Role of CT using modified Response Evaluation Criteria in Solid Tumors (RECIST criteria) in evaluation of malignant pleural mesothelioma

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ABSTRACT

Background: Malignant pleural mesothelioma is a rare and aggressive tumor that the growth pattern of it poses unique difficulties in measurement and response assessment. however, robust and reproducible assessment of response is critically important in the conduct, interpretation, and reporting of clinical trials.

Objectives: The aim of this study is to assess the value of CT and modified RECIST criteria in follow up patients of malignant pleural mesothelioma patient during treatment with chemotherapy.

Patients and methods: We evaluated 20 malignant pleural mesothelioma patients undergoing to chemotherapy. Tumor thickness is measures perpendicular to the chest wall or mediastinum in two positions at three separate levels on thoracic CT scans. The sum of the six measurements defined a pleural unidimensional measure. A reduction of at least 30% on two occasions 6 weeks apart defined a partial response; an increase of 20% over the nadir measurement known as progressive disease. Patients who fulfilled the criteria for neither PR nor PD called CD. The validity of the modified criteria was gauged by clinical evaluation.

Results: In our study, CT and modified RECIST criteria were used as the method of choice in response evaluation of malignant pleural mesothelioma. Our study showed as follow up results of each group and comparison between clinical evaluation and modified RECIST criteria show over all accuracy 73.3% with P value = 0.03 and these results confirm accuracy of CT with modified RECIST criteria as good predictor of disease outcome.

Conclusion: These Modified RECIST criteria for tumor response correlate with clinical evaluation and can be used to measure outcome in pleural mesothelioma.

Key words: malignant pleural mesothelioma, CT, modified RECIST criteria, response therapy.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an infrequent neoplasm. However, it is the most common primary pleural malignancy [**1**].

It is considered a locally aggressive neoplasm that originate in the serosal membrane that lines the thoracic cavity which causing chest wall, mediastinum invasion as well as diaphragm [**2**]. The Malignant pleural mesothelioma has become an important health issue over recent years since the incidence of malignant pleural mesothelioma has risen for some decades with its peak between 2010 and 2020 due to occupational exposure patterns [**3**].

The malignant mesothelioma has strong association with asbestos exposure. So those employed in manufacturing and industrial use of asbestos and those remotely connected with asbestos or living near asbestos plants are at risk of developing

mesothelioma. however, reports suggest that mesothelioma developed secondary to radiotherapy also genetic factors may play an important role in developing malignant pleural mesothelioma [4].

The prognosis is poor, with average survival time of 1 year after diagnosis. many factors have been shown to correlate with reduced survival time like intrathoracic lymph node involving, extensive pleural involvement and distant metastatic disease [5].

Radiological imaging plays an important role in diagnosis, staging, treatment planning, assess treatment response and patient's follow-up. Several modalities are available including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and PET/CT. CT scan is the primary imaging modality used as it has the ability to provide anatomical details of both normal and abnormal structures also as it relatively low cost and wide availability [6].

CT key findings that suggest MPM include nodular pleural thickening, unilateral pleural effusion and interlobar fissure thickening. Growth typically leads to lung encasement by the tumor that as ring-like [5].

Most patients with malignant pleural mesothelioma are candidates for chemotherapy during the course of their disease. To assess the response based on conventional CT criteria and its measurements is considered challenging due to the circumferential and axial growth pattern of MPM. Such difficulties discourage an accurate clinical study results evaluation and make the clinical management of patients critical. Several radiological response systems have been proposed, but neither WHO criteria nor the recent RECIST criteria (unidimensional) nor hybrid criteria (unidimensional and bi-

dimensional) seem to apply to tumor measurement in this disease. Recently, modified Response Evaluation Criteria in Solid Tumors for malignant pleural mesothelioma have been published [7].

