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Original Article

Outstanding Problems with Response Evaluation Criteria in Solid Tumors (RECIST) in Breast Cancer

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Background: In 1999 European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States and National Cancer Institute of Canada published Response Evaluation Criteria in Solid Tumors (RECIST) as a revision of the WHO criteria to achieve a unified, objective set of criteria for assessing antitumor activity. The present paper discusses breast cancer assessment using RECIST and discusses various outstanding problems in breast cancer therapy.

Methods: The subjects were 50 advanced/recurrent breast cancer patients who were eligible/completed cases and were registered in various clinical trials at Gunma Cancer Center from 1995-2000. The subjects were investigated with regard to the application of RECIST to evaluate the appropriateness and efficacy of the criteria for these patients, in comparison with General Rules for Clinical and Pathological Recording of Breast Cancer formulated by the Japanese Breast Cancer Society (JBCS). In addition, a study was conducted of the survival rate as a function of the initial site of metastasis in 258 recurrent cases.

Results: Of the 50 cases judged to be eligible by the JBCS General Rules, 16 cases (32%) were judged to be ineligible by RECIST. The results using the two sets of criteria were the same for CR and PD, while there were some differences in PR and SD/NC.

Conclusion: To fully adopt RECIST for breast cancer, the following should be discussed further: (1) the exclusion of bone lesions (2) assessment of long NC (3) difference in survival by metastatic lesion site (4) eligible cases are reduced due to the exclusion of target lesions having a diameter of less than 2.0 cm.

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Key words: RECIST, Breast cancer

In 1979 the World Health Organization (WHO) issued criteria for the objective assessment of the antitumor activity of antineoplastic agents. Based on those criteria, in 1981 Miller *et al.*[1] published "Reporting Results of Cancer Treatment", which was widely adopted. The WHO criteria have been adopted throughout the world. For this purpose, whereas it is desirable to carry out assessments of antitumor drug efficacy by an objective and universal approach, these criteria have been variously modified by investigators in various countries and facilities in response to current scientific advances in attempts to make them more appropriate for the local setting. As a result, there are cases in which different assessments are performed, making it necessary to rethink the original criteria with the goal of achieving greater objectivity and universality. For this purpose, in 1999 a committee comprised of representatives from the European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States and National Cancer Institute of Canada published Response Evaluation Criteria in Solid Tumors (RECIST)[2] as a revision of the WHO criteria with the objective of achieving a unified, objective set of criteria for assessing antitumor activity.

In Japan, assessment of the efficacy of anticancer drugs in the treatment of breast cancer has been carried out in accordance with the General Rules for Clinical and Pathological Recording of

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Abbreviations:
RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization, JBCS, Japanese Breast Cancer Society; CR, Complete response; PR, Partial response; NC, No change, PD, Progressive disease

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Table 1. The JBCS General Rules vs RECIST – Definition of Efficacy Criteria –

The JBCS General Rules	RECIST
Measurable Lesion	Target Lesion (longest dimensions ≧ 2.0 cm)
Change in sum of products of each lesion.	Change in sum of the longest diameters of each lesion.
(No definition of the maximum no. of selected lesions. Assess by organ and evaluate globally.)	(Up to 5 lesions per organ, and up to 10 in case of multiple sites.)
CR: Disappearance of all lesions at 4 weeks.	CR: Disappearance of all target lesions at 4 weeks.
PR: Decrease by at least 50% at 4 weeks.	PR: Decrease by at least 30% at 4 weeks.
NC: Neither PR nor PD criterion met.	SD: Neither PR nor PD criterion met (6 weeks).
(Long NC: at 24 weeks) *	PD: 25% increase or appearance of new lesion(s).
PD: 25% increase or appearance of new lesion(s).	
Unmeasurable Lesion	Nontarget Lesion
CR: Disappearance of all lesions at week 4.	CR: Disappearance of all lesions and normalization of tumor markers at 4 weeks.
PR: Obvious improvement at 4 weeks.	non-CR/non-PR: Persistence of one or more non-target lesion(s) and/or persistence of tumor marker level above the normal limits.
NC: Neither PR nor PD criterion met.	PD: Clear progression or appearance of new lesion(s)
(Long NC: at 24 weeks) *	
PD: Clear progression or appearance of new lesion(s).	

