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Tumor response assessment by measuring the single largest lesion per organ in patients with advanced non-small cell lung cancer

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ABSTRACT

Background: The criterion of two target lesions per organ in the RECIST 1.1 is an arbitrary one, not being supported by any objective evidence. We compared tumor responses, respectively, using the RECIST 1.1 (measuring two target lesions per organ) and modified RECIST 1.1 (measuring the single largest lesion in each organ) in patients with advanced non-small cell lung cancer (NSCLC).
Materials and methods: We reviewed medical records of patients with advanced NSCLC who received a first-line chemotherapy between January 2004 and December 2013 and compared tumor responses according to the two criteria using computed tomography.
Results: A total of 64 patients who had at least two target lesions in any organ according to the RECIST 1.1 were included in the study. The differences in the percentage changes of the sum of tumor measurements between the RECIST 1.1 and mRECIST 1.1 were all within 10%. Thirty-three patients (51.6%) showed an increase in the absolute value of the percentage change when adopting the mRECIST 1.1, instead of the RECIST 1.1. The tumor responses showed high concordance between the two criteria ($k = 0.899$). Only three patients (4.7%) showed disagreement of the responses between the RECIST 1.1 and mRECIST 1.1. The overall response rates (20.3% vs. 20.3%) and disease control rates (89.1% vs. 90.6%) of first-line chemotherapy were not significantly different between the two criteria.
Conclusion: The modified RECIST 1.1 was comparable to the original RECIST 1.1 in the response assessment of patients with advanced NSCLC. Our result suggests that it may be possible to measure the single largest target lesion per organ for evaluation of the best tumor response.
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1. Introduction

An accurate assessment of tumor response is critical for clinical trials of new drugs as well as routine anti-cancer treatments. Since the early 1980s, the World Health Organization (WHO) has adopted WHO response criteria as the standard method for evaluating the tumor response [1]. The total tumor size is determined bi-dimensionally by the sum of the products of the two longest diameters in the perpendicular dimensions of all target lesions. Since the details for selecting target lesions were not clearly described in the WHO guidelines, however, the assessment of tumor response has been shown to be poorly reproducible between investigators [2,3]. In clinical practice, measuring all target lesions with two dimensions and then calculating the sums of their products are not only time-consuming but also hold a potential risk of error.

The Response Evaluation Criteria in Solid Tumors (RECIST) Working Group proposed in 2000 the RECIST guideline version 1.0 (RECIST 1.0) to simplify and clarify tumor response criteria [4]. Major features of the original RECIST 1.0 included the definition of the minimum size of target lesion by computed tomography (CT), the use of uni-dimensional measurements instead of the bi-dimensional method for evaluation of tumor size, and instructions about how many target lesions to evaluate. The RECIST 1.0 criteria adopted a total of 10 target lesions with a maximum of 5 lesions per organ. It has been widely accepted as the standardized method for tumor response assessment. However, a number of issues and questions including the number of target lesions, the size of lymph nodes (LNs) to be measured, and the application of new imaging technologies has been newly raised on RECIST 1.0 [5,6].

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The RECIST Working Group published in 2009 the revised RECIST guideline version 1.1 (RECIST 1.1), based in part on the evaluation of the database of more than 6500 patients from 16 clinical trials [6,7]. The most important modifications included the maximum number of target lesions, LN measurement, and the definition of disease progression [8,9]. Especially, the maximum number of target lesions to be assessed has been reduced from 10 to 5 in total, and from 5 to 2 per organ with metastases. While the total of 10 target lesions in the RECIST 1.0 was arbitrarily selected, the RECIST 1.1 defined a total of 5 lesions through the patients' data analysis [7] and statistical simulating studies [10,11]. However, the criterion of 2 target lesions per organ was still an arbitrary decision, not being supported by any objective evidence. Interestingly, Zacharia et al. reported that measuring the single largest lesion of hepatic metastases yielded almost the same response classification as measuring up to 5 target lesions in patients with colorectal cancer (CRC) [12]. This finding indicates that the ideal number of target lesions per organ to accurately evaluate tumor response still needs to be determined in further studies.

We assumed that measuring the single largest lesion in each organ (modified RECIST 1.1) might yield almost the same response classification as measuring two target lesions per organ (RECIST 1.1). In this study, we compared the tumor responses by CT between the RECIST 1.1 and mRECIST 1.1 in patients with advanced non-small cell lung cancer (NSCLC).

2. Patients and methods

2.1. Patients

This study obtained the Institutional Review Board's approval with a waiver of patients' informed consent according to the Korean Ethical Guidelines for epidemiological research. We retrospectively reviewed the medical records of patients with advanced NSCLC who received a first-line chemotherapy between January 2004 and December 2013 at Kangnam Sacred Heart Hospital, Seoul, South Korea. The patient was eligible for the study if he or she had the following criteria; histologically confirmed non-small cell carcinoma of the lung, radiologically or histologically confirmed advanced disease (stage IIIB or IV), having at least 2 measurable lesions in any organ by RECIST version 1.1, no history of other cancer, no history of previous chemotherapy or radiotherapy except for adjuvant treatment, and CT tumor assessments at baseline and after chemotherapy. Patients who had shown the substantial progression of non-target lesions or development of new lesions at the follow-up CT were excluded from the final analyses.

2.2. CT examinations

All CT examinations were performed on a 64-multidetector CT (MDCT) scanner (SOMATOM Sensation 64, Giemens Healthcare) with the administration of 80 mL (at a rate of 3 mL/s) of an intravenous contrast medium, iopromide (Ultravist 300, Bayer Medical Systems), with a scan delay of 30 s. The images were reconstructed with a slice thickness of 5 mm and were directly uploaded on the Picture Archiving and Communication System (PACS) workstation (PiView Star, INFINITT Healthcare Co. LTD., Seoul, Korea).

2.3. Tumor measurements

We re-evaluated each patient's tumor measurements from the original CT images. CT tumor measurements were performed manually on axial CT image planes using the calipers of a measurement tool on the PACS. The target lesion description and CT size measurement, the sum of the longest diameters of target lesions, the description of non-target lesions, the development of new lesions, and the tumor response for each patient were recorded by the consensus of two experienced investigators according to the RECIST 1.1 and mRECIST 1.1, respectively. For cases showing a significant discrepancy between the two investigators, a board-certified chest radiologist finally re-evaluated the CT results. Briefly, the maximum number of target lesions to be assessed was 5 in total, with a maximum of 2 per organ (RECIST 1.1) or a single largest lesion in each organ (mRECIST 1.1). LN measurements were performed in its short axis according to RECIST 1.1 criteria, defining LNs of at least 15 mm as target lesions. LNs with at least 10 mm but less than 15 mm in its short axis were considered as non-target lesions, and LNs with a short axis of less than 10 mm were regarded as normal. According to the RECIST 1.1, lytic or mixed lytic-blastic bone lesions with measurable soft tissue component were also regarded as target lesions.

2.4. Definitions of tumor response

Patients received various regimens as a first-line chemotherapy in practical setting. The CT scans for evaluating tumor response were obtained at baseline and after 2 or 3 cycles of the first-line chemotherapy, and tumor responses were determined with no interval confirmation. The definitions of treatment response were in accordance with the original RECIST version 1.1. Complete response (CR) was defined as the complete disappearance of all tumor lesions. Partial response (PR) was defined as a reduction in the sum of tumor measurements by at least 30%. Progressive disease (PD) was defined as at least 20% increase in the sum of tumor measurements. In addition, an absolute increase of at least 5 mm was a prerequisite for PD. Appearance of new lesions or substantial progression of non-target lesions was also defined as PD. All other forms of tumor response were classified as stable disease (SD).

2.5. Statistical analysis

A paired Student's *t* test was used to estimate the statistical significance of changes in the number of target lesions at baseline between RECIST 1.1 and mRECIST 1.1. Chi-square test was used to compare the overall response rates (ORR) and disease control rates (DCR; CR + PR + SD) between two groups. All *p* values were based on a two-sided hypothesis, with a value of less than 0.05 being considered significant. The level of concordance of the tumor responses between two criteria was assessed using κappa statistics. A kappa value of more than 0.75 was interpreted as showing excellent agreement.

3. Results

3.1. Patient characteristics

During the study period, a total of 129 patients with advanced NSCLC received the first-line chemotherapy with a variety of regimens. Fifteen patients (11.6%) had not been evaluated for tumor response, and 37 patients (28.7%) had no target lesion or only one target lesion per organ according to RECIST 1.1. According to the inclusion criteria, eleven patients (8.5%) who showed the progression of non-target lesion or development of new lesions were also excluded from the study. Finally, a total of 64 patients (49.6%) who had at least two measurable lesions in any one organ were included in the final analyses.

Patients' baseline characteristics are summarized in Table 1. The patients consisted of 49 male (76.6%) and 15 female, with a median age of 62 years (range, 29–89 years). Thirty patients (46.9%) had adenocarcinoma and 23 (35.9%) had squamous cell carcinoma. Fifty-nine (92.2%) patients had stage IV NSCLC and the remaining five had IIIB disease. Almost all patients (98.4%) had measurable

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