

Volumetry – an alternative to assess therapy response for malignant pleural mesothelioma?

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Original research

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Abstract

Purpose: The purpose of this study was to assess robustness of volumetric measurement of malignant pleural mesothelioma (MPM) before and after chemotherapy to modified RECIST.

Method: Thirty patients with digitally available chest CT scan before and after 3 cycles of chemotherapy were included. Three readers assessed independently tumor response using two different methods: Modified RECIST criteria and tumor volumetric approach using dedicated software (Myrian, Intrasense, France).

Inter-rater reliability of uni-dimensional and volumetric measurements was assessed using intraclass correlation. Tumor response classification for modified RECIST was compared to volumetric approach applying uni-dimensional RECIST volumetric equivalent criteria.

Results: The determination of uni-dimensional tumor measurement (RECIST) revealed a low inter-rater reliability (0.55) and a low interobserver agreement for tumor response classification (general kappa 0.33). Only 14 patients were classified equally.

A high inter-rater reliability (0.99) and interobserver agreement (general kappa 0.9)) was found for absolute tumor volumes (volumetric measurements). 27 cases were classified equally.

The number of cases classified as “stable disease” was higher for volumetric approach using tumor equivalent criteria compared to modified RECIST.

Conclusion: Volumetric measurement of MPM on CT-scan using Myrian software is a reliable, reproducible and sensitive method to measure tumor volume and hence therapy response after induction chemotherapy.

Keywords:

Malignant pleural mesothelioma; Computed tomography; volumetry; Induction chemotherapy; RECIST; therapy response;

Introduction

Although survival rates for patients with MPM are still very low, improving outcome is observed after multimodality therapy including platinum-based chemotherapy (1). To assess tumor volume per se as a prognostic marker for overall survival (2) and its response to chemotherapy, adequate methods are necessary. Nowadays there is no satisfying “gold standard” technique for tumor measurement in MPM. The reason for this is the irregular “rind-like” growth of the pleural mesothelioma providing major challenges for adequate tumor assessment. The World Health Organization (WHO) has introduced the bi-dimensional response criteria for tumors in general (3). This method has been used for many years, but was insufficient for some patients and did not suit well to the growth pattern of MPM. During the last years the uni-dimensional response criteria based on RECIST (Response Evaluation Criteria in Solid Tumor) have been suggested and investigated to evaluate the response to treatment in solid tumors (4). Modified RECIST criteria developed by Byrne and Nowak respect additionally the rind-like growth of the tumor (5) and has become the standard for MPM, despite the method not only showed a high inter-observer variability, but also an over-classification of tumors according to theoretical studies (6, 7).

Today volumetry gains more and more importance to assess tumor volume (8-12). For liver surgery volumetry is a well established method for the measurement of tumor size before liver surgery in order to decide whether the remaining liver volume will be sufficient (11, 12). Dedicated software is necessary to measure the tumor volume on cross-section images by using a segmentation technique. Although many programs focus on hepatic measurements, they can easily be used for other tumors as for example MPM. Preliminary studies using volumetry for MPM show promising results (2, 13-15).

The aim of this study was to compare the volumetric approach to the measurements assessed by modified RECIST concerning the interobserver reliability and tumor response after induction chemotherapy.

Patients and Methods

Patient Selection

Digitally available chest CT scans obtained before and after chemotherapy of 30 patients with biopsy-proven MPM in stage cT1-3 cN0-2 cM0 including all histological subtypes considered for a multimodality approach at the Department of Medical Oncology and the Division of Thoracic Surgery of the University Hospital Zurich during the time period from May 1999 until January 2008 were retrospectively analyzed. The study was proven by the local ethical committee. Informed consent was obtained.

All patients were treated with induction chemotherapy followed by extrapleural pneumonectomy (EPP). Neoadjuvant chemotherapy consisted of three cycles of cisplatin and gemcitabine or since March 2003 of cisplatin and pemetrexed with vitamin supplementation. Neoadjuvant chemotherapy consisted of three cycles of cisplatin 80 mg/m² day 1 and gemcitabine 1000 mg/m² on days 1, 8 and 15 administered every 28 days or since March 2003 of cisplatin 80 mg/m² day 1 and pemetrexed 500 mg/m² on day 1 administered every 21 days with vitamin supplementation.

Computed tomography (CT) imaging

For the underlying analysis only patients with digitally available computed tomography (CT) imaging data were included. Pre- and post-chemotherapy chest CT

images were available for 30 patients (median age: 60y (range 48 - 71y); female n = 2; male n = 28). One out of three different CT scanners: GE LightSpeed VCT (GE Health Systems, Milwaukee, WI), Siemens Somatom Sensation and Definition (Siemens, Erlangen, Germany) were used. 22 patients received intravenous iodinated contrast agent on both exams. (120 mL Iodixanol (270 mg iodine per mL, Visipaque; Amersham Health, Buckinghamshire, England). The scan delay after starting contrast material injection was 30 sec (n=13) and 60 sec (n=9). 8 patients did not receive contrast agent on the pre-chemotherapy chest CT, as the scan was used for positron-emissions-tomography fusion.

