Relationship between tumorsize of malignant pleural mesothelioma and its response to chemotherapy

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Purpose: Malignant pleural mesothelioma (MPM) is an extremely lethal neoplasm and continues to be an important health problem in communities facing occupational or environmental exposure to asbestos. One of the most significant problems in the treatment of MPM is the lack of a standardized criterion for the evaluation of response to chemotherapy. In this study, differences between the tumor volumes of International Mesothelioma Interest Group (IMIG) stages, chemotherapy response, and patient response times were investigated. Patients and methods: We used the initial tumor volume determinations from patients with MPM with the point-counting technique indicated in the Cavalieri principle of stereologic design. Results: We observed reduction in tumor volumes from tumor treatment until posttreatment. We found that those patients with the shortest period between initial diagnosis of a tumor volume of 200 mm^3 or greater had increases in volume of greater than 50 mm^3. Conclusion: There is still no standardized evaluation of MPM responses after chemotherapy to chemotherapy using classic criteria. However, our studies on tumor volume continuer.

Key words —— Cavalieri principle, stereology, computed tomography, malignant mesothelioma, volume estimation

INTRODUCTION

Malignant mesothelioma is a rare tumor that can affect the pleura, peritoneum, and pericardium.[1,2] Malignant pleural mesothelioma (MPM) is an extremely lethal neoplasm[3,4] continues to be an important health problem in communities facing occupational or environmental exposure to asbestos.[5–7] Our clinic is in the Medical Faculty of Osmangazi University, Eskisehir, Turkey. The district of Eskisehir is located in central Anatolia. Environmental exposure to asbestos is due to the use of asbestos-contaminated white-soil, common in the rural parts of Eskisehir. Many patients with MPM are admitted to our clinic every year, and the incidence of this aggressive tumor is increasing and expected to continue doing so.[8,9]

In the literature, the median survival of MPM patients is reported to be about 1 year. There seems to be no consensus on its treatment or the function of chemotherapy in the treatment of the illness. The response rate to chemotherapy is approximately 20%, 30%.[10] It is reported that in cases showing a response to chemotherapy, the life expectancy of the patient is extended. However, research continues on combinations of different treatments in the management of MPM.[11,12]

Previous studies have shown that one of the most significant problems in the treatment of MPM is the lack of a standardized criterion for the evaluation of response to chemotherapy.[13] There is a problem in the two-dimensional detection of the tumor since it spreads into the surrounding pleura. In general, "the recede description" which depends on the subjective judgment of the observer, is more commonly used than techniques for objective evaluation. Endeavors to find solutions to problems encountered during the evaluation of response to chemotherapy in MPM continue.[14–16]

We used the initial tumor volume determinations from patients with malignant mesothelioma

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with the point-counting technique indicated in the Cavalieri principle of stereologic design. This technique has previously been used success fully in the determination of organ volume. In this study, differences between the tumor volumes, International Mesothelioma Interest Group (IMIG) stages, chemotherapy response, and patient response times were investigated.

PATIENTS AND METHODS

Patients —— All of the 48 patients included in the study were diagnosed and followed up in the Department of Chest Diseases, Medical Faculty, Osmangazi University. The diagnosis of MPM was based on histopathologic examination of pleural tissue samples, obtained by Computed Tomagraphy (CT) guided biopsy, thoracoscopy, or thoracotomy. The total sample group was composed of 56.3% (27) men and 43.8% (21) women. Patient ages ranged from 26 to 81 (mean ± S.D. 57.7 ± 11.2) years, with the male mean age of 58.1 ± 11.4 years and the female mean age 57.3 ± 11.2 years. Eight (16.7%) patients from the total group of 48 were still living at the time of analysis. Of the 48 patients, 38 (78.2%) had environmental exposure to asbestos.

The samples were histochemically stained with hematoxylin-eosin, Alcian blue, and mucicarmine. Immunohistologic procedures for carcinoembryonic antigen (CEA) and LeuM1 were performed.

All of the patients were admitted to the chemotherapy treatment program. Chemotherapy plus immunotherapy regimens were administered according to the following schedule: Cisplatin, 30 mg/m^2 IV qd on days 1 and 2; mitomycin, 8 mg/m^2 IV on day 1; and subcutaneous Interferon α2a, 4.5 million IU twice weekly. The courses were repeated every 4 weeks.