* To be recorded separately, but not included in assessment of response rate.

Table 2. RECIST-Definition of Overall Best Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	None	CR
CR	Non-CR/non-PD	None	PR
PR	Other than PD	None	PR
SD	Other than PD	None	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Breast Cancer formulated by the JBCS[3]. Evaluation of the suitability of those rules is being performed on the basis of criteria for assessing the efficacy in relation to measurable lesions (with no provision regarding the size), and unmeasurable lesions/evaluable lesions. On the other hand, the key points of RECIST are that measurable lesions (longest dimension: ≧ 2.0 cm; helical CT: ≧ 1.0 cm) are considered to be the target lesions, while the concept of evaluability is not taken into account. Accordingly, although bone lesions are important metastatic lesions of breast cancer and respond to hormonal therapy, etc., they are outside of the scope of RECIST because they cannot be measured. In addition, the JBCS General Rules[3] and RECIST are basically concordant regarding the CR, PR, NC/SD and PD efficacy categories, but there are differences in relation to the evaluation of PR, PD, the overall efficacy, etc. Regarding PR, the JBCS General Rules assess the tumor reduction rate on the basis of the change in the sum of the product of the bidimensional measurements, and define this value as 50% or more. In RECIST, PR is defined as a 30% decrease in the sum of the unidimensional measurements (i.e., the longest dimension) of target lesions. Moreover, the JBCS General Rules define PD as an increase in size of at least 25%, while RECIST stipulates an increase of at least 20%. For the assessment of the overall efficacy, the JBCS General Rules provide for an overall evaluation which is based on the efficacy evaluations for each organ. RECIST, on the other hand, treats them uniformly and aims at achieving an overall evaluation on the basis of the target lesions, nontarget lesions and the presence or absence of new lesions (Tables 1, 2). Also, the JBCS General Rules

include the concept of long NC (i.e., at least 24 weeks), whereas RECIST does not. There are thus various points of difference between the JBCS General Rules and RECIST, which can represent problems when comparing the results of their respective applications. Therefore, the present paper reflects on the breast cancer assessment criteria proposed by RECIST and discusses various outstanding problems in the field of breast cancer therapy.

Subjects and Methods

The subjects were 50 patients with advanced recurrent breast cancer who were judged to be eligible cases who had completed therapy and were registered in phase Ⅱ and Ⅲ trials of chemo- or hormonal therapeutic agents in Japan at Gunma Cancer Center during the last 5 years (April 1995～March 2000). The problems listed below were investigated in relation to the application of the RECIST to evaluate the eligibility and efficacy of these patients, compared with the JBCS General Rules[3]. Previous evaluations by the JBCS General Rules, which were assessed by each committee in the clinical trials, were reconfirmed at Gunma Cancer Center, while efficacy re-assessments by RECIST were performed in accordance with the guidelines[4] at Gunma Cancer Center, and extramurally re-assessed at the Breast Cancer Center, Showa University, Toyosu Hospital.

In addition, for the purpose of discussing the difference in prognosis according to metastatic organ, a study was conducted of the survival rate as a function of the initial site of metastasis (i.e., skin/local, lung, liver, bone, cervical lymph nodes, other) in 258 recurrent breast cancer cases seen among a total of 1546 cases of recurrence in patients who underwent radical surgery (Stages Ⅰ～Ⅲ) during the last 27 years (April of 1972～March of 1999). Each efficacy assessment was compared by U-test. The data for the survival rates as a function of the initial site of metastasis were analyzed by Kaplan-Meier's method, while the statistical significance of differences was analyzed by the log-rank method.

Investigated Problems

1. Eligible cases
2. Validity of the RECIST method for efficacy assessment on the basis of unidimensional measurement
3. Handling of long NC (at least 6 months) cases
4. Problems arising from treating that prognosis as the same regardless of the metastatic organs
5. Handling of bone lesions

Table 3. Details of Ineligible Cases by RECIST

Ineligible cases: 16 (32%)	
Unmeasurable cases (Longest diameter < 2.0 cm)	8 (50%)
Pulmonary nodular metastasis	6
Soft tissue (skin, lymph nodes) metastasis	2
Practically unmeasurable cases	8 (50%)
Bone metastasis	4
Pleurisy, bronchopulmonary lymphangitis	3
Others	1

