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Three-dimensional evaluation of chemotherapy response in malignant pleural mesothelioma

Guntulu Ak[a,*], Muzaffer Metintas[a], Selma Metintas[b], Huseyin Yildirim[a], Ragip Ozkan[c], Hilmi Ozden[d]

[a] Department of Chest Disease, Eskisehir Osmangazi University, Medical Faculty, Eskisehir, Turkey
[b] Department of Public Health, Eskisehir Osmangazi University, Medical Faculty, Eskisehir, Turkey
[c] Department of Radiology, Eskisehir Osmangazi University, Medical Faculty, Eskisehir, Turkey
[d] Department of Anatomy, Eskisehir Osmangazi University, Medical Faculty, Eskisehir, Turkey

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ABSTRACT

Objectives: Measurement of tumor response to chemotherapy in malignant pleural mesothelioma (MPM) is problematic because of non-spherical tumor growth patterns and difficulty in choosing target lesion. In this study, we aimed to determine the effectiveness of tumor volume measurement for evaluating chemotherapy response.
Methods: Fifty-seven MPM patients were included. Chemotherapy responses were evaluated by computed tomography (CT) using volumetric method, World Health Organization (WHO), and modified Response Evaluation Criteria in Solid Tumor (RECIST). The tumor volume was measured using the Cavalieri principle of stereological approaches.
Results: According to the volumetric method, median survival was 10.0 months for progressive disease (PD), 14.0 months for stable disease (SD) and 16.0 months for objective response (OR). According to the WHO method, median survival was 11.3, 14.0, and 13.0 months, respectively. For modified RECIST, median survival was 10.0, 14.0, and 14.0 months, respectively. The correspondence between the WHO and modified RECIST methods was substantial ($K = 0.66$), as was that between the volumetric and WHO methods ($K = 0.64$); however the correspondence between the volumetric and modified RECIST methods was only moderate ($K = 0.52$).
Conclusions: The most suitable chemotherapy response measurement technique is the volumetric method because of non-spherical tumor growth patterns in MPM. However, larger studies should be performed to better establish the suitability of this method. We recommend our method for determining the chemotherapy response in mesothelioma cases. However, modified RECIST criteria can also be applied due to favourable prediction of survival, ease of application, and moderate correspondence with the volumetric method.

1. Introduction

The incidence of malignant pleural mesothelioma (MPM) is increasing worldwide, and is expected to rise further as the result of widespread exposure to asbestos in recent decades [1,2]. No particular therapies had accepted as a standard of care due to generally low response rates [3]. However, the development of new effective chemotherapeutic agents and therapeutic combinations, has recently resulted in frequent use of chemotherapy for MPM treatment [4,5].

Tumor in patients with pleural mesothelioma has non-spherical growth pattern along the pleural surface. Therefore, evaluation of the chemotherapy response due to the local extension of the tumor is difficult. There is no "gold standard" technique for tumor measurement in MPM. Bi-dimensional response criteria established by the World Health Organization (WHO) have been used for many years [6]. However, WHO criteria are poorly suited to the growth pattern of MPM and insufficient for some patients. Therefore, suggested to evaluate the response to treatment in solid tumors uni-dimensional response (Response Evaluation Criteria in Solid Tumor (RECIST)) criteria has been used for MPM [7]. It was become research topic [8,9]. Recently, modified RECIST criteria were developed by Byrne and Nowak, due to difficulty in selecting the target lesion and measuring the longest diameter of the tumor [10]. Although these modified RECIST criteria have become standard for mesothelioma, some investigators have shown the high grade of inter-observer variability [11]. Additionally, theoretical studies have identified weaknesses in the modified RECIST criteria that have resulted in over-classification of tumors [12].

* Corresponding author. Tel.: +90 222 2392979; fax: +90 222 2394714.
E-mail address: guntuluak@yahoo.com (G. Ak).