A comprehensive update of tumor assessment (RECIST 1.1) introduce a new concepts such as revised smallest lymphadenopathy diameter non-measurable lesions approach and taking in consideration the added recommendations from RECIST 1.1 including: minimally measurable and measurable lesions definition, non-pleural disease considerations, non-measurable pleural disease characterization, pathological lymph nodes definition, and bilateral pleural disease accommodations [8].

The current clinical method for assessment malignant mesothelioma tumor response is the modified Response Evaluation Criteria in Solid Tumors (m RECIST) guidelines, which based on two linear measurements of tumor thickness to be summed from each of three axial sections in CT scans. To classify patients according to response categories, progressive disease (PD) defined as summed measurement increase between scans larger than 20%, partial response (PR) defined as summed measurement decrease of 30% or more, and stable disease (SD) is any measurement change between −30% and +20% [9].

AIM OF THE WORK

To study the correlation between the percent change in tumor burden using modified RECIST criteria, as depicted by CT, and overall survival and clinical evaluation of patients during chemotherapy.

PATIENTS AND METHODS

I- Patients

This 9 months retrospective study involved 20 pathologically proven mesothelioma patients: 10 males (50.0%) and 10 females (50.0%), age range 39-67 years (average of 55.45years). Most of patients presented with chest pain and dyspnea. The patients were referred to the diagnostic radiology department at Al-Demerdash hospital from the medical or surgical oncology clinic at AL-Demerdash hospital between May 2018 and February 2019 for base line and follow up CT chest examination.

Inclusion criteria of patient selection includes patients presented clinically with progressive chest symptoms with radiological pleural thickness on spiral CT scan and pathologically proven MPM of biopsied plural sample and still didn't start any kind of treatment, any patients started treatment will be excluded from the study. Contrast enhanced chest CT scans were performed in all patients prior to the first cycle of chemotherapy, and then before the third and sixth cycles.

Clinical correlation of the mRECIST results with patient general condition and clinical response to individually designed chemotherapy regimen was done after contact the referring physician, that is considered as reliable comparative parameter.

II- Methods

All patients were subjected to:

1. History taking and clinical examination (general and chest examination).
2. Laboratory investigations: mostly complete blood picture, bleeding profile, and kidney function test
3. Plain chest radiograph in PA view.
4. Contrast enhanced CT scan of the chest using a GE OPTIMA 66SE MSCT 64CT scanner in Al-

Demerdash hospital where axial cuts were obtained with additional sagittal and coronal reconstruction images.

A- Patient Preparation;

A full history was obtained from all patients, including the following points: personal history (e.g, age, sex, and residence), present history (e.g, main complaint, any accompanying disease, histopathology, and prior radiological studies) & past history of asbestos exposure or radiation treatment.

All patients were asked for 6 h fasting prior the scan. The patient take off all metallic items, including pants with zipper, bra, belts, bracelets, etc, and the patient was given disposable gown to wear. In patient's arm a suitable I.V. cannula size was inserted with 5 ml saline injection to ensure patency.

B- Patient position:

At the end of the waiting time, the patient was asked to void, then she/he was placed in the supine position with arms up. the head first entry direction.

Table (1): Contrast enhanced multislice CT technique parameters in Al Demerdash Hospital .

GE OPTIMA 66SE MSCT 64CT scanner	
Scout	Kv 110 , mA 25, Holding breath
Scan type	Helical
Detector raw	4
Helical thickness	1.0 mm
Interval	1.0 cm
FOV	351 mm
Kv	110
Ma	25
Total exposure	0.8 sec
Contrast	Non ionic contrast, iodine, conc.350, 40-50 ml 3ml/sec,pressure 250
Fasting 6 hours before the examination	

III- CT reviewing with measurement using mRECIST criteria

The modified RECIST criteria that we follow are consistent of:

- Measuring of tumor thickness perpendicular to the chest wall or mediastinum in two positions at three fixed levels on axial cuts of the CT chest.
- The sum of the six measurements was defined as a unidimensional pleural measurement.
- Transverse cuts (at least one cm apart) related to anatomical landmarks in the thorax were chosen to allow reproducible assessment at later time points.
- At 2nd (before third cycle of chemotherapy) and 3rd (before sixth cycle of chemotherapy) reassessment, the same patient preparation and CT protocol had performed, pleural thickness was measured at exactly the previous position and at the same level and by the same observer. This was not necessarily the greatest tumor thickness at that time.
- In addition, Nodal, subcutaneous, and other bi-dimensionally measurable lesions were measured uni-dimensionally and added to obtain the total tumor measurement as per the RECIST criteria.

To categorize the patient response after three, follow up the Complete response (CR) was defined as all target lesions disappearance with no evidence of tumor elsewhere, and partial response (PR) was defined as at least a 30% reduction in the total tumor measurement. Progressive disease (PD) was defined as an increase of at least 20% in the total tumor measurement

over the nadir measurement, or the appearance of one or more new lesions. Patients with stable disease (SD) were those who fulfilled the criteria for neither PR nor PD. A confirmed response required a repeat clinician observation on two occasions 4 weeks apart.

RESULTS

This was retrospective study conducted at the diagnostic radiology department Al-Demerdash hospital in the period between May 2018 and February 2019 on a total of 20 pathologically proven mesothelioma patients.

This study had 10 males and 10 females showing no gender predominance. Table 2 shows the age groups between the studied patients. Their mean age group was 55.45.

Table (2): Age groups of the studied patients

		No. = 20
Sex	**Females**	10 (50.0%)
	Males	10 (50.0%)
Age (years)	**Mean ± SD**	55.45 ± 8.04
	Range	39 – 67

Table (3): Geographic distribution among the studied patients.

	Shobra el kheima	Helwan	Elsharqya	Others
Number	5	6	2	7
Percentage	25%	30%	10%	35%

Most cases (65%) lived or worked in industrial areas (Shobra Elkeima, Helwan, and Elshargya).

Table (4): change of tumor size among the studied patients.

tumor size	No. = 20
Median (IQR)	-13 (-36 - 15.4)
Range	-81.2 - 82.4
Increased	11 (55.0%)
Decreased	9 (45.0%)

About 55% of the cases in this study showed an increase in total tumor size in comparison to baseline tumor size , while the percentage of patients with a decrease in total tumor size represent 45 %.

Table (5 & 6): show the classification of patients as assessed by the CT and mRECIST criteria, followed by the table with their clinical correlation:

	CR	PD	SD	PR
Number	0	5	8	7
Percentage	0%	25%	40%	35%

classification by CT	Clinical examination			Test value	P-value	Sig.
	PD	SD	PR			
	No. = 7	No. = 5	No. = 8			
Progressive disease (PD)	3 (42.9%)	1 (20.0%)	1 (12.5%)			
Stable disease (SD)	4 (57.1%)	3 (60.0%)	1 (12.5%)	10.398	0.034	S[*]
Partial response (PR)	0 (0.0%)	1 (20.0%)	6 (75.0%)			

*statistically significant

Table (7): Relationship between findings by CT and clinical examination

Response by CT	Clinical examination		Test value	P-value	Sig.
	Non responders	Responders			
	No. = 12	No. = 8			
Non responders	11 (91.7%)	2 (25.0%)	9.377	0.002	HS
Responders	1 (8.3%)	6 (75.0%)			

Both groups showed highly significant positive correlation of CT with clinical examination results (p value = 0.002).

Table (8): Comparison of tumor size between 2nd follow-up and smallest sum of target lesion (Nadir) by CT in the PD group.

	2nd follow up	Nadir	Test value	P-value	Sig.
Median (IQR)	150.88 (138.76 – 246.99)	112.78 (109.11 – 135.43)	-2.023	0.043	S
Range	40.45 – 334.56	33.21 – 212.41			

According to mRECIST criteria, we found a significance different between the summation of total tumor size in the second follow-up and Nadir with P value = 0.04.

Table (9): Comparison of tumor size between 2nd follow- up and baseline by CT in the PR group

	2nd follow up	Baseline	Test value	P-value	Sig.
Median (IQR)	76.75 (34.25 – 116.16)	150.31 (65.77 – 197.8)	-2.366	0.018	S
Range	28.29 – 138.09	62.5 – 216.95			

According to the mRECIST criteria, we found a significance different between summation of total size tumor of second follow-up and baseline with P value = 0.02.

Table (10): Comparison of tumor size between 2nd follow-up and baseline by CT in the SD group

SD	Baseline	Second follow up	Test value	p-value	Sig.
Median (IQR)	119.01 (97.30 – 148.56)	117.20 (90.37 – 144.85)	0.700	0.484	NS
Range	69.11 – 173.53	53.32 –166.43			

According to the m RECIST criteria, we noticed non-significance different between summation of the total tumor size of the second follow-up and baseline P value =0.48.

DISCUSSION

The malignant pleural mesothelioma (MPM) is considered the most common pleural malignancy. Although it is a rare malignant disease but recent studies have proven increase its incidence worldwide **[10].** MPM is known for its aggressive nature regarding its local disease extent, local spread, and distant metastases. Its survival lies somewhere between 12-18 months even with treatment since it has shown different treatment options resistance **[2].** All the latter leads to the importance of early detection and diagnosis of MPM with proper staging in order to give the patient a better chance of early treatment

and a better survival time [11]. Most of MPM patients presented with progressive chest pain and dyspnea.

The asbestos exposure is the most commonly known cause of MPM although, although other causative factors exist [7].

CT is the most widely method used for MPM diagnosing. However other modalities like MRI and PET CT can be used as well [5].

The aim of the study is to show the correlation between percent change in tumor burden and overall survival and clinical evaluation of patients during chemotherapy.

This study was conducted at the radiology department of the Al-Demerdash hospital on 20 pathologically proven MPM cases, 10 of which were males and 10 were females with a mean age of 55.45

Although it is a male-predominant disease worldwide, our study showed no difference in prevalence of the disease between both genders, which disagrees with [12], who state that MPM has a higher incidence in male than female and also with (5, 2), who state that it is more common in male than in female, with a ratio of 4:1 and [13] state an obvious predominance among males as well as [11], stating that male comprise 60–84 % of all cases of malignant pleural mesothelioma [7]. Also disagree with this and state that male rates are much higher than female rates in virtually all countries [7]. explained that 80% of patients with pleural malignant mesothelioma are male, agreeing with [14] that a strong male predominance exists in MPM and with [15] that it occurs predominantly in male as well as [16] that MPM occurs predominantly in male (ratio of male to female 5:1).

This study also showed the highest disease prevalence in the 6th and 7th decades, agreeing with [2] which described that MPM has a peak incidence in the 6th and 7th decades of life. [5] mentioned that MPM most commonly occurs in patients aged 50–70 years, [14] stated that MPM is usually diagnosed in the 5th to 7th decades of life and with [15] agreed that it usually presents in the 6th through 8th decades as well as [16] resulted that the median age at diagnosis is 72 years in the United States with the age range between 45 and 85 years.

65% of cases in our study live in occupational areas, agreeing with the fact that asbestos exposure is the most common cause of MPM, as explained by [2] which said MPM is mostly diagnosed in 40%--80% of patients with a history of occupational asbestos exposure that the incidence of MPM is 10% in asbestos workers, in contrast to only 0.01% -- 0.24% in the general population. This also agrees with [17], who stated that the majority of the cases diagnosed in the United States with malignant pleural mesothelioma are related to asbestos exposure agreeing with [5] that mentioned MPM is associated with asbestos exposure in approximately 40%--80% of patients, and the incidence of MPM in persons with asbestos exposure is 10% [18]. agree with all the previous studies stating that a history of heavy and long-term exposure to asbestos is the established cause of MPM [7]. state that very few common malignancies have such a direct relationship with an exposure to a definitive carcinogen as mesothelioma and asbestos exposure, also industrialized countries have highest rate than other countries, indicating mass production and use of asbestos in industry [7]. also agree that asbestos is the principal carcinogen associated with MPM and that it was rare before the widespread use of asbestos agreeing with [14] that