The mean time delay between the pre- and post-chemotherapeutic CT was 100 days (SD \pm 13.5 days). The slice thickness ranged between 2 mm and 3.75 mm, whereas in 19 cases pre- and post-chemotherapeutic CT had identical slice thickness.

All data were stored on internal PACS (picture archiving and communication system) and sent to a dedicated workstation for tumor volumetry.

Imaging analysis

Modified RECIST criteria

Response to chemotherapy was evaluated by modified RECIST criteria and tumor volumetry (5). Three readers performed imaging analysis independently (one thoracic surgeon in training (M.T. 3 years of experience), two radiologists (R.P.G. 2 years and T.F. 10 years of experience). Modified RECIST criteria were assessed using a dedicated film reading workstation (Impax 5.2, AGFA, Germany). Both, pre- and post-chemotherapeutic CT images were available simultaneously on two screens and could be linked by each reader individually at the same anatomical position. The thickness of the tumor was measured perpendicular to the chest wall and mediastinum at two positions on three different levels with a minimal craniocaudal

distance of 1 cm according the modified RECIST criteria (5) (**Figure 1**). The images were stored locally, but not visible for the other readers.

Volumetric approach

All three readers measured independently the tumor volume using dedicated software, featuring semiautomatically segmentation with linear interpolation, allowing manual adjustments if necessary (Myrian, Intrasure, France). Although this software was previously developed for liver segmentation and volumetry, it can easily be used also for other types of volumetries as the linear interpolation segmentation algorithm is not liver specific.

The segmentation and tumour volume quantification consisted of the following steps:

(1) The normal lung tissue including the bronchi and vessels was marked semiautomatically by thresholding and region growing. (2) Pleural effusion and atelectatic lung were marked with a magnetic lasso function. (3) After fixing normal lung tissue, pleural effusion and atelectatic lung, the outer part of the pleura was segmented semiautomatically. Manual interaction could be reduced by segmentating only every fourth to fifth slice. Interpolation between the marked slices was performed automatically using a linear algorithm (**Figure 2**). The sum of the voxels included in the segmented tumour multiplied by the voxel volume led to the volume. The value of the resulting volume was saved as screenshots to the PACS system.

The time needed to apply modified RECIST and volumetric measurement including eventually editing was approximately 3 min and 10 to 15 min per case, respectively.

Analysis of data

The sum of all measurements based on modified RECIST and the tumor volume after chemotherapy was subtracted from the sum and tumor volume before chemotherapy. The results were divided by the volume before chemotherapy and multiplied by 100. Thus, the percent change of measurements according modified RECIST and total tumor volume was computed.

For volumetry volume equivalent criteria of spherical tumors was applied.

Progressive disease (PD) corresponded to >73% increase of tumor volume. Partial response (PR) was defined as >65% decrease of volume, and stable disease (SD) as a change between -65% and +73%. This definition reflects a spherical growth, which was already suggested by Oxnard et al. (6, 7).

A kappa-statistic was used to assess agreement of tumor response classification between readers. Inter-rater agreement was considered as poor, $\kappa \leq 0.2$; fair, $\kappa = 0.21 - 0.4$; moderate, $\kappa = 0.41 - 0.6$; good, $\kappa = 0.61 - 0.8$; excellent, $\kappa = 0.81 - 1.0$ (16).

Inter-rater reliability of uni-dimensional and volumetric measurements for absolute values was assessed using intraclass correlation in an analysis of variance with random factors patient and reader. Inter-rater reliability is the ratio of the patient variance component and the sum of all variance components (17). Wilcoxon signed rank test was used to compare absolute measurements between readers. A p-value of less than 0.05 was considered to indicate statistical significance. Inter-rater agreement of the absolute measurements was assessed using Bland Altman analysis. The differences in measurements according modified RECIST was correlated to the third root of total tumor volume change using Pearson correlation. All statistical analysis was performed using dedicated software (SPSS for Mac, version 13.0, SPSS, Chicago IL, USA and Microsoft Excel 2003, Microsoft,

Redmond, Washington, USA including Analyse-it, version 2.12, Analyse-it software,
Leeds, UK).

Results

Between 1999 until January 2009, 159 patients were enrolled with the intent to treat with induction chemotherapy followed by EPP. From 30 patients (n=2: cisplatin + gemcitabine; n=28: cisplatin + pemetrexed) pre- and post-chemotherapy digitally computed tomography scans were available for this analysis.

Modified RECIST criteria

Figure 3a demonstrates the classification according to modified RECIST by the three readers. In 14 of 30 cases were identically classified into PD, SD or PR using modified RECIST criteria. In 16 cases there was a mismatch. In 15 cases of mismatch, one reader classified the patients different to the other two readers. In one case, all three readers classified tumor response differently. There was no systematic bias visible. The general kappa value was 0.33 between the 3 readers meaning a moderate inter-rater agreement concerning tumor response (**Table 1**).