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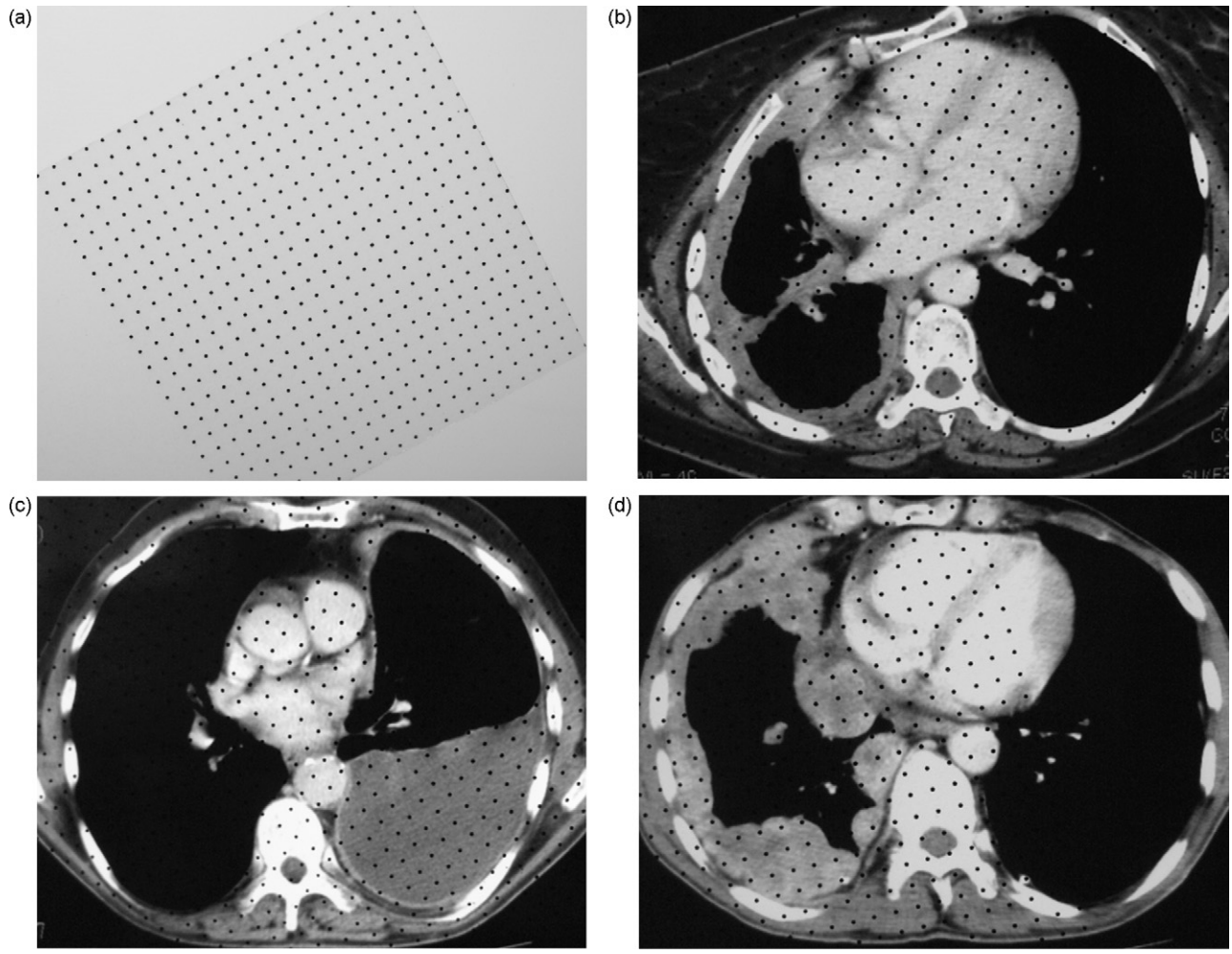

Fig. 1. Point-counting grid (a); estimation of tumor volume using the point-counting method (b–d).

