Malignant pleural mesothelioma: staging and radiological response criteria in patients treated with immune checkpoint inhibitors.

Authors

Serafina Martella[1], Marco Maria Aiello[1*], Valentina Bertaglia[2], Riccardo Cau[3], Nerina Denaro[4], Andrea Cadoni[5], Silvia Novello[2], Mario Scartozzi[5], Giuseppe Novello[1], Hector Josè Soto Parra[1], Luca Saba[3], Cinzia Solinas[2], Michele Porcu[3**].*

[1]Department of Medical Oncology, University Hospital Policlinico San Marco, Catania, Italy

[2]Department of Oncology, San Luigi Gonzaga Hospital, University of Turin, Turin, Italy

[3]Department of Radiology, AOU Cagliari, Monserrato (CA), Italy

[4]Department of Medical Oncology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

[4]Department of Medical Oncology, AOU Cagliari, Monserrato (CA), Italy

*Contributed equally: co-first authors

**Corresponding author: Michele Porcu (e-mail: micheleporcu87@gmail.com / institutional mail: m.porcu@aoucagliari.it); Department of Radiology, AOU Cagliari – S.S: 554, km 4,500 – CAP: 09042 – Monserrato (Cagliari, Italy)

Short title: Malignant pleural mesothelioma and ICI: a radio-oncological review

Abstract

Malignant Pleural Mesothelioma (MPM) is a rare and challenging cancer associated with asbestos fiber exposure, which offers limited treatment options. Historically, platinum-based chemotherapy has been the primary approach, but recent developments have introduced immunotherapy as a promising alternative also for the treatment of this disease. Nevertheless, the unique growth patterns and occasionally ambiguous progressive characteristics of MPM make the interpretation of radiological assessments complex. Immunotherapy further complicates matters by introducing unconventional treatment response patterns such as Hyperprogression and Pseudoprogression. Consequently, there is a growing imperative to integrate the standard RECIST criteria with the mesothelioma-specific mRECIST criteria (version 1.1), as outlined in iRECIST. This comprehensive review is driven by the intent to provide a valuable resource for radiologists and clinicians engaged in the diagnosis, treatment, and monitoring of MPM in the era of immunotherapy. Specifically, the current imaging methods employed for staging and follow-up will be exposed and discussed, with a focus on the technical specificities and the mRECIST 1.1 methodology. Furthermore, we will provide a discussion about major clinical trials related to the use of immunotherapy in MPM patients. Finally, the latest advancements in radiomics, the applications of artificial intelligence in MPM, and their potential impact on clinical practice for prognosis and therapy, will be discussed.

Key Points

• Multiple imaging modalities are necessary to stage malignant pleural mesothelioma (MPM).

• Imaging response criteria for assessing treatment effectiveness in MPM are founded on the mesothelioma-specific mRECIST 1.1 criteria.

• If a "progressive disease" pattern is detected during follow-up imaging while undergoing immune-checkpoint-inhibitor therapy, a subsequent imaging evaluation is necessary to confirm or refute this pattern.

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1) Introduction

Malignant pleural mesothelioma (MPM) is a rare cancer that originates from the mesothelial cells of the pleura. The prognosis is grim, with a five-year survival rate of less than 10% [1,2]. Based on the type of malignant cells, MPM is categorized into three subtypes: epithelioid, biphasic, and sarcomatoid. Epithelioid is the most prevalent subtype (constituting 50-70% of cases), while patients with sarcomatoid histology experience shorter survival compared to the other subtypes [3].

MPM is often diagnosed at an advanced stage due to its asymptomatic nature. Common symptoms include breathlessness, weight loss, pleural effusion, lung thickening, and chest pain [4,5]. Diagnosis of MPM can be challenging and necessitates both radiological and clinical support. Pleural biopsy and cytological examination of pleural effusion are the two predominant diagnostic methods [6,7]. Treatment strategies, depending on the stage, encompass multimodal approaches involving surgical resection, radiotherapy, chemotherapy, or systemic treatments alone.