Comparing absolute values (cm) of tumor response for modified RECIST criteria between each reader no significant differences were found ($p \geq 0.47$). Intraclass correlation coefficient was 0.55, indicating a poor correlation of tumor response between all three readers (**Table 1, Figure 4a**).

Bland-Altman analysis for testing the degree of agreement between the three readers for tumor response revealed minimal mean differences (**Table 1, Figure 4b**). The limits of agreement were wide compared to the maximal difference between pre- and post-chemotherapeutic measurements (reader 1: 5.05 cm; reader 2: 4.14 cm; reader 3: 6.41 cm), reflecting the poor agreement.

Tumor Volumetry

Figure 3b shows no mismatch classifying the tumor response according to volumetric approach with volumetric software when using volume equivalent criteria by the three readers. This result led to a high general kappa value of 0.89 between the 3 readers indicating an excellent inter-rater agreement concerning tumor response (**Table 1**).

The volumetric measured tumor response did not show significant difference between all three readers ($p \geq 0.42$). Intraclass correlation coefficient for volumetric tumor response was 0.99 between all three readers, indicating a very close agreement between the measured volumes of all three readers (**Table 1, Figure 5a**).

Bland-Altman analysis for testing the degree of agreement of tumor response between the three readers revealed small mean differences (≤ 66 mL), indicating a good correlation between the readers (**Table 1, Figure 5b**). The maximal changes in tumor volume were 560 mL for reader 1, 557 mL for reader 2 and 567 mL for reader 3.

Comparison of modified RECIST to volumetric tumor response

The Pearson correlation of the measured changes according modified RECIST and volumetry was 0.57 for reader 1 ($p=0.0009$), 0.67 for reader 2 ($p<0.0001$) and 0.45 for reader 3 ($p=0.0129$), indicating a moderate correlation.

In 8 cases (reader 1), 9 cases (reader 2) and 7 cases (reader 3) the tumor response was contrary comparing the changes based on modified RECIST to the percentage change based on volumetry.

When classifying the tumor response according to modified RECIST and volume equivalent criteria a large number of cases, classified as “partial response” and

“stable disease” on modified RECIST would have been classified as “stable disease” and “progressive disease” on volumetric approach.

Discussion

The results of the present study show a high intraclass correlation and interobserver agreement for the absolute measured tumor volumes by specialized software. Our results indicate that volumetry is highly reliable, reproducible and reader independent compared to modified RECIST and hence useful for the assessment of chemotherapy response by using volumetric measurement in CT scans.

The radiological evaluation of therapy response to chemotherapy during treatment of MPM is challenging due to the special rind-like growth pattern of the tumor. But also other features including the involvement of multiple thoracic levels, separate nodular or pleural thickening, growth along fissures, and accompanying atelectasis, pleural fluid and fibrosis make the accurate assessment of this special tumor difficult (18). As the WHO and RECIST criteria could not be used for the distinct growth pattern of MPM, Byrne et al. introduced modified RECIST criteria (5). This method was specifically developed for better assessment of changes in pleural mesothelioma, measuring the tumor uni-dimensionally at two sites in three different levels on axial cross-section images (5). This method has the drawback that the position of tumor measurement can be chosen randomly by each reader, which leads to a large intra- and interobserver variability (6, 7).

Volumetry has gained a wide interest and acceptance for preoperative assessment of liver volume in cases of living-liver donor transplantation. Additionally there are several studies using volumetric evaluation of tumor response for different kind of tumors, e.g. liver metastases, lung nodules or lymph nodes (8-10, 12). These studies showed a low intra- and interobserver variability for tumor volumetry.

There are also some reports about the use of a volumetry approach for MPM (2, 7, 13-15). The volumetric approach was used for two different types of outcome study. Pass et al.(2) and Lee et al.(15) primarily focused on the potential of prognostic

information for overall survival from the preoperative or pretherapeutic determined volume. The other studies as well as the present one investigated the volumetry approach to assess tumor response after chemotherapy (7, 13, 14). All these studies have small numbers of patients (max n = 55; Ak et al.(13)). Therefore, no references or standards in terms of PD, SD, or PR are defined using tumor volumetry measurement. For modified RECIST criteria tumor response is defined as 30% decrease for PR and 20% increase for PD. Alternative response criteria for a typical spherical tumor model are 65% volume decreases for PR and 73% volume increase for PD. This alternative response criterion can be adopted for MPM, but is not suited for volumetric approach (7, 13). The reason for is the wide range of SD classification. Although this would not be a limitation per se, it diminishes the values of volumetry, which has the capability to already discriminate even minimal changes of volume. Ak et al. retrospectively defined a $\geq 15\%$ increase in tumor volume as progressive disease and a $\geq 50\%$ decrease in tumor volume as partial response based on the overall survival time (13). But the patients analyzed did not receive a standardized chemotherapy and pre- and post CT-scan interval are not known. Therefore a direct comparison with our results is not possible. Plathow et al. did not find a difference between modified RECIST and volumetric approach using modified RECIST equivalent criteria (14). This finding corresponds to our results, as in both studies the changes in classification were equal.