Evaluation of Response Based CT Scanning —— All patients underwent a conventional CT scan of the thorax using a Toshiba TCT 600 Scanner (Toshiba Company, Tokyo, Japan) with 5–10 mm slice thickness and contrast enhancement in the pre- and posttreatment period. All scans were printed separately using a lung and soft tissue window setting with suitable Hounsfiel units for each patient. The CT features were evaluated by a panel of two chest physicians.

The response to treatment was determined after the third course of therapy had been administered by means of a thoracic CT scan, while other scans were also used if indicated. The evaluation of the response by the physicians was not hindered. A complete response (CR) was defined as the complete disappearance of all lesions and the absence of signs and symptoms for > 4 weeks, without the appearance of new lesions. A partial response (PR) was defined as a decrease of > 50% compared with pretreatment measurements in the sum of the products of the perpendicular diameters of all measurable lesions, and no appearance of new lesions over a period of 4 weeks. Regression occurred when there was a definite decrease in tumor size for lesions not dimensionally measurable (as agreed on by two independent investigators), and no appearance of new lesions over a period > 8 weeks. Stable disease was characterized as a < 50% reduction or < 25% increase (in relation to the tumor size at entry) in the sum of the products of the perpendicular diameters of all measurable lesions over a period > 8 weeks, with no new lesions appearing. Progressive disease was an increase in the product of two perpendicular diameters of all measured lesions by > 25% over the initial tumor size at entry, and was defined as a definite increase in tumor size. Patients demonstrating CR, PR, or regression were considered to have had an objective response (OR).

Cavalieri Principle for the Estimation of MPM Tumor Volume: Initial and Follow-up Tumor Volume Determinations —— The volume of solid tumor (T status) in MPM was objectively quantified using the point-counting technique. This technique is based on the Cavalieri principle of modern stereology. Using the Cavalieri principle, an unbiased estimate of the volume of an object of arbitrary shape and size may be obtained efficiently and with a known precision.[17] The volume of the irregularly shaped objects can be estimated from a set of two-dimensional slices through the object, providing that they are parallel, separated by a known distance, and begin randomly within the object, criteria which are met by standard scanning techniques such as CT or magnetic resonance imaging (MRI), as well as by other techniques.[18, 19]

In the Cavalieri principle, the cut surface areas of the sections are assessed and the multiplication of the total cut surface area by the mean of the section thickness provides an estimation of the volume of the examined object. In addition to using specific software during evaluation, the cut surface area of each section or slab is also estimated by means of the point- counting grids. The point-counting grid, which has some point sets at distinct densities on

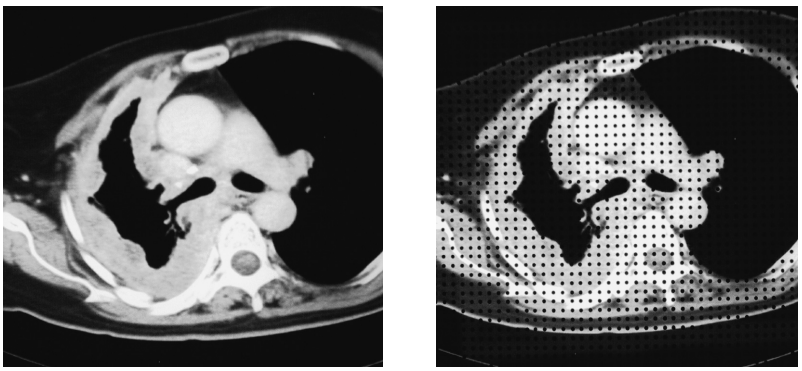

Fig. 1. "Grid of acetate" *i.e.*, a Transparent Sheet with a Scale Including Dots Equal Intervals Placed upon Lesion Regions of Consecutive Sections

a transparent sheet, is superimposed onto sections randomly and the points hitting the involved section cut surface are counted (Fig. 1). Finally, the volume of the object is estimated by using the following formula:

$$Volume = t \times (a/p) \times \sum P$$

where $\sum P$ is the total number of the points hitting the lesion cut surface area, t: the section thickness (mm), and a/p the representative area of each point on the point-counting grid found using the reduction ratio of printed films as mm.[20)]

In the Cavalieri principle, a researcher obtains the coefficient of error (CE) to evaluate the reliability of the point density of the grids and sectioning intervals. The CE, or relative standard error, represents the precision of the volume estimate obtained using the Cavalieri principle. There are a number of formulas used to obtain the CE. A well-known CE prediction formula for the Cavalieri estimation method developed by Gunderson and Jensen was used during this study.[21)] The formula gives information on the required number of slices and density of the point-counting grid.