Surgery is viable for early stages, but a curative approach remains feasible for only a minority of cases [8-10]. Historically, for advanced MPM cases, the preferred treatment has been the platinum-pemetrexed doublet chemotherapy. However, the results have not been notably promising, revealing a median overall survival (OS) of 12.1 months in the pemetrexed/cisplatin arm compared to 9.3 months in the control arm (cisplatin alone) [11].

In recent years, remarkable outcomes have been observed with immune checkpoint inhibitors (ICIs) in various tumor types,such asmelanoma and non-small cell lung cancer (NSCLC). This has prompted exploration of these novel therapeutic agents for treating advanced MPM [12,13]. A substantial challenge in both clinical trials and real-life management of MPM lies in interpreting radiological images to assess treatment response [14,15].

The objective of this review is to provide an overview of the radiological evaluation criteria used in MPM. This aims to shed light on the most suitable approach considering the emerging standard of ICI treatments.

2) Risk factors for MPM development

MPM is often linked to prolonged exposure to asbestos, with a latency period typically spanning around 25 years. Its pathogenesis appears to be contingent on the interplay between environmental and genetic factors that modulate the tumor microenvironment. Specifically, when mesothelial cells come into contact with asbestos fibers, the subsequent secretion of CCL2 chemokines triggers the phagocytosis of asbestos fibers by macrophages. This, in turn, activates pro-inflammatory pathways mediated by tumor necrosis factor (TNF)-α, culminating in carcinogenesis and the survival of tumor cells [16] (Figure 1).

In rare instances, a genetic predisposition to MPM onset has also been documented. Germline variants in the tumor suppressor BRCA1 gene, which accelerate the impact of asbestos on mesothelial cells, have been observed in approximately 10% of MPM patients [17]. Furthermore, other mutations, such as germ-line variants in the DNA repair PALB2 and BRCA2 genes, seem to play a role in the carcinogenic process of asbestos in preclinical models [18].

3) MPM: staging, imaging evaluation, response assessment and future developments.

MPM develops by inducing pleural thickening with multifocal solid masses, affecting the pleural fissures, chest wall, or mediastinum. Owing to this distinct growth pattern, both staging and the evaluation of treatment response pose

challenges in clinical practice and trials [15,19]. The subsequent sections will delve into discussions on staging, radiological evaluation, and response assessment. Additionally, a brief overview of forthcoming promising advancements will be provided, aiming to assist radiologists and clinicians in the diagnosis and monitoring of MPM.

3.1) Staging and imaging evaluation

The 8th edition of the Tumor, Node, and Metastasis (TNM) descriptor system, incorporated within the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual and developed by the International Association for the Study of Lung Cancer (IASLC), is the conventional system employed for staging MPM [20-23]. This system also guides therapeutic management [24-26]. An overview of the TNM classification is provided in Table 1, and the staging system is detailed in Table 2.

Concerning local staging, assessment hinges on the T parameter [27], with a crucial need to distinguish between surgically resectable ($T \leq 3$) and unresectable tumors ($T = 4$) to determine the initial therapeutic approach [20,22,27-30].

Computed Tomography (CT) is the primary cross-sectional imaging method recommended by the British Thoracic Society (BTS) for MPM evaluation [27,28]. It serves as the mainstay for staging [20]. Specifically, a multi-row CT scanner should be used for chest scans following contrast medium administration (50-75 ml at 3-4 ml/s). Axial images with 1- to 3-mm thickness, reconstructed with a soft-tissue kernel, should be obtained [15]. Acquisition parameters, including field of view (FOV), voltage (80-130 kVp), and tube current (100 to 200 mA), must be tailored to the patient's physique [15]. However, CT's capability for local staging is constrained by the limited contrast resolution between the tumor and adjacent chest wall structures [29,30]. While CT is sensitive and specific in identifying features, such as pleural enhancement, pleural nodularity > 1 mm, and mediastinal pleural and interlobar involvement, its accuracy in assessing chest wall or diaphragmatic infiltration is hampered by low sensitivity (17-29%), despite high specificity (100%) [27].