Results

Study of Eligible Cases

Of the 50 cases judged to be eligible by the JBCS General Rules, 16 cases (32%) were judged to be ineligible by RECIST. Those ineligible cases consisted of eight cases (pulmonary nodular metastases, soft tissue metastases, etc.) which were handled as having unmeasurable lesions (smaller than 2.0 cm in diameter), and eight cases of bone metastasis, carcinomatous pleurisy, etc., which were handled as unmeasurable lesions (Table 3). When these 16 cases, judged to be ineligible by the RECIST, were evaluated for their response according to the JBCS, the response rate (CR + PR) was 50% (8/16), and the rate of long NC was 31% (5/16). Cases with bone metastases alone accounted for 80% of those long NC cases (Table 4).

Validity of the RECIST Method for Efficacy Assessment on the Basis of Unidimensional Measurement

For the purpose of comparison, the JBCS General Rules were applied to the 34 cases judged to be eligible on the basis of the RECIST (Table 5). The response rate (CR + PR) according to the JBCS General Rules was 52.9% (18/34), whereas the response rate according to the RECIST was 47.0% (16/34). Breakdown of those results on the basis of the efficacy evaluation categories revealed that the results with the two sets of criteria were the same for CR and PD, while there were some differences in relation to PR and SD/NC. However, overall responses were not significantly different (p=0.744).

Table 4. Response Rate by the JBCS General Rules of the Ineligible Cases by RECIST

	No. Cases	CR	PR	NC	Long NC	PD	Response Rate (CR + PR) %
Unmeasurable lesion (< 2.0 cm)	8	2	3	1	1	1	62.5% (5/8)
Practically unmeasurable lesion	8	0	3	0	4	1	37.5% (3/8)
Total	16	2	6	1	5	2	50.0% (8/16)

Table 5. The JBCS General Rules vs RECIST – Evaluation on Eligible Cases by RECIST–

	No. of Cases	CR	PR	SD		PD	Response Rate (CR + PR)
				NC	Long NC		
JBCS	34	2	16	8	1	7	52.9% (18/34)
RECIST	34	2	14	11		7	47.0% (16/34)

p=0.744

Significance of Long NC (At Least 6 Months) Cases

According to the JBCS General Rules, cases of NC which have continued for at least 6 months are handled as long NC. When the JBCS General Rules were applied to the 50 cases of advanced recurrent breast cancer included in the present study, the results of assessment of the clinical response showed 52% (26/50) CR + PR, 12% (6/50) long NC, 18% (9/50) NC and 18% (9/50) PD. Fig 1 presents a comparison of the duration of survival as a function of the clinical response, and it is seen that there was no statistically significant difference between the CR + PR group and the long NC group (p=0.403).

Problems Arising from Treating the Prognosis as the Same Regardless of the Metastatic Organs

At Gunma Cancer Center, a study was conducted of the 258 recurrent breast cancer cases to determine the survival rates as a function of the various sites of the initial recurrence. The initial sites of recurrence consisted of 85 cases (32.9%) of skin or local recurrence, 56 cases (21.7%) of lung, 16 cases (6.2%) of liver, 55 cases (21.3%) of bone, 29 cases (11.2%) of cervical lymph nodes, and 17 cases (6.6%) of recurrence at other sites. Analysis of the survival duration as a function of the various sites of the initial recurrence revealed that the survival was significantly better in cases with skin/local and bone recurrences, compared with recurrences in the lung and liver (lung vs. skin/local: p=0.0001; lung vs. bone: p=0.001; and lung vs. liver: p=0.3102) (Fig 2).

Handling of Bone Lesions

Metastasis to the bone is seen at a high incidence in breast cancer patients. The historical incidence of bone metastases in breast cancer patients at Gunma Cancer Center is 21.3%, as described above. This incidence is equivalent to the incidence of pulmonary metastases (21.7%) and follows only that of skin/local metastases (32.9%). In addition, bone metastases respond well to hormonal therapy, and even in the present study 67% (4/6) of the long NC cases had bone metastases (Fig 1).