In this study, each patient's chest was scanned in both sagittal and horizontal planes and consecutive sections were taken in 10 mm slice thickness. The scan-plane thickness is constant due to the stepwise movement of the scanner. The images of the chest sections were printed on films in square frames of 8 × 7.5-cm side length. The magnification ratios were between 0.24/1 and 0.29/1 cm for each individual chest and section plans of printed films. A square grid test system with $d = 0.5$ and 1 mm between test points, *i.e.*, a/p 0.25 and 1 mm^2 representative area per point, were used to estimate the cut surface area of the slices. The representing area per point in the grid was corrected with the magnification of printed sections, and by this means the real area per point was calculated between 2.97 and 4.16 mm^2 for the chest in both section planes. The films were placed, in turn, on a light bow and the transparent square grid test system was superimposed uniformly, randomly covering the entire image frame. The superimposing of the test system was repeated twice for each image frame and the points hitting the tumor area section cut surface area were counted for each section. The mean of the two repeated number points counted for any section was used to estimate the section cut surface area for the horizontal scan plan and the volume of the tumor was then estimated using the formula previously described.[17, 20–22)] Two investigators estimated the volumes of the tumor area on each image of the horizontal plane using the same sets of printed sections of the chest to check the accuracy and the validity of the estimates.

The calculated tumour volume, CE of estimates, and other related data were simply performed using Microsoft Excel as a spreadsheet. After initial set-up and preparation of the formula, the point counts were entered for each scan, and the final data were obtained automatically. The CT images of the patients obtained prior to treatment and following triple-agent chemotherapy were used for the estimation of the volume size of the MPM tumors. This method was used to evaluate the response to chemotherapy.

Statistical Analysis —— Data were analyzed on a computer using the SPSS 10.0 program. Survival length, along with the median and mean event times, was estimated according to the Kaplan-Meier method, with 95% confidence intervals (CI). Differences in time distributions between the groups were tested for statistical significance using the log-rank test. The duration of survival was defined as the pe-

riod between the time of diagnosis and the time of death, or last contact if the patient had not died at the time of analysis.[23] The one-way ANOVA test was used to compare the mean tumor volumes among the chemotherapy response groups.

RESULTS

Initial tumor volumes obtained in point-counting measurements ranged from 11.10 to 1164 mm^3 (mean ± SEM 366.76 ± 307.22 mm^3, median 271.64 mm^3). No difference was observed in pretreatment tumor volume ($P = 0.334$) in male patients (mean ± SEM 342.9 ± 60.84 mm^3) compared with female patients (397.45 ± 65.51). The mean (± SEM) initial tumor volume for patients with exposure to asbestos was 363.61 ± 50.13 mm^3, and 378.75 ± 100.03 mm^3 for those without exposure to asbestos ($p = 0.698$).

Most (70.8%) of the 48 patients in this series were found to have disease metastasized to the nodal (hilar and/or mediastinal) area. The tumor volumes for patients not having nodal metastases (mean ± SEM 201.95 ± 73.36 mm^3) were significantly smaller ($p = 0.001$) than for those patients with nodal metastases (mean ± SEM 434.44 ± 51.01 mm^3).

All 48 patients were staged according to the IMIG staging system. Five patients (10.4%) had stage I disease, 9 (18.8%) stage II, 15 (31.2%) stage III, and 19 (39.6%) stage IV. Due to a lack of equal distribution of stages, no stage-by-stage increase in tumor volume was seen ($p = 0.08$). Nevertheless, stage III (mean ± SEM 436.11 ± 86.72 mm^3) tumors had a moderately larger volume than stage II (mean ± SEM 255.49 ± 110.57 mm^3) ($p = 0.06$).