We have hypothesized that indefinable shapes can be represented as spheres with defined volumes, thereby allowing three-dimensional evaluation of the chemotherapy response. The three-dimensional evaluation of tumor response and the measurement of all known lesions might be more suitable for MPM due to its non-spherical growth pattern. In a previous study, the tumor volume was measured using the Cavalieri principle [13]. It could be useful for response evaluation in MPM. In the present study, we aimed to determine the effectiveness of tumor volume measurement for evaluation of the chemotherapy response and also discuss to the relationship between prognosis and response categories of three- (volumetric method), bi- (WHO) and, uni- (modified RECIST) dimensional measurement method in MPM. In addition, we determined the degree of correspondence between these three methods.

2. Materials and methods

2.1. Patients

Fifty-seven consecutive patients with histologically confirmed MPM were evaluated in this study. After diagnosis, chemotherapy was given to the patients, and they were subsequently followed until the end of life. Patients who received another therapy in addition to chemotherapy (extrapleural pneumonectomy, decortication, radiotherapy or intracavitary therapy), those who were not followed up, and those whose responses were not measured on time or whose responses were measured using a different computed tomography (CT) technique were excluded.

2.2. Point-counting method

The volumes of organs and structures can be obtained using the Cavalieri principle of stereology [14,15]. In previous studies, volumes of different organs were estimated using the Cavalieri principle [16–18]. A modified formula has been used for volume estimation from radiological images [13,16]. In this study, the modified formula was applied to estimate tumor volume. The modified formula is $V = t \times [SU/SL \times d]^2 \times \sum P$, where V is the volume, t is the thickness of consecutive sections, SU is the scale unit of the printed film, d is the distance between the test points of the grid, SL is the measured length of the scale printed on the film, and $\sum P$ is the total number of points hitting the sectioned cut surfaces of the tumor.

First, films were placed on a light bow and the distances between consecutive tomography slices (t) were determined. Second, a scaling coefficient was calculated using a scale unit that was marked on thoracic CT scans (SU and SL). A grid was formed by marking points on a transparent film at constant intervals (Fig. 1a). The real linear distance was obtained by multiplying the scaling coefficient with the distance between two points on the grid ($d = 0.2$ cm). The obtained value was squared. Thus, the areas against for each point on grid were calculated. Third, the transparent square grid was superimposed randomly on all slices that included tumor, respectively. All points on tumors were counted (P). The points derived

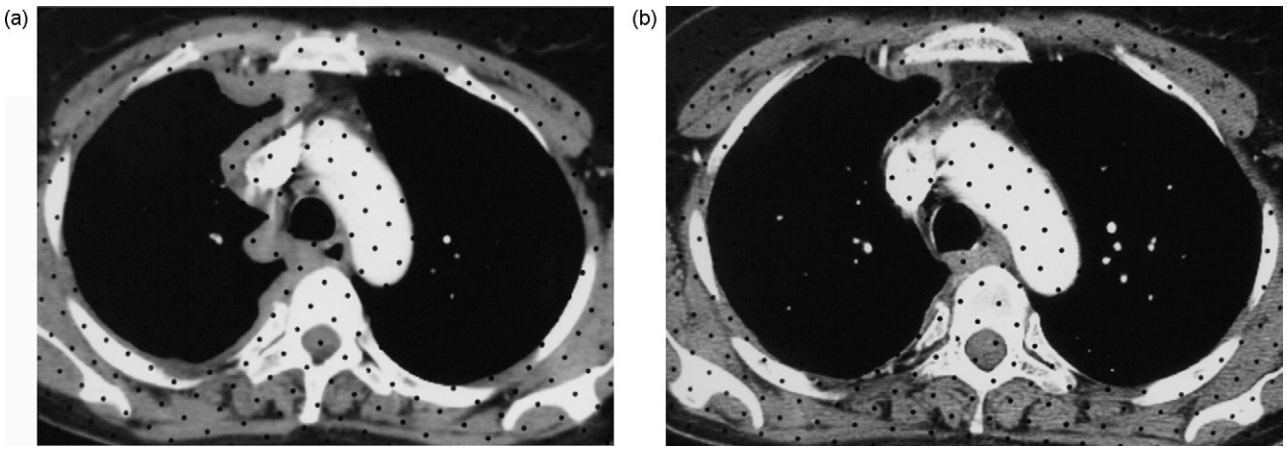

Fig. 2. Measurement of tumor volume before (a) and after (b) chemotherapy.

from each slice were summed ($\sum Pi$). These values were formulated to estimate the tumor volume ((Figs. 1b–d and 2a, b).

2.3. Response evaluation

The tumor response was evaluated by three experienced readers for the three methods. Tumor measurements were performed on transverse-cut thoracic CT scans using WHO [6], modified RECIST [10], and volumetric methods before and after two or three cycles of chemotherapy. According to WHO criteria, a complete response (CR) was defined as the complete disappearance of all disease with no new lesions; partial response (PR) was defined by a ≥50% decrease in the sum of the products of the longest diameters of each lesion and the respective perpendicular diameters; an increase of ≥25% of this sum was defined as progressive disease (PD); stable disease (SD) was defined by <50% decrease or <25% increase [6]. According to modified RECIST criteria; tumor thickness perpendicular to the chest wall or mediastinum instead of the longest diameter was measured at two positions in three separate levels on transverse-cut CT scans; levels were at least 1 cm apart and related to anatomical landmarks to allow reproducible assessment at later time points. CR was defined as the complete disappearance of all known disease with no new lesions; PR was defined by a ≥30% decrease in the sum of the longest diameters of target lesions; PD was defined by a ≥20% increase of this sum; SD was defined by a <30% decrease or <20% increase [10].

Volumetric response criteria were defined as follows. Tumor volume before chemotherapy was subtracted from tumor volume after chemotherapy; the result was then divided by the volume before chemotherapy and multiplied by 100. Thus, the percent change of total tumor volume was estimated. Second, response criteria were estimated. The patients were classified into three groups based on median survival obtained from previous studies [10,19]: these groups were ≤8 months; 9–16 months; >16 months. The predictive value of changes of total tumor volume was estimated by receiver operating characteristics (ROC) analysis for three groups. In volumetric response criteria, CR was defined as disappearance of all target lesions with no evidence of tumors elsewhere; PR was defined as a total tumor volume decrease of at least 50%; PD was defined as increase of 15% or more in total tumor volume, or appearance of new lesions; and SD was defined as neither partial response nor progressive disease. Objective response (OR) was defined as complete and partial response for the three methods.

2.4. Statistical analysis

Statistical analyses were performed using statistical software (SPSS, version 13.0). Volumetric response criteria were estimated by ROC analyses. Median survivals with 95% confidence intervals (CI) were estimated according to the Kaplan–Meier method. Differences in time distributions between groups were tested for statistical significance using the log-rank test. Kappa analysis was performed to determine the correspondence between the three methods. Kappa values were defined as: 0, no correspondence; 0–0.2, slight; 0.2–0.4, fair; 0.4–0.6, moderate; 0.6–0.8, substantial; 0.8–1.0, almost perfect correspondence.

3. Results

Patient characteristics are depicted in Table 1.

Median survival times based on chemotherapy response are shown in Table 2.

For the three evaluation methods, the median survival of patients with SD and OR was longer than that of patients with PD (for SD and OR, respectively; according to WHO $p = 0.009$, $p = 0.034$; according to modified RECIST $p = 0.015$, $p = 0.006$; according to volumetric method $p \leq 0.05$, $p = 0.013$). However, there was no difference between SD and OR ($p = 0.283$ for WHO; $p = 0.476$ for modified RECIST; $p = 0.071$ for the volumetric method).

Kaplan–Meier survival curves based on the three tumor response criteria are shown on Figs. 3–5.

Chemotherapy response rates of the patients are shown in Table 3.

The agreement between WHO and modified RECIST was substantial ($K = 0.66$), as was the agreement between the volumetric and WHO methods ($K = 0.64$). However, the agreement between

Table 1
Patient characteristics.

Patient number	57
Mean age (years)	59.2 ± 12.9 (26–90)
Male:female, *n* (%)	31:26(54.4%:45.6%)
Karnofsky performance status	81.0 ± 8.4 (60–100)
Histopathology, *n* (%)	
Epithelial	43 (75.4)
Mix	9 (15.8)
Sarcomatous	2 (3.5)
Unidentified	3 (5.3)
Stage—IMIG*, *n* (%)	
I	4 (7.0)
II	6 (10.5)
III	24 (42.1)
IV	23 (40.4)

* International Mesothelioma Interest Group.

Table 2
Median survival times of patients based on chemotherapy response.

	PD	SD	OR	Test value
WHO*	11.3 (8.427–14.173)	14.0 (5.598–22.402)	13.0 (5.447–20.553)	Log-rank = 9.246, $p = 0.010$
Modified RECIST*	10.0 (3.459–16.541)	14.0 (9.734–18.266)	14.0 (7.763–20.237)	Log-rank = 10.089, $p = 0.006$
Volumetric method*	10.0 (7.6–12.4)	14.0 (10.736–17.264)	16.0 (6.298–25.702)	Log-rank = 9.774, $p = 0.008$

WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumor; PD, progressive disease; SD, stable disease; OR, objective response.
* Median survival (months) (95% CI).

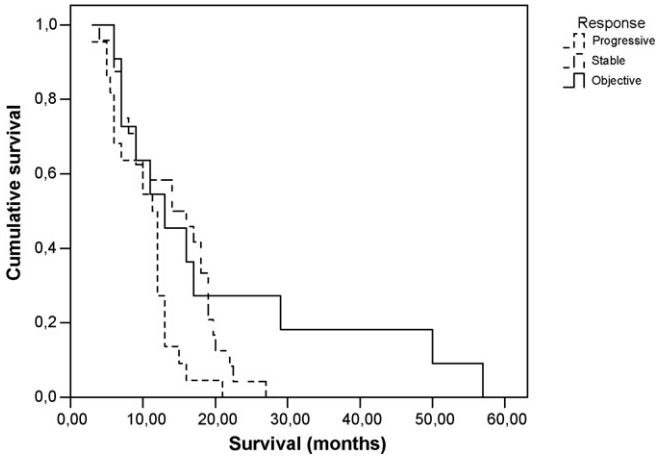

Fig. 3. Kaplan–Meier survival curves for WHO criteria.

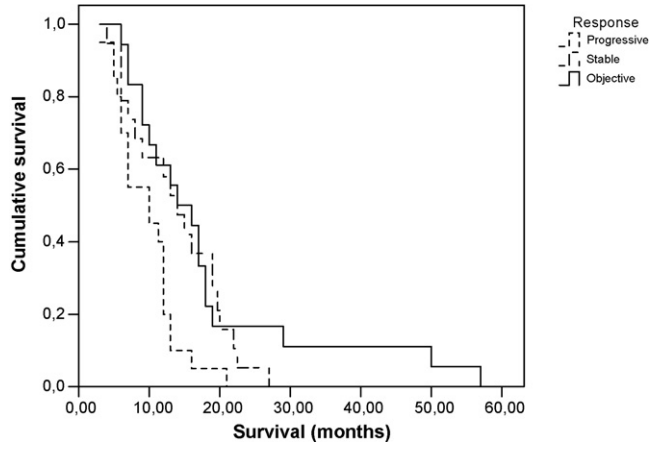

Fig. 4. Kaplan–Meier survival curves for modified RECIST criteria.

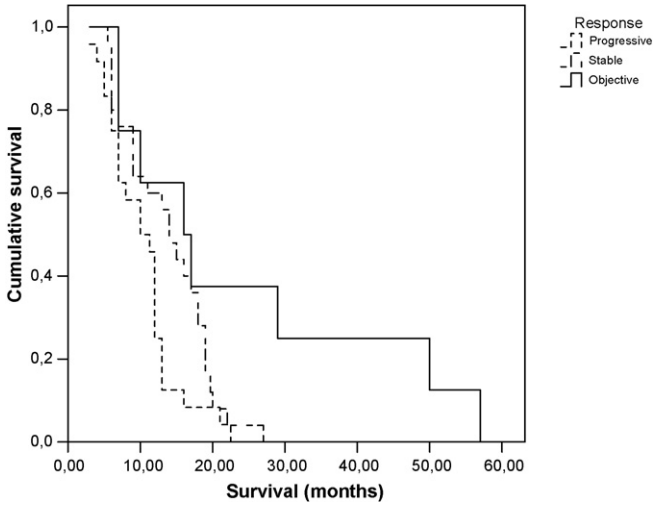

Fig. 5. Kaplan–Meier survival curves for volumetric method.

the volumetric method and modified RECIST was moderate ($K = 0.52$).

4. Discussion

Evaluation of tumor responses in MPM is difficult because of the growth pattern of the tumor. Tumor has distinct features including growth as a rind around the hemithorax, involvement of multiple thoracic levels, separate nodular or pleural thickening, growth along fissures, and accompanying atelectasies, pleural fluid and fibrosis [20]. WHO and RECIST criteria were poorly suited to the distinct growth pattern of MPM. Therefore, the modified RECIST criteria were specifically developed for better assessment of changes in pleural mesothelioma [10]. Although the modified RECIST criteria select measurement sites, their use might be insufficient in some patients. Tumors are measured at two sites in three different levels on CT scans. After chemotherapy, the same measurements are made at the same sites using anatomical landmarks. However, sites with the "longest diameter" can change due to altered thoracic structures after chemotherapy. This situation can be causes to the inter-observer variability. Additionally, the difficulty in choosing the target lesion still remains. In the present study, we aimed to measure all known lesions because of this difficulty as well as the non-spherical growth pattern of the tumor.

Previous studies have utilized three-dimensional evaluation of tumor responses [12,21,22]. Prasad et al. evaluated patients with liver metastases from breast cancer [21]. Lesions were spherical, and volumetric measurement results were different from results obtained using bi- and uni-dimensional techniques. In other studies, mesothelioma was evaluated [12,22]. Oxnard et al. evaluated the volumetric consistency of the modified RECIST response criteria in geometric models that simulated idealized mesothelioma morphologies and growth patterns; this study demonstrated the weakness of current modified RECIST criteria [12]. In the two mesothelioma studies, volumetric response criteria were based on rough mathematical equivalents of WHO and RECIST response criteria. Zhao et al. developed a computer method for volumetric response assessment in MPM [22]. This method utilizes a sequential segmentation strategy to dissect the pleural tumor from the surrounding non-tumor tissues. It was concluded that this computer method could be applied to clinical trials because it allowed reliable detection of tumor regression and progression, and also provided a better assessment of the response to therapy [22]. However, a major limitation of these studies is that they could not have taken all lesions into account.

Despite these previous attempts, a routinely applied method has not yet been found for tumor volume calculation in MPM. Previ-

Table 3
Chemotherapy response rates.

	PD, *n* (%)	SD, *n* (%)	OR, *n* (%)
WHO	22 (38.6)	24 (42.1)	11 (19.3)
Modified RECIST	20 (35.1)	19 (33.3)	18 (31.6)
Volumetric method	24 (42.1)	25 (43.9)	8 (14.0)

WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumor; PD, progressive disease; SD, stable disease; OR, objective response.

ous study has calculated tumor volume by reshaping the tumor in mesothelioma patients through the Cavalieri principle of stereological approaches [13], which is commonly used in the literature to calculate the volume of organs or structures [14–18]. A correlation was found between patient survival and tumor volume [13]. In the present study, we wanted to determine whether this technique could be beneficial for evaluating the response to chemotherapy.

According to mathematical formula, a uni-dimensional measurement decrease of 30% and a bi-dimensional measurement decrease of 50% are both equivalent to approximately the same three-dimensional measurement decrease of 65% in a sphere. Also, a uni-dimensional measurement increase of 12% or 21% and a bi-dimensional measurement increase of 25% or 46% are three-dimensional measurement increase of 40% or 77% [7,23]. If three-dimensional response criteria is determined using the WHO and RECIST response criteria, the partial response limit is 65% and the progressive disease limit is around 40% or 77%. We considered that most patients would thus be evaluated as having stable diseases and that misclassification might arise. We therefore decided to establish response criteria using statistical methods, specifically ROC analysis.

Based on the obtained ROC curve, a $\geq$15% increase in tumor volume for progression and a $\geq$50% decrease in tumor volume for partial response were found. When the chemotherapy response was evaluated based on these criteria, a significant correlation was established between the chemotherapy response and median survival. We considered even a 15% increase in tumor volume as an indication of failed chemotherapy. However, considering that the survival of SD patients was longer than that of PD patients, chemotherapy should still be continued in the patients with SD. Modified RECIST and WHO criteria also showed a correlation between chemotherapy response and median survival. However, WHO criteria showed a longer survival for patients with SD than for patients with OR, although this difference was not statistically significant. This indicates that bi-dimensional measurement is not suitable for evaluation of the chemotherapy response in patients with mesothelioma. We found that the survival of SD and OR patients was the same when using modified RECIST criteria. However, these survivals were the different when using the volumetric method; it is possible that with increased numbers of cases this difference could be significant (Table 2).

It has been previously suggested that the agreement between WHO and RECIST evaluation is poor, and that RECIST underscores the tumor response in the majority of cases [8,9]. In some previous studies, volumetric measurement gave different results from bi- and uni-dimensional techniques [21], and the use of modified RECIST criteria resulted in over-classification of tumors [12]. In the present study, the agreement between the volumetric and WHO methods was substantial, but the agreement between the volumetric method and modified RECIST was only moderate. When using RECIST, the rate of OR patients was higher, but their survival was similar. Previous studies have also demonstrated the high grade of inter-observer variability during manual measurement using modified RECIST criteria in MPM [11]. Automated and semi-automated measurement techniques have been developed in response to these concerns [11,22,24]. Due to the difficulty of the measurement technique in our study, inter-observer variability was not evaluated. However, as indicated in the previous study, we tried to obtain the most accurate measurements by using 5 mm thickness CT sections [16].

Recently, metabolic responses have been studied. The use of standardized uptake values for evaluation could be problematic in patients applied talc pleurodesis and in some epithelial subtypes which metabolic activity is slow. Although some studies have provided promising results, the utility of metabolic evaluation remains unclear [25].

Morphological assessment using advanced imaging techniques is likely the best method for evaluating the chemotherapy response in MPM. Atelectasies and fibrosis might impede morphological evaluation, although this effect would occur for all three methods. After chemotherapy, the thoracic structures change is not important because we recommend measuring all known lesions defined as tumor using the volumetric method.

The most important limitation of our study is manual measurement of the tumor volume using CT on the light box. Manual measurements are time-consuming and tiresome. However, when considering the given effort for treatment and follow-up as well as the treatment costs, we recommend using this method until new measurement software can be developed. Also, the patient number was low. This made it difficult to determine volumetric response criteria. Larger studies are needed in order to determine the volumetric response criteria that correlate best with survival. Another issue might arise from the using of talc pleurodesis. In this study, talc pleurodesis applied patients were not separately assessed. However, this problem can be overcome by quality imaging and contrast-enhanced CT. This drawback was also a problem for WHO and RECIST methods used in this study.

When considering the non-spherical growth pattern of tumor and the difficulty in choosing target lesion, the most reliable approach for evaluation of tumor response in mesothelioma might be direct measurement of tumor volume change in three dimensions as completely as possible. However, larger studies are needed to confirm the suitability of this method. We recommend the use of our method for determining the chemotherapy response in mesothelioma cases. However, modified RECIST criteria can also be applied due to favourable prediction of survival, ease of application, and moderate correspondence with the volumetric method.

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