Discussion

The RECIST[2] were proposed in response to some confusion in the field of breast cancer therapy. With the passage of time and technical progress in the field, various investigators have made their own modifications to the WHO criteria of 1979. These modifications created problems in the quest to achieve objective and universal assessment of the antitumor activity of therapeutic modalities, making it necessary to rethink the original criteria with the goal of achieving greater objectivity and universality of the assessments. This background

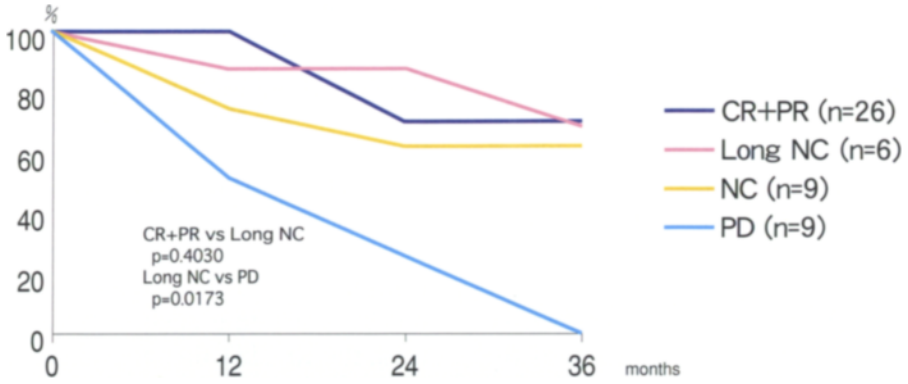

Fig 1. Overall survival advanced/recurrent breast cancer –significance of long NC–

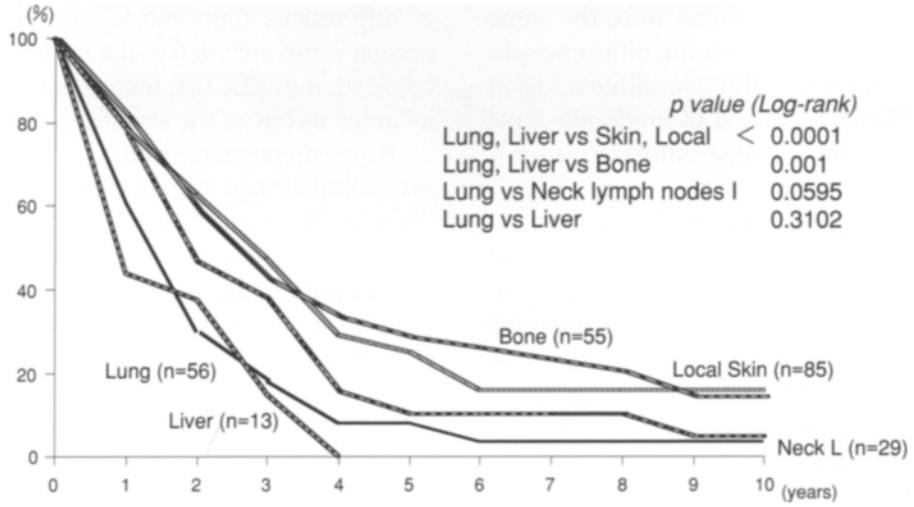

Fig 2. Survival of the various sites of the initial recurrence (Kaplan-Meier Method)

gave birth to the RECIST.

In Japan, as well, effort has been made to promote mutual, accurate assessment of research results generated by various institutions and investigators around the world. However, a serious problem has been how to handle the special properties of different cancers.

The key points of the RECIST are that measurable lesions (long dimension: ≧ 2.0 cm; helical CT: ≧ 1.0 cm) are considered to be the target lesions, while the concept of evaluability is not taken into account. Moreover, measurable lesions are defined as having a long diameter of ≧ 2.0 cm (helical CT: ≧ 1.0 cm). In addition, the RECIST define target lesions as up to five lesions per organ, and up to a total of 10 lesions in the case of there being lesions in multiple organs. The assessment of the response is performed on the basis of the change in the sum of the unidimensional measurements of the long dimension of each lesion, with no consideration of difference in prognosis according to metastatic organs. All lesions other than the target lesions are handled as nontarget lesions, and assessment of the overall response is carried out by focusing on the response of the target lesions, with consideration given to the nontarget lesions and whether or not there are also new lesions.

In this study, to investigate a qualitative difference between the JBCS General Rules and RECIST, we re-assessed the eligibility of the patients who were eligible by the JBCS General Rules, in accordance with RECIST. Although the number of cases was small (50), 32% of the cases were excluded. Most of those ineligible cases were handled as having unmeasurable lesions alone because the lesions were small, with a diameter of less than 2.0 cm, or as practically unmeasurable bone lesions.