The median potential follow-up for the 48 patients was 23 months, with 40 of the 48 patients dead from mesothelioma as of the last analysis. The median survival time for all patients was 11.20 ± 1.19 months (95% CI, 8.88–13.52), and the mean time was 15.32 ± 2.68 months (95% CI 10.06–20.57). The median survival time of patients with nodal metastases was 10.10 ± 1.73 (95% CI 6.71; 13.49), and 13.20 ± 4.33 (4.71; 21.69) for patients without nodal metastases (log-rank test 1.40; $p = 0.2362$).

As seen in Fig. 2, a pretreatment volume of 200 mm^3 (median survival time ± SEM 21.30 ± 1.42 months) or greater was associated with a moderately worse prognosis (log-rank test = 2.34; $p = 0.12$), compared with a pretreatment volume of less than 200 mm^3 (9.20 ± 2.02 months).

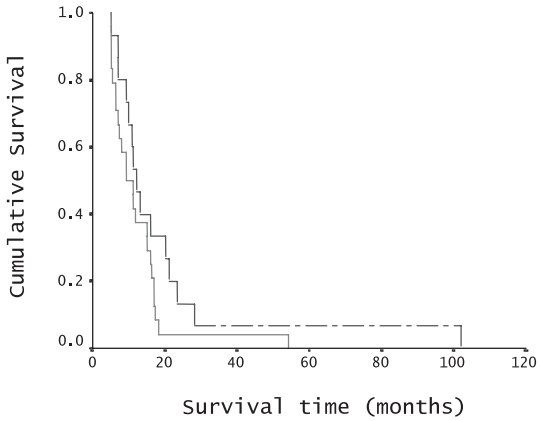

Fig. 2. Influence of Pretreatment Tumor Volume on Overall Survival of Patients with MPM ($p = 0.12$)

The response to treatment was determined in only 43 patients. Among the 43 patients, assessments were made of 14 ORs (32.6%), 1 CR (2.3%), 8 PRs (18.6%), and 5 (11.6%) regressions. Fourteen patients (32.6%) had stable disease and 15 patients (34.9%) had progression.The median time for progressive disease was 7.0 ± 0.74 months (95% CI, 5.54; 8.46), while for patients with stable disease the median survival time was 11.10 ± 4.46 months (95% CI, 2.36; 19.84), and for patients with OR the median survival time was 11.20 ± 2.68 (95% CI, 5.94; 16.46) months. Progressive responders had a significantly shorter median survival time than patients with OR and stable disease (log-rank test = 6.36; $p = 0.04$).

According to the evaluation of chemoimmunotherapy response, pretreatment and posttreatment tumor volumes are shown in Table 1 and Fig. 3. Averages for the greatest progression of tumor not responding to chemotherapy were calculated (Table 1). Twelve patients with progressive evaluation undergoing new methods of treatment, 21 stable patients, and 9 patients with OR evaluations were accepted in the study. Evaluation was made using both the classic tumor evaluation technique with other forms of management and the Cavalieri principle. Differences in the results obtained after chemotherapy using the two techniques are shown in Table 2. Evaluation using the Cavalieri principle revealed more progression in patients than the previous method ($p = 0.000$).

The results of median patient survival times using the Cavalieri principle were: for progressive dis-

Table 1. Pretreatment (V_1) and Posttreatment (V_2) Tumor Volume by Evaluation of Chemoimmunotherapy Response

Evaluation of response	V_1 (mm^3) (X ± SE)	V_2 (mm^3) (X ± SE)	Results obtained from volume variation	$[(V_1-V_2)/V_1] \times 100$ (X ± SE)
Progressive	415.2 ± 82.4	459.5 ± 68.1	$p = 0.56$	−99.5 ± 50.3
Stable	289.0 ± 70.9	270.7 ± 71.1	$p = 0.72$	2.5 ± 10.3
Objective	349.4 ± 83.3	132.4 ± 32.3	$p = 0.01$	51.9 ± 7.0
	$F = 0.640$; $p = 0.53$	$F = 7.52$; $p = 0.002$		

Table 2. Comparison of Chemotherapy Responses Using the Classic IMIG System and Cavalieri's Principle

Cavalieri evaluation group	Classic IMIG evaluation group			Total
	Progressive	Stable	Objective	
Progressive	8	4	—	12
Stable	6	9	6	21
Objective	1	1	7	9
Total	15	14	13	42

Table 3. Differences in Pre and Postchemotherapy Tumor Volumes and Survival Times

