.

2. Who Handbook of Reporting Results of Cancer Treatment. Geneva (Switzerland): World Health Organizations Offset Publication No. 48, 1979.

3. Prasad, SR., Jhaveri, KS, Saini, S., Hahn, PF, Halpern, EF, Sumner, JE. CT Tumor Measurement for Therapeutic Response Assessment: Comparison of unidimensional, bidimensional, and volumetric techniques- initial observations. Radiology. Vol 225: 416-419, 2002.

4. Tran, LN, Brown, MS, Goldin, JG, Yan, X., Pais, RC, McNitt-Gray, MF, Gjertson, D., Rogers, SR, Aberle, DR. Comparison of Treatment Response Classifications between Unidimensional, Bidimensional, and Volumetric Measurements of Metastatic Lung Lesions on Chest Computed Tomography. Acad Radiol. Vol 11: 1355-1360, 2004.

5. Park, OP, Lee, S, Song, SY, Kim, K., Kim, WS, Jung, CW, Park, YS, Im, YH, Kang, WK, Lee, MH, Lee, KS, Park, K. Measuring Response in Solid Tumors: Comparison of RECIST and

WHO Response Criteria. Jpn J Clin Oncol. Vol 33(10): 533-537, 2003.

6. Therasse, P. Measuring the clinical response. What does it mean? European J of Cancer. Vol 38: 1817-1823, 2002.

7. Partridge, SC, Gibbs, JE, Lu, Y, Esserman, LJ, Tripathy, D, Wolverton, DS, Rugo, HS, Hwang, ES, Ewing, CA, Hylton, NM. MRI Measurements of Breast Tumor Volume Predict Response to Neoadjuvant Chemotherapy and Recurrence-Free Survival. Am J Roentgenol. Vol 184(6): 1774-1781, 2005.

8. Shah, GD, Kesari, S, Xu, R, Batchelor, TT, O'Neill, AM, Hochberg, FH, Levy, B, Bradshaw, J, Wen, PY. Comparison of linear and volumetric criteria in assessing tumor response in adult high-grade gliomas. Neuro-Oncology. Vol 8: 38-46, 2006.