With regard to the handling of lesions as unme-

asurable because they are less than 2.0 cm in diameter, it should be noted that advances in diagnostic imaging techniques have now made it possible to actually detect lesions less than 2.0 cm in the early stage of recurrence on an outpatient basis. Accordingly, in the RECIST, the handling of all lesions of less than 2.0 cm as unmeasurable is unrealistic and represents a problem in that the number of target lesions is reduced.

On the other hand, there have been many overseas reports which support the validity of the approach of unidimensional measurement of lesions[4-7]. In the present study, we compared the results obtained when the JBCS General Rules were applied to the RECIST-eligible cases. The results with the two sets of criteria were the same for CR and PD, but there were some differences in PR and SD/NC. However, the overall conclusion was that the RECIST approach of unidimensional measurement is valid for assessment of tumor response.

However, in the evaluation of anticancer agents, CR and PR cases are handled as responders, but cases achieving durable NC, which prolongs overall survival and time to progression, are not recognized as responders. We have experienced patients who have maintained a NC status for a long period of time, with a good quality of life, especially in cases undergoing hormonal therapy.

For example, it was recently reported that anastrozole, an aromatase inhibitor, achieved long NC ($\geqq$ 24 weeks) and therefore survival prolongation[8]. In addition, it was reported that the conventional categories of CR and PR are inadequate for the clinical evaluation of angiogenesis inhibitors, tumor dormancy therapy, etc[9]. We think this points out that there is an important need for another efficacy assessment category, such as long NC, which will serve as an index of survival prolongation.

In our present analysis of the duration of survival in each of the clinical response categories, there was no statistically significant difference between the CR + PR group and the long NC group. This finding indicates that the survival prolongation seen in long NC has true meaning.

Moreover, we surmise that this finding supports the validity of the inclusion of long NC as a response assessment category in the JBCS General Rules, which stipulate continuation of an NC status for at least 6 months. In this context, it can also be surmised that it is necessary for the RECIST to include a clear definition of long NC as a response assessment category.

Breast cancer is a disease which readily metastasizes to multiple organs, and the results of analyses performed at Gunma Cancer Center reveal that there are large differences in the duration of post-recurrence survival as a function of the metastasized organ. It is from this standpoint that in the JBCS General Rules, overall assessment of anticancer therapies had conventionally been carried out by evaluating each organ separately. In contrast, the RECIST do not evaluate each organ separately in the case of metastasis to multiple organs, but instead simply assesses the change in the total tumor mass in each patient. RECIST is suitable for an objective evaluation of anti-tumor effect, however, differences in prognosis according to metastatic organs is not included in the criteria. For the future application of RECIST, metastatic organs should be included as one of the stratification factors.

Bone metastasis occurs at high frequency in breast cancer and is a very important aspect of this disease. At Gunma Cancer Center, bone metastasis shows a high incidence of 21.3% in cases of first recurrence of breast cancer. In addition, bone metastases are metastatic lesions which show an especially good response to hormonal therapy when long NC is included. However, the RECIST do not provide for evaluation of cases with bone metastatic lesions alone since they are considered to be nontarget lesions because they are practically unmeasurable.

The complete exclusion of bone metastases from the RECIST, in spite of the fact that the bones are an important metastatic organ in breast cancer, can be considered to be an important flaw given the objective of investigating and developing candidate drug therapies for breast cancer from diverse standpoints.

It is clear that the objective of the RECIST to establish a standard method for objective assessment of the tumor response is extremely important. However, the present study has demonstrated that the placement of excessive emphasis on the aspect of objectivity can result in insufficient attention being paid to the special features of different cancers. That is, the particular problems which must be solved before the RECIST can be fully adopted in the field of breast cancer therapy can be summarized as follows: (1) the exclusion of cases with bone metastatic lesions alone from the assessment, (2) the need to elucidate the significance of long NC and establish a "long NC" assessment cat-

egory, (3) the problem of prognoses as a function of organ metastasis and (4) the fact that the number of subject cases is reduced due to the exclusion of target lesions having a diameter of less than 2.0 cm. Further investigation with a larger number of cases will be of great interest.

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