Pretreatment tumor volume	Postchemotherapy volume changes (V_1-V_2)	Duration (months)	95% CI	
200 mm^3 or more	≥50 mm^3 reduction	9.20 ± 5.24	(4.50; 19.46)	Log-rank = 0.07 $p = 0.79$
	A small increase and reduction from 50 mm^3	11.20 ± 2.74	(5.82; 16.58)	
Less than 200 mm^3	≥50 mm^3 reduction	7.00 ± 2.90	(1.32; 12.68)	Log-rank = 5.79 $p = 0.016$

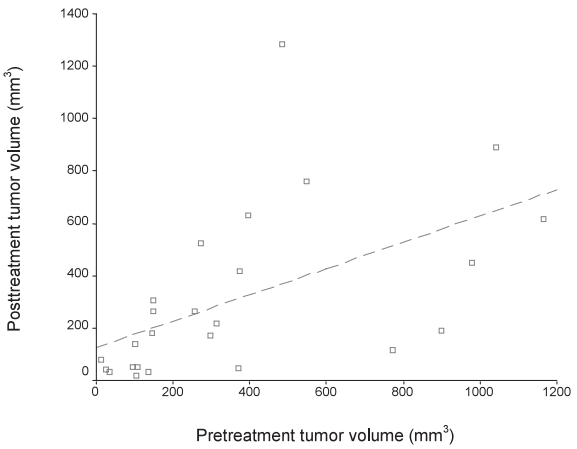

Fig. 3. Scattergram of Pretreatment and Posttreatment Volume in All Patients with MPM Shows a Low Correlation ($r = 0.57$)

ease patients 9.20 ± 2.40 (95% CI: 4.50; 13.90) months; for stable patients 15.20 ± 2.74 (95% CI: 9.82; 20.58) months; and for OR patients 10.10 ± 1.34 (95% CI: 7.47; 12.73) months. We were unable to find any significant difference in terms of survival time in patients unresponsive to chemotherapy (log-rank test = 2.30; $p = 0.32$).

Results for both the classic technique and the classic system for tumor volume determination showed no significant differences, whereas chemotherapy response results obtained at the time of tumor development and after treatment showed differences (V_1-V_2). Tumor volume determinations of less than 200 mm^3 before chemotherapy were seen to shrink by at least 50 mm^3 posttreatment although this seemed to make no difference in terms of survival period (Table 3, Fig. 4) (log-rank test = 5.79; $p = 0.016$).

DISCUSSION

MPM remains a staging and management enigma to both medical and thoracic surgical oncologists. CT is essential in the clinical management of mesothelioma. However, in the staging of MPM,

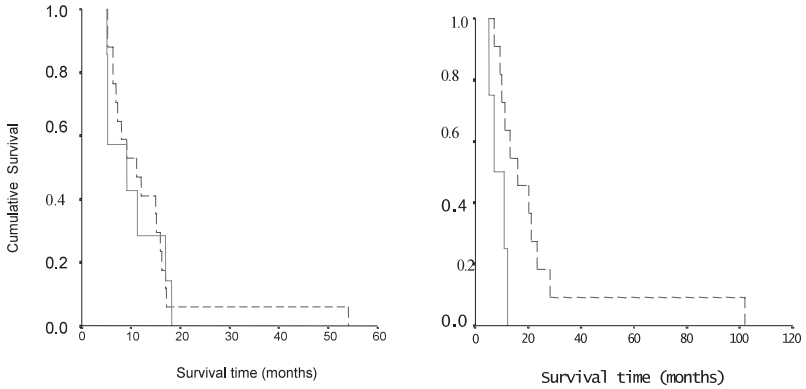

Fig. 4. Influence of Decreasing Tumor Volume on Overall Survival of Patients Who Received Chemotheraphy for MPM ($p = 0.01$)

the most difficult CT findings to interpret have in the past been chest wall involvement, mediastinal lymph node involvement, transdiaphragmatic extension of the tumor, peritoneal studding, and solid organ metastases less than 2 mm in size.[24–26)]

Pass *et al.*[16)] noted that determination of the stage and tumor volume was important both prior to and after surgical treatment of MPM. In progressive studies the determination of tumor volume must be carried out by nonsurgical means. Studies prior to this have not investigated both the chemotherapy results and tumor volume determinations of patients with MPM. However, in various tumors other than MPM the effects of treatment on tumor volume can be assessed.[27, 28)] We studied the tumor volume over time in patients with MPM who had received chemotherapy.