occupational exposure to asbestos is the leading cause of MPM [15] mentioned that MPM is usually associated with history of chronic asbestos exposure and 80% of patients will have a definite asbestos exposure history and [19] had stated that occupational exposure to asbestos accounts for more than 80% of the cases, making MPM a preventable disease

According to the modified RECIST criteria, about 55% of the cases in this study showed an increase in tumor size, while the percentage of patients with a decrease in tumor size represent 45 %. The response status of all 20 patients was followed up according to the modified RECIST criteria and their clinical evaluation. Patients were divided into one of two groups: responding patients ('responders') and patients with SD or PD ('non-responders'). Both groups showed highly significant positive correlation with clinical examination with resulted p value of 0.002. This result shows great agreement with [20] that stated the implementation of the modified RECIST criteria in therapy response assessment for MPM showed a significant correlation between percent change in tumor burden and overall survival and clinical evaluation. in our study, eight patients who clinically showed responders, 6 of them remained responders by CT scoring, and 2 of them showed non-responder criteria. On the other hand, twelve patients who clinically showed non-responders ,11 of whom remained non-responder by CT scoring, and 1 of them showed responder criteria.

According to the mRECIST criteria in this study results, patients classified into five patients (25%) are progressive (PD), eight cases (40%) are stable (SD), while seven cases (35%) are partial response (PR) during treatment, and which agrees with [21] that result showed 0% CR, 9% PD, 54% SD, and PR 37%.

According to the modified RECIST criteria in evaluation of the tumor size measurement in our study, in five patients showed progressive disease (PD) (Fig 1), we found a significance different between the summation of total tumor size of the second follow-up and Nadir (smallest summation of target lesion) with P value of 0.04. Also, in seven patients showing partial response (PR) (Fig 2), we found a significance different between the summation of total tumor size in the second follow-up and baseline with a P value of 0.02. these results were consistent with [20], which showed the percent change in tumor burden from baseline either by increasing or decreasing as measured according to modified RECIST criteria for mesothelioma.

On the contrary , eight cases showed stable disease (SD) non-significance differente between summation of total size tuomor of second follow-up and baseline P value of 0.48. These results is agreed with [22] who compared absolute values (cm) of tumor response for modified RECIST criteria between each reader, no significant differences were found (p ≥ 0.47).

As both follow-up results of each group and comparison between clinical evaluation and modified RECIST criteria showed an accuracy of 73.3% with a P value of 0.03, These results confirm the accuracy of modified RECIST criteria by CT as a good predictor of disease outcome with the highest value in partial response PR groups (sensitivity 75%, specificity 91.7%, positive predictor value PPV 85.7 %, and negative predictor value NPV 84.6%). This disagreed with [23] which showed patients who had modified RECIST measurements obtained from chemotherapy. The