Different methods were used for tumor calculation, like the Cavalieri principle, which is a point-count method (13) model-based tumor volumetry (7) or voxel-based volumetry (2, 14). The software used in our study is a voxel-based volumetry, whereas the voxel size was less than 3mm^3 .

We acknowledge the following limitations: As for volumetry all image data had to be available digitally, our study only includes a small number of patients. Therefore the determination standard of references for volumetric response is not possible.

To perform volumetry accurately the source data should allow a clear discrimination of the different structures, like the atelectatic lung, pleural fluid, tumor and lymph nodes. Although different CT scan techniques were used (with or without contrast material and different delay for contrast material injections) might be another limitation of the study, it did not influence the results, as the tumor could be delineated on all CT scans. Nevertheless the reduced differentiation required additional manual interaction. On delayed phase (about 120 sec after I.V. contrast material injection) contrast CT different entities can be distinguished best, allowing a fast and accurate tumor volumetry. Based on this experience, we changed our scanning protocol for patients with MPM, performing only a chest CT-scan with a delay of 120 sec after starting i.v. contrast material injection.

Tumor volumetry is still more time-consuming since 10 to 15 min per reading is necessary. This is especially demanding if numerous manual adjustments have to be done. New segmentation algorithms (e.g. object-based segmentation) may enhance semiautomatic segmentation. Using the interpolation algorithm there might be tiny marking errors on some slices, but they do not significantly influence the result as shown by the high inter-rater correlation.

In conclusion tumor volumetry is according to our results a reproducible and reliable method to show small tumor changes, having a high interobserver agreement compared to modified RECIST criteria. We will continue to validate prospectively the value of tumor volumetry to determine chemotherapy response criteria correlating best with survival data.

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Table

Table 1: Intraclass correlation and Bland Altman Analysis of absolute values for modified RECIST and volumetric approach

			Reader 1 vs. 2	Reader 1 vs. 3	Reader 2 vs. 3
Modified RECIST [cm]	Intraclass correlation coefficient		0.571	0.584	0.479
	Bland-Altman Analysis	Bias	-0.4 cm	-0.14 cm	0.26 cm
		95% CI	-0.99 to 0.19 cm	-0.78 to 0.51 cm	-0.38 to 0.91 cm
		95% Limits of Agreement	-3.53 to 2.73 cm	-3.51 to 3.24 cm	-3.12 to 3.65 cm
Volumetric approach [mL]	Intraclass correlation coefficient		0.995	0.998	0.995
	Bland-Altman Analysis	Bias	- 2.79 mL	-2.46 mL	-0.32 mL
		95% CI	-11.7 to 6.12 mL	-8.52 to 5.39 mL	-9.31 to 9.95 mL
		95% Limits of Agreement	-49 to 43 mL	-34 to 29 mL	-50 to 50 mL

Table 2: Comparison of response between modified RECIST criteria and volumetric approach.

		<i>Volumetric response based on tumor equivalent volume</i>		
		Partial response	Stable disease	Progressive disease
<i>Modified RECIST</i>	Partial response	2/2/1	4/5/4	2/0/2
	Stable disease	0/0/1	14/13/13	2/7/1
	Progressive disease	0/0/0	2/2/4	4/1/4

Figure legend

Figure 1

Measurement of MPM according modified RECIST criteria.

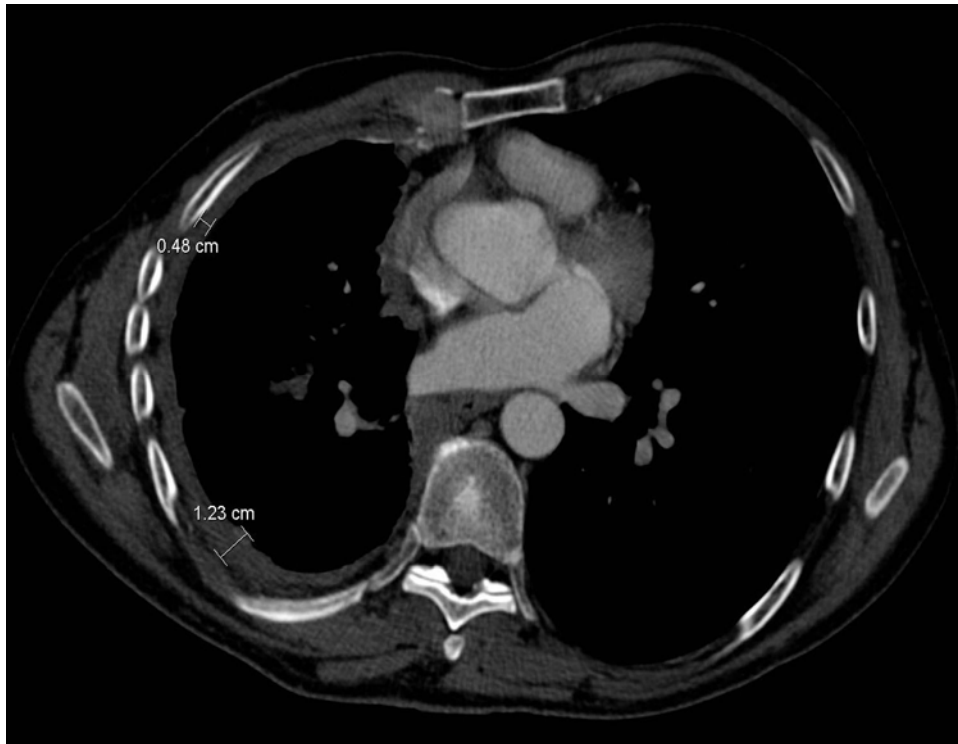


Figure 2

Volumetry of MPM: Figure 2a shows the marked tumor (blue) on a single CT-slice.

Figure 2b shows the entire tumor volume (blue).

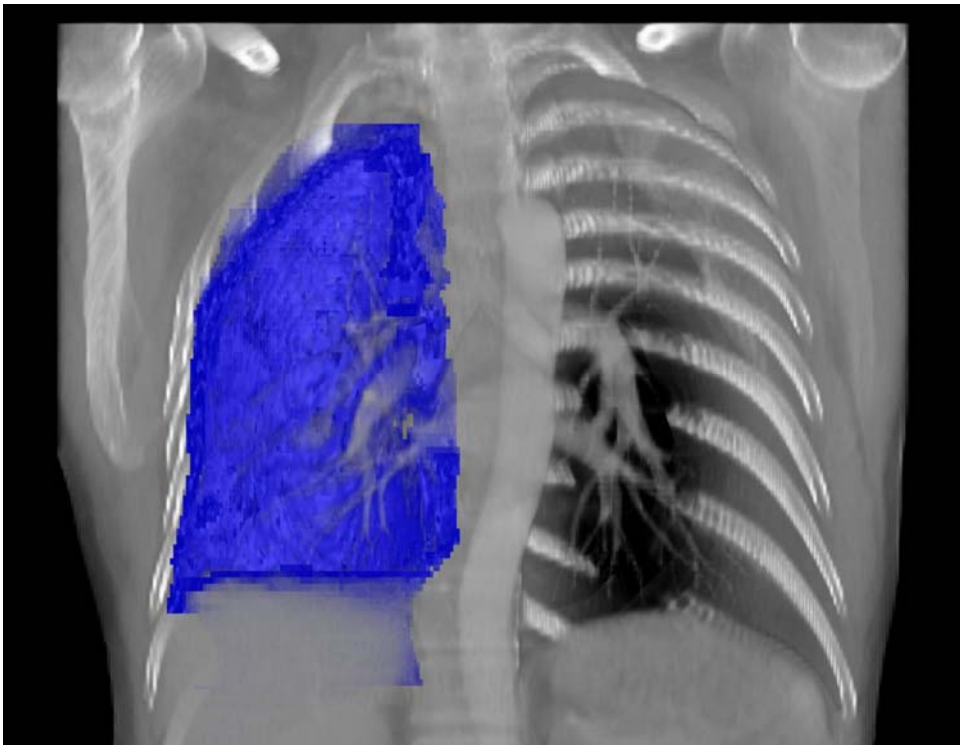
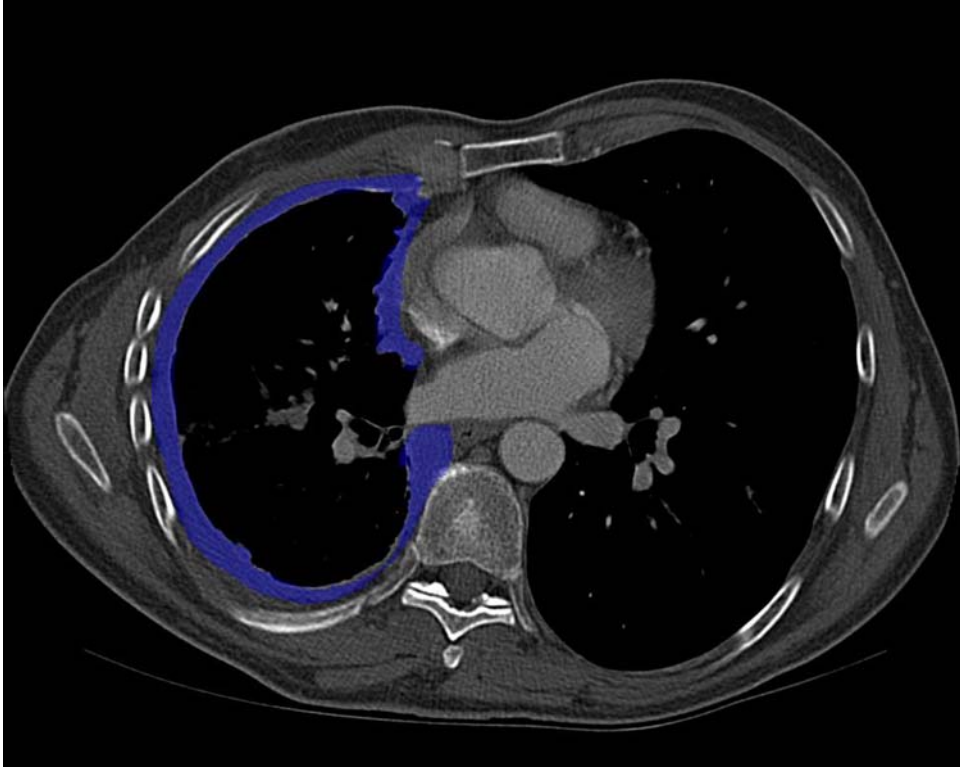


Figure 3

Interobserver distribution of cases according the classification PR, SD and PD for modified RECIST (**Figure 3a**), and tumor volumetry applying volume equivalent criteria (**Figure 3b**).

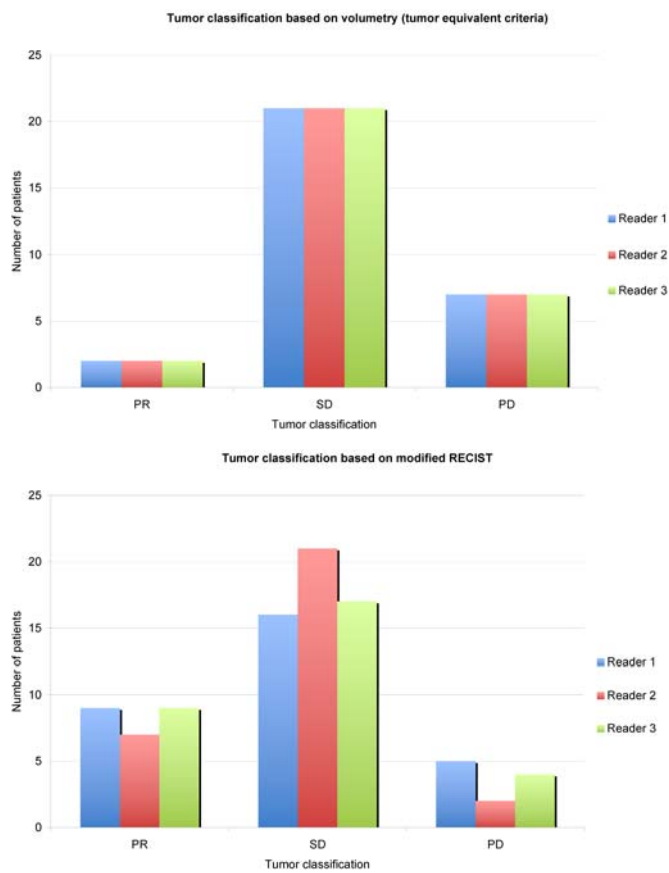


Figure 4a

Figure 4a depicts a poor correlation of absolute tumor response values (pre- minus postchemotherapeutic measurements) between reader 1 and 3 for modified RECIST based tumor measurements. The intraclass correlation coefficient was 0.584.

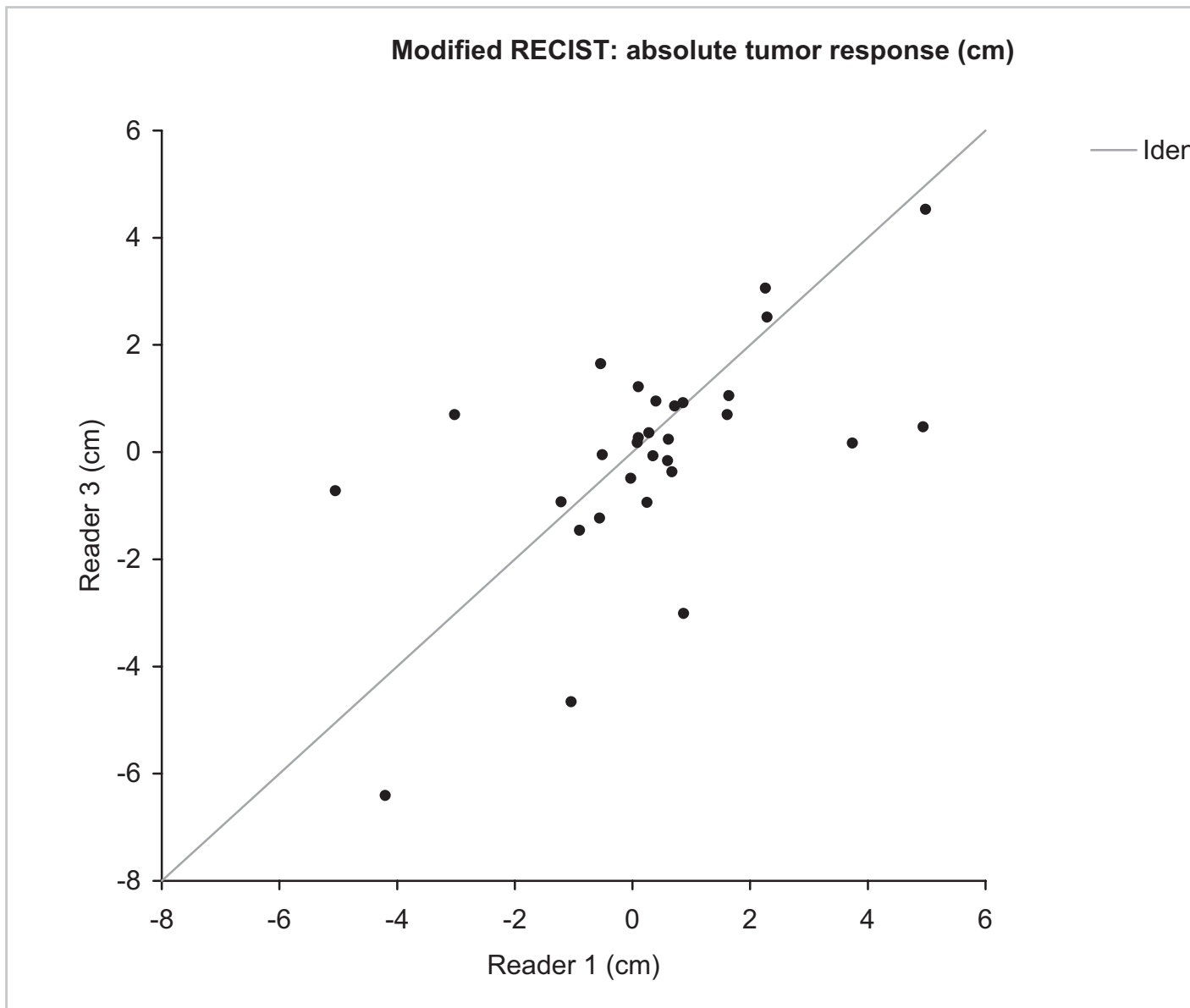
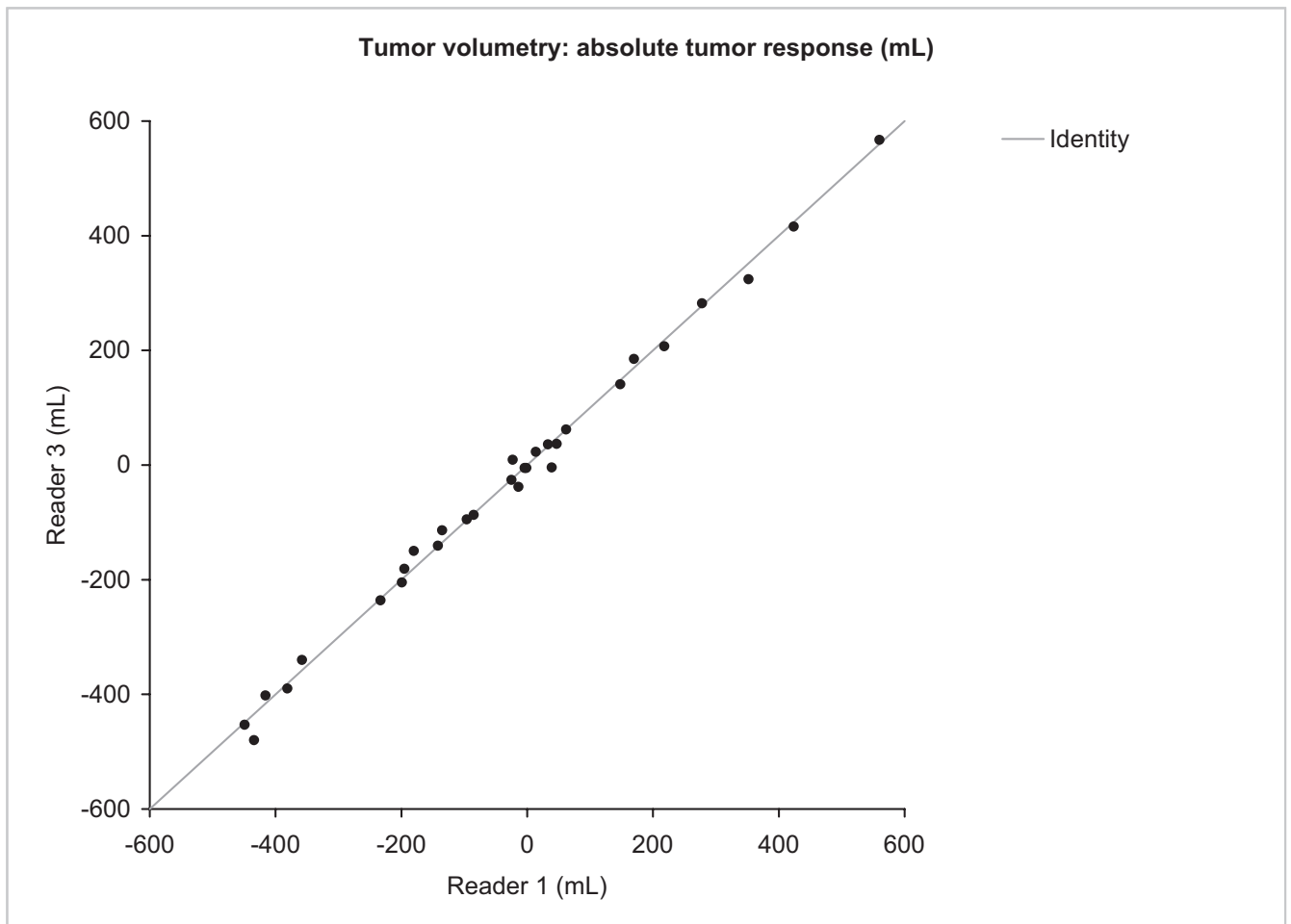


Figure 4b



Bland-Altman plot for modified RECIST shows a broad bandwidth of the 95% limits of agreement for the differences between Reader 1 and 3 compared to the mean values, indicating a poor agreement.

Figure 5a

Figure 5a depicts an excellent correlation of absolute values (pre- minus postchemotherapeutic measurements) between reader 1 and 3 for volumetric tumor measurements. The intraclass correlation coefficient was 0.998.

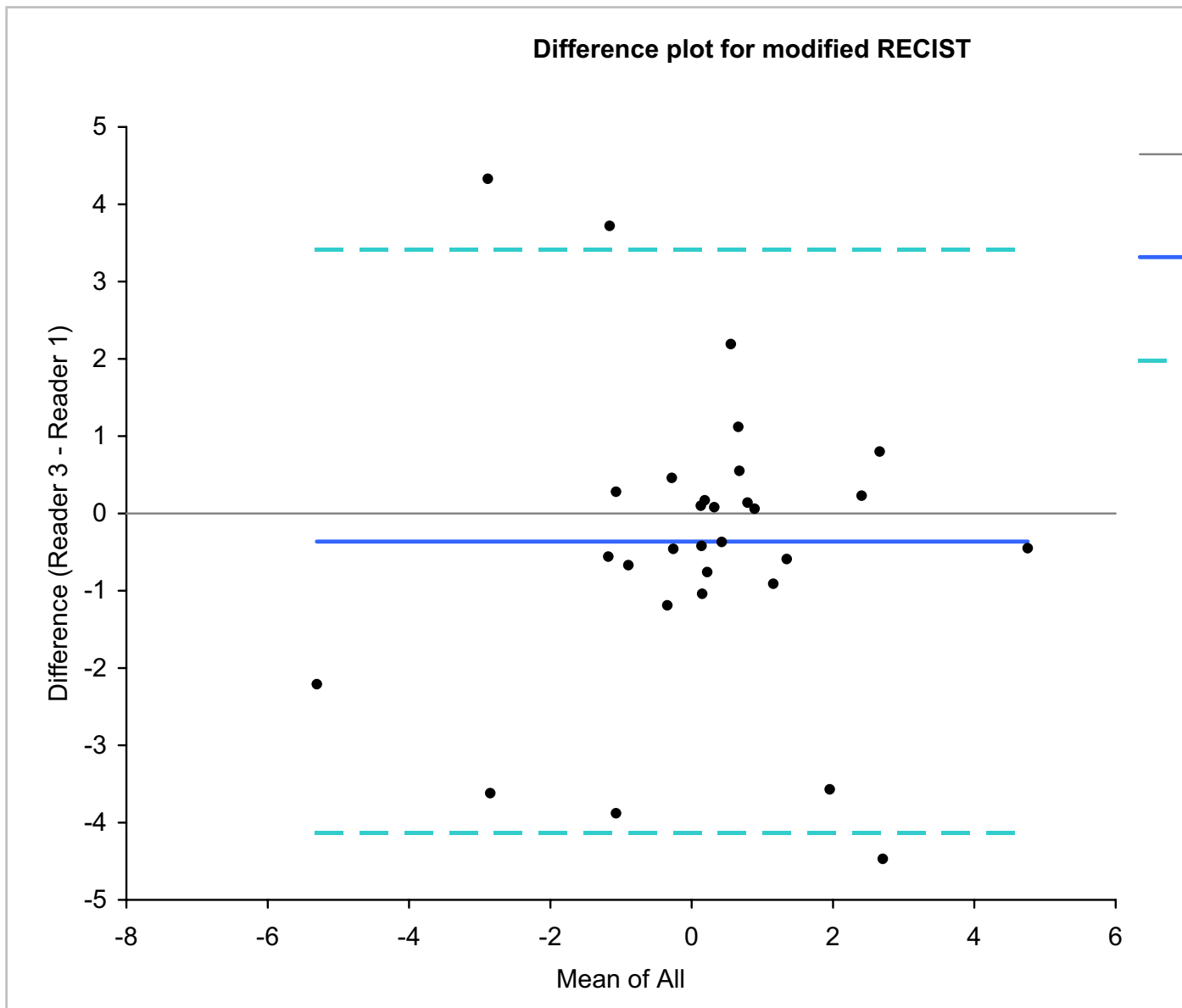


Figure 5b

Bland-Altman plot for tumor volumetry shows a small bandwidth of the 95% limits of agreement for the differences between Reader 1 and 3 compared to the mean values, indicating an excellent agreement.