Different types of methods can be used for the measurement of tumor volumes. Three are more appropriate than others. Determination of total volume via CT measurements is appropriate. The estimation of the volume using the stereologic approach applied in this study provides unbiased data about the volumetric quantities of the examined structure. The stereologic method has been applied in a series of studies using both invasive and noninvasive generation of sections providing unbiased organ volume estimations. However, we have not seen a study evaluating mesothelioma volume using a combination of CT scanning and the Cavalieri principle. In the present study, we aimed to apply the Cavalieri principle to estimate the volume of mesothelioma lesions. In the stereologic method, the tracing of images is not required. The classic CT evaluation obtained, especially oblique and axis views, can yield a wider variety of results.[17, 18)] In our study, the Cavalieri method applied with a stereologic point-counting technique can be used in the determination of tumor volume. Our results showed that the values obtained in this way are reliable and reproducible. Moreover, the Cavalieri approach could be easily applied without altering routine radiologic imaging techniques and the data obtained show little interobserver variation.[17–20)] The use of this method allows a 3-D probe to explore the lesion surface as a spatial grid. This is because essentially a spatial grid is a regular system of test lines in three dimensions with a known length per unit volume of space, L/U cm/cm^3, and we can assume that a surface of unknown finite areas is hit by a spatial grid uniformly at random with isotropic orientation. The Cavalieri method is inherently efficient and has been shown to be unbiased when applied invivo. This estimation of tumor volume using a mathematical equation that allows the transformation from percentage carcinoma to cubic centimeters of tumor seems to be a relatively easy method and requires only minimal extra time.

Besides the given advantages of the Cavalieri principle, stereologic methods provide data to researchers for making appropriate changes in the sampling or estimating procedures. Therefore the method presented here supplies a CE of measurements with each volume, giving a percentage of the potential variability in any given volume measurement. When the CE of these measurements is large, it can generate obvious problems in accuracy and hence interpretation. These problems may arise if too few slices or too few points are taken into account. The observer is able to change the spacing of points in the grid or the number of slices available in any CT study to obtain a reasonable coefficient of error value.[17, 21)]

The given values of the tumor volumes are un-

biased since the first slice hits the lesions randomly, followed by systematic sections with a known, fixed interval. The point counting is unbiased, since the set of systematic points is placed randomly on the radiologic images.[18] However, there may be some bias sources for the estimation of mesothelioma volume using the CT technique. The most important factor that must be taken into consideration is thoracic motion due to respiration during scanning and partial voluming artifacts. To manage this problem, each cross-sectional CT scan should be taken during the inspiration phase, and the accuracy of the present method depends on the same inspiratory effort to relocate the structures exactly as in the previous scan.[17]

Mesothelioma, like other types of chest lesions, has an ellipsoidal shape. We believe that a better, fault-free result is obtained using the Cavalieri method in the evaluation of the response to chemotherapy in a tumor volume obtained posttreatment, when changes in the location of the lesion are noted from the same dimensions.[14] Mesothelioma undergoes local progression without metastases until late in the stage of the disease. In this study, tumor volume revealed the presence of nodules while a significant degree of increment was observed. This result is consistent with findings reported by Pass *et al.*[16] The most difficult diagnosis is the definite presence of a nodule using classic methods. The presence of nodules is revealed during phase III of the IMIG phases. In addition to this, a clear increase in phase III tumor volume resulted.

The repsonse to chemotherapy evaluated using the classic method prior to treatment did not reveal significant differences in tumor volume, while it was again observed that the posttreatment patients with an evaluated OR demonstrated an increase in tumor volume.

The main aim of our study was to determine the relation between tumor volume after treatment and prognosis. A cut-off value can be significant in evaluation of prognosis. However, a cut-off value in the serial quantitative determination of tumor volume is difficult to evaluate during the final stages of the illness. Many more studies need to be carried out in the future.

In our study, we observed an important reduction in tumor volumes from diagnosis to the posttreatment period. We found that patients with the shortest period between initial diagnosis of a tumor volume of 200 mm^3 or greater had postchemotherapy increases in volume of more than 50 mm^3. Mesothelioma a tumor that does not respond readily to chemotherapy. Because of this, although tumor volume decreases, no significant difference is seen in terms of survival time.

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