relative change between baseline and follow-up showed no significant association with clinical evaluation and overall survival (p = 0.25).
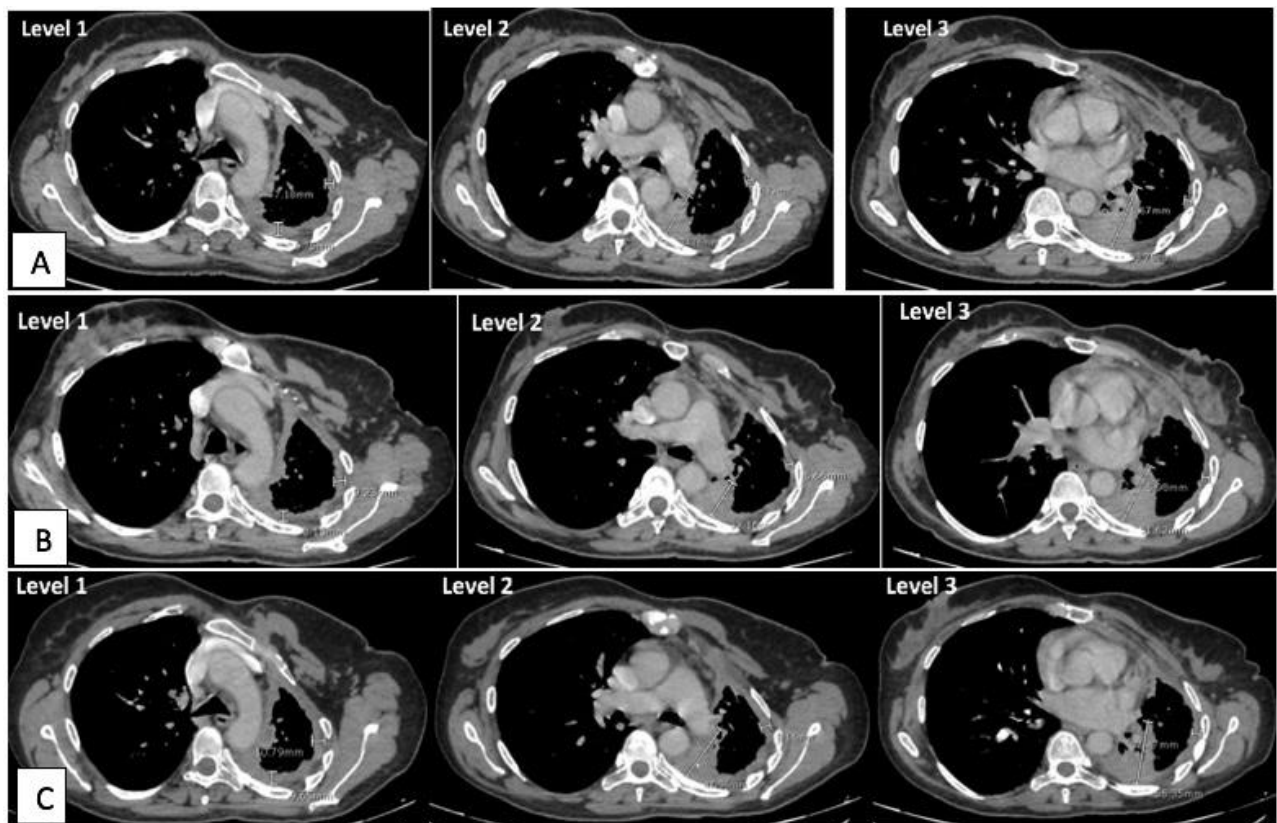
Fig 1: 53-year-old female patient lived beside cement pipe factory, presenting with chest pain and dyspnea. biopsy proven left MPM. Axial cuts of contrast enhanced CT scans with mRECIST, (A) first base line, (B) second after 3rd CHT cycle, (C) third after 6th CHT cycle showed left-sided circumferential irregular non-uniform pleural thickening involving all the pleural surfaces, total tumor measurement is increases by about 23.08% **(increase of at least 20% in the total tumor measurement over the nadir)**, so according to mRECIST, it classifies progressive disease (PD). clinically patient complaining of intractable hemoptysis and aggressive loss of weight.
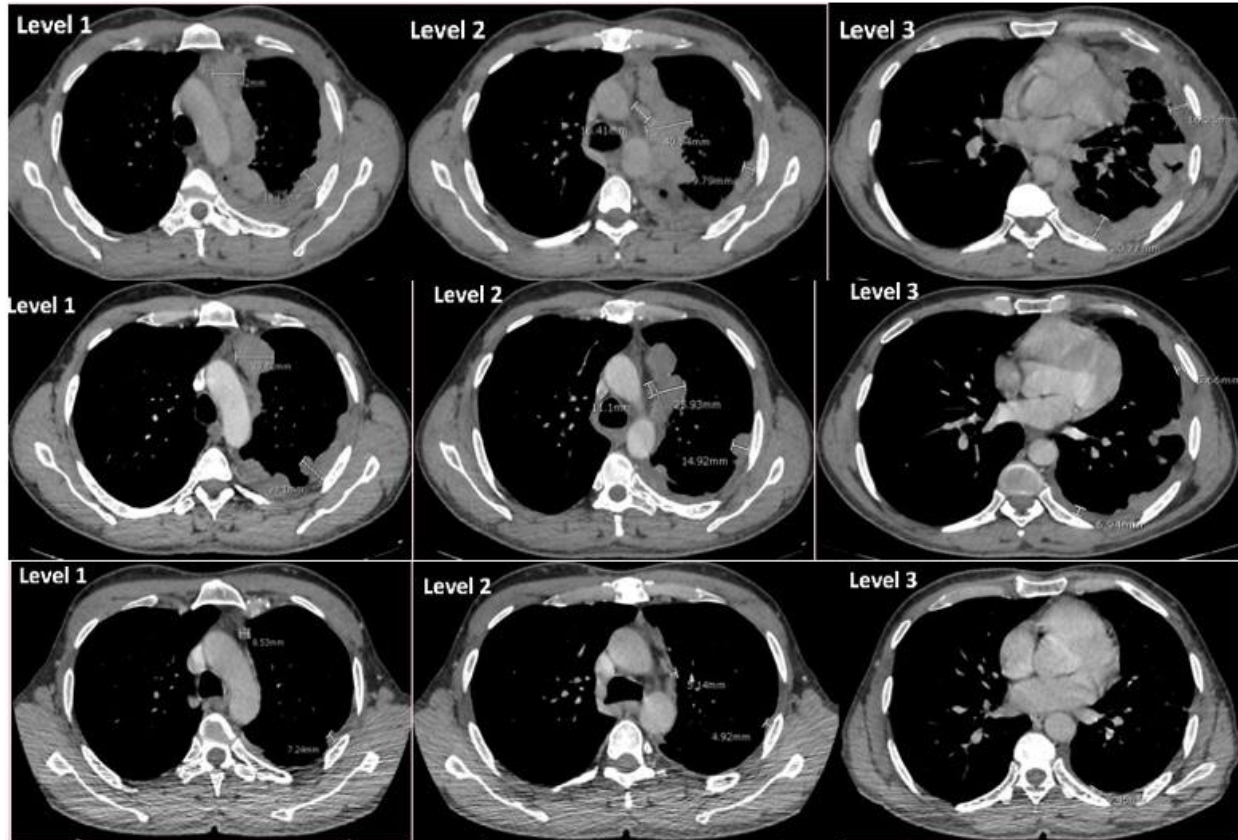
Fig 2: 45 years old male patient worked in glass factory foe 20 years, presented by progressive dyspnea. biopsy proven left MPM. Axial cuts of contrast enhanced CT scans with mRECIST, (A) first base line, (B) second after 3rd CHT cycle, (C) third after 6th CHT cycle showed left-sided circumferential irregular pleural thickening involving all the pleural surfaces with mediastinal lymphadenopathy, total tumor measurement decreases about 81.18% **(decrease of at least 30% in the total tumor measurement)**, According to mRECIST considered partial response (PR). Clinicaly patient is improved on selected CHT, chest pain is almost disapear, and no evidence of new clinical symptoms appears.

CONCLUSION

During our study period, routine CT was used to follow-up and implement modified RECIST criteria in therapy response assessment for malignant pleural mesothelioma showed a significant correlation between percent change in tumor burden and clinical evaluation and overall survival.

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