In recent years, technological advancements have enabled the utilization of Magnetic Resonance Imaging (MRI) for MPM assessment [15,19]. Thanks to its inherent high contrast resolution and soft-tissue differentiation, MRI surpasses CT in identifying invasion of mediastinal fat, diaphragm, endothoracic fascia, and chest wall [27,31]. Consequently, MRI often results in upstaging patients compared to CT due to its superior local invasion identification [27,31]. A consensus paper from the National Cancer Institute (NCI) Thoracic Malignancy Steering Committee published in 2019 recommends incorporating gadolinium-based contrast-enhanced MRI for MPM evaluation where feasible [15]. The utilization of gadolinium-based contrast medium further enhances the already high contrast resolution of MRI, especially in highly vascularized tumoral tissues, improving the assessment of the relationships between MPM and surrounding structures in local staging [15,32]. The MRI protocol involves 1.5 or 3 T scanners with a body array coil, utilizing T1-weighted and T2-weighted single-shot acquisitions on coronal and axial planes with 5 mm section thickness, 1.5 mm interslice gap, 400 mm FOV, 320 x 224 matrix size, and 3D T1-weighted volume interpolated gradient echo acquisitions to cover the entire chest and diaphragm in a single breath-hold. The protocol should also include Diffusion-Weighted Imaging (DWI) and post-contrast sequences [15,27]. DWI is performed with 3 to 6 b-values ranging from 0 to 1000 s/mm^2, generating Apparent Diffusion Coefficient (ADC) maps [15]. For post-contrast sequences, multiplanar T1 sequences should be obtained following administration of a standard gadolinium-based contrast medium dose of 0.1 mmol/kg of patient's body weight [15,27]. Additionally, an optional free-breathing Dynamic Contrast Enhancement (DCE) 3D gradient echo sequence during contrast medium administration can be used to assess MPM vascularization and pharmacokinetics before and after therapy [15]. In fact, the DCE technique enables the analysis of tumoral vascular perfusion, even in cases of minimal pleural thickenings[15,32].

For the N and M parameters of the TNM descriptor system, ^{18}Fluoro-Deoxy-Glucose Positron Emission Tomography CT (^{18}FDG PET/CT) is the preferred modality [15]. ^{18}FDG PET/CT demonstrates heightened sensitivity and specificity for N and M staging compared to CT alone. Thus, incorporating ^{18}FDG PET/CT in conjunction with other imaging techniques is crucial for accurate TNM staging and guiding appropriate therapeutic approaches [15,27,28,33]. Regarding the protocol, the administered ^{18}FDG dose should follow dose calculator charts, and the study should be rescheduled if basal serum glucose exceeds 200 mg/dl. Imaging is typically performed 60 minutes post-tracer administration. A non-contrast low-dose CT scan from the head to the proximal thighs during shallow breathing should be acquired for attenuation correction prior to the PET scan. The PET scan, encompassing the same FOV, should follow immediately after the CT scan, with each bed position acquired over approximately 3 minutes. A standardized uptake value (SUV) equal to or higher than 2 is reliable for distinguishing malignant from benign findings, with a sensitivity of 88-100% and specificity of 88-92% [27,28,34]. It's important to note that ^{18}FDG PET/CT should be avoided in patients who have undergone prior talc pleurodesis or in populations with a high prevalence of tuberculosis, as these conditions can lead to false-positive results or overestimation of disease burden [15,27,28].

The main technical features of the main acquisition parameters for each imaging technique recommended in MPM TNM staging and follow-up are reported in Table 3.

Lastly, imaging-guided biopsies are often necessary for MPM diagnosis, and these can be performed using the fine-needle aspiration (FNA) technique, usually with the guidance of CT or ultrasound in selected cases [27,28]. An example of MPM's TNM staging is presented in Figure 1.

3.2) Imaging response assessment

It is recognized that the assessment of treatment response in Malignant Pleural Mesothelioma (MPM) is associated with a significant degree of intraobserver variability, primarily due to the distinctive characteristics of this tumor, including its unique circumferential rind-like morphology [15,27].

One strong prognostic indicator for MPM is tumor size, which remains a challenge within the realm of radiology. Broad response criteria have not yet been definitively established [8,19], particularly with regard to the linear measurements outlined in the RECIST criteria, which are not considered the optimal choice [15,35].

In an effort to address these existing limitations, the recent consensus paper published by the NCI Thoracic Malignancy Steering Committee in 2019 [15] aimed to provide useful guidance regarding the methodology to be adopted for assessing MPM treatment response. According to this paper, the preferred approach for evaluating treatment response in MPM is the mesothelioma-specific modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria version 1.1 [20]. This system is applied to contrast-enhanced CT scans (acquired using the aforementioned protocol within four weeks prior to treatment initiation) [15,20]. It is worth noting that CT scans should ideally be analyzed using a soft-tissue kernel reconstruction and window [20].

Similar to RECIST 1.1 [35], the calculation of tumor burden involves summing the measurements of "pleural" and measurable "non-pleural" target lesions, as well as measurements of "pathologic" lymph nodes [15,20].

In terms of "pleural" target lesions, a fundamental principle of mRECIST 1.1 dictates that the measurement of the primary pleural tumor should be taken perpendicular to the mediastinum and chest wall, rather than along its longest diameter [15,20]. Specifically, a minimum measurable "pleural" target lesion must be $\geq$ 7 mm, and up to six pleural measurement sites should be selected during the baseline examination (with a maximum of two measurements per CT section, and sites chosen across no more than three CT sections, each separated by at least 10 mm) [15,20]. Ideally, these measurement sites should be positioned superior to the level of the left atrium and below the level of the aortic arch to

minimize potential heartbeat artifacts [20]. In cases where the disease affects both hemi-thoraces, the pleura is still considered a single "organ" In this scenario, a maximum of six pleural measurements can be selected from bilateral disease, as deemed clinically appropriate, with up to three CT sections per hemithorax independently chosen [15,20].

Analogous to RECIST 1.1 [35], when other measurable "non-pleural" target lesions with a minimum diameter of 10 mm are present (e.g., in the liver or abdominal cavity), the longest diameter of a maximum of five lesions in total (with a maximum of two per organ) must be measured and then included in the sum representing tumor burden [15,20].

Lymph nodes are considered "pathologic" when their shortest diameter is ≥ 15 mm. In such cases, their shortest diameter must be measured and included in the calculation of tumor burden. Pathological lymph nodes with a short axis ≥ 10 mm but < 15 mm should be classified as "non-target lesions," and their presence should be duly noted and monitored. Pathological nodes with a short axis < 10 mm are considered non-pathological, and they should not be recorded or followed [20].

Finally, "non-measurable" lesions (such as pleural effusion) and "measurable but non-measured" pleural disease should be described using descriptive notations [15,20]. A practical example of tumor burden assessment is depicted in Figure 2.

The frequency of re-evaluating tumor burden during treatment should be determined based on the adopted protocol and the goals of the trial, as well as the timing of follow-up after treatment completion [35]. All follow-up CT scans for a given patient should adhere to the same parameters used for the baseline scan, and measurements should be conducted by the same observer using consistent image display parameters [15,20]. Tumor burden assessment must follow the same modalities described earlier. In particular, pleural lesion measurements must be taken at the same CT sections and measurement sites chosen during the baseline CT scan [18,20]. During follow-up CT scans, measurements should also be obtained for all sites that have reduced in size below the minimum measurable size, with a default value of 2 mm assigned to thin tumoral lesions that appear too small to measure [15,20].

Regarding the response classification criteria of mRECIST 1.1, they can be categorized into four distinct response patterns (as detailed in Table 4) [15,20,35,36,37]:

- Complete Response (CR): This occurs when all "pleural" and measurable "non-pleural" target lesions disappear, and any of the "pathological" lymph nodes (both target and non-target) have reduced to a short axis < 10 mm during the follow-up imaging [15,20,35,36]. This response pattern can only be confirmed at a subsequent time-point as specified in the protocol (typically 4 weeks later) [36].
- Partial Response (PR): This is indicated by a reduction of at least 30% in tumor burden during the follow-up imaging, with the baseline tumor burden serving as the reference point [36]. Similar to CR, PR can only be determined at a subsequent time point as specified in the protocol (typically 4 weeks later) [36].
- Stable Disease (SD): This is characterized by either a decrease in tumor burden of less than 30% compared to the baseline, or an increase of less than 20% compared to the smallest tumor burden observed during the study (i.e., the nadir), provided there are no clear new non-pleural lesions or pleural thickening surpassing the minimum measurable size (i.e., ≥ 7 mm) [15,20,36].
- Progressive Disease (PD): This is indicated by an increase of at least 20% in the tumor burden (with an absolute increase of ≥ 5 mm), using the nadir as a reference point [15,20,36]. The identification of a clear new non-pleural lesion or pleural thickening exceeding the minimum measurable size (i.e., ≥ 7 mm) would also be classified as PD [20].

  For clinical trials that incorporate immunotherapy, the principles of iRECIST are applied to the mRECIST criteria for defining the pattern of PD response, due to the necessity of considering pseudoprogression and

delayed response [15,20,35,36,37]. In these scenarios, when PD is detected in a follow-up imaging, it is designated as immunotherapy unconfirmed PD (iUPD), and an additional imaging assessment between 4-8 weeks must be conducted [15,34,36]. If this subsequent follow-up imaging reveals a further tumor burden increase of ≥ 5 mm, or an additional increase in non-target lesions, or the appearance of new target or non-target lesions in comparison to the previous imaging assessment, then the response will be categorized as immunotherapy Confirmed PD (iCPD). Conversely, if the response pattern in the subsequent assessment meets the criteria for Stable Disease (SD), Partial Response (PR), or Complete Response (CR) in comparison to the baseline tumor burden, the response will not be classified as iCPD, but rather as SD, PR, or CR, as observed.

Practical examples of response-to-treatment evaluations are provided in Figure 3 and Figure 4.

Finally, the metabolic response to treatment can be assessed using ^{18}FDG PET/CT with the European Organization for Research and Treatment of Cancer (EORTC) criteria [38] or the PET Response Criteria in Solid Tumors (PERCIST) criteria [39]. While these criteria are widely applicable for evaluating MPM response, their usage is not currently recommended in clinical trials due to insufficient validation of ^{18}FDG PET/CT as a response assessment tool in the current literature [15,20].

3.3) Future developments

The recent technological advancements in the radiological field are reshaping the traditional imaging approach to MPM. For instance, as previously discussed, MRI demonstrates superior results in delineating the disease's relationships with surrounding structures compared to CT, owing to its inherent higher contrast resolution [27,31]. Recent technical improvements in MRI technologies, particularly in terms of hardware and parallel imaging, now enable the acquisition of high-quality images in shorter time frames [27,40]. However, the clinical application of MRI in MPM study is yet to be well-defined [15].

Another promising avenue of research involves the development of quantitative and semi-quantitative imaging metrics to assist clinicians and radiologists in more accurately assessing treatment responses [15,20,40], and a practical example of this can be found in the research conducted by *Doi et al. [41]*, in which the authors identified the total lesion glycolysis in ^{18}FDG PET/CT as an independent prognostic factor of MPM. A topic of great interest is the pursuit of a precise and reproducible method for evaluating overall tumor volume [20,40]. By comparing tumor volume before and after treatment, the need for specific tumor measurement guidelines could be obviated. Nevertheless, manual segmentation is time-consuming and susceptible to interobserver variability [40]. While various commercial software solutions for semi-automatic tumor segmentation have emerged, volumetric assessment for MPM is not currently recommended for clinical trials, except as a research tool, due to insufficient validation in the current literature [18,20]. Standardizing and harmonizing volumetric measurement techniques, as well as cross-platform validation, are necessary prerequisites before their clinical adoption [15].

The development of other quantitative and semi-quantitative imaging metrics relies on introducing new or existing imaging techniques and employing specific algorithms capable of extracting information not discernible to the human eye [40,42]. A case in point is the assessment of MPM microvascular properties through DCE sequences in MRI to gauge chemotherapy response [40,42,43,44]. Similarly, the emerging CT spectral imaging technology for chest malignancies allows for generating iodine maps that analyze the tumor's microvascular structure [45,46]. Additionally, the utilization of texture analysis and radiomics algorithms has opened avenues for identifying histopathological markers

of disease, contributing to a more comprehensive assessment of treatment response beyond volumetric approaches [42]. A recent study by *Pavic et al.* [47] successfully built an ^{18}FDG PET/CT model predicting progression-free survival in MPM patients based on the extraction of 1410 ^{18}FDG-PET/CT features.

While the development of these quantitative and semi-quantitative metrics for MPM is still in its early stages, further validation studies are warranted to establish their utility in the clinical context. It is reasonable to anticipate that their evolution will significantly impact the clinical assessment of MPM in the near future.

4) Mesothelioma and ICIs

Advanced and metastatic MPM pose one of the most challenging treatment scenarios. The EMPHACIS trial established the cisplatin plus pemetrexed combination as the standard-of-care for unresectable MPM in the front-line setting, gaining FDA approval in 2004 [11]. In the pemetrexed/cisplatin arm, the median OS was 12.1 months compared to 9.3 months in the control arm (P = 0.020, two-sided log-rank test). The hazard ratio for patient mortality in the pemetrexed/cisplatin arm compared to the control arm was 0.77. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months (P = 0.001). However, the results of the platinum-based first-line chemotherapy were not convincingly strong, and the scientific evidence regarding the real impact of second-line treatments on MPM patient survival remains weak. This has prompted the need for novel therapeutic approaches.

In the most recent decade, ICIs have emerged as a promising treatment alternative for several solid tumors, including MPM. Multiple clinical trials evaluating the use of ICIs as monotherapies or in combination have reported improved OS compared to standard care, leading to the incorporation of immunotherapeutic agents into routine clinical practice [48,49].

Several clinical trials as monotherapy as combinations therapy have evaluated immunotherapy in MPM and data are reported in Table 5 (50-60).

The phase III randomized trial, CheckMate743, evaluated nivolumab plus ipilimumab versus platinum/pemetrexed chemotherapy as first line in 605 patients with unresectable MPM [50]. With a median follow-up of 43.1 months, nivolumab plus ipilimumab continued to prolong OS versus chemotherapy. Median OS was 18.1 versus 14.1 months [HR 0.73 (0.61–0.87)], and 3-year OS rates were 23% versus 15%, respectively. Three-year PFS rates were 14% versus 1%, and objective response rates were 40% versus 44%. At 3 years, 28% versus 0% of responders had an ongoing response [51]. In epithelioid subtypes, a trend for OS benefit was observed, but statistical significance was not reached (median OS: 18.2 months versus 16.7 months, HR:0.85, 95% CI: 0.69-1.04), while non-epithelioid histology was associated with significantly prolonged median OS (18.1 months versus 8.8 months, HR: 0.48, 95% CI: 0.34-0.69) [51]. Sarcomatoid subtypes are known to be less responsive to chemotherapy, while they remain sensitive to immunotherapy [51].

A phase 2 Dutch trial (INITIATE) assessed nivolumab/ipilimumab as subsequent therapy in patients with MPM [53]. The disease control rate was 68% at 12 weeks (23/34; 95% CI, 50%–83%) [53].

Another phase 2 randomized trial (IFCT-1501 MAPS2) evaluated nivolumab with (or without) ipilimumab as subsequent therapy for patients with MPM [54]. The median OS was 15.9 months (95% CI, 10.7–not reached) in the nivolumab/ipilimumab arm and 11.9 months (95% CI, 6.7–17.7) with nivolumab alone [54]. There were more grade 3 to 4 AEs in the nivolumab/ipilimumab arm when compared with the nivolumab alone arm (26% vs. 14%) [54].

The KEYNOTE-028 trial enrolled 26 patients with advanced MPM to receive the anti-PD-1 pembrolizumab after experiencing progression on first-line chemotherapy. The overall response rate (ORR) was 20%, with a median

progression-free survival (mPFS) of 5.5 months and a median OS of 18.7 months in patients with PD-L1 positive MPM. For the unselected population, the median OS was 18.0 months [55].

Results from the KEYNOTE-158 trial, a single-arm multi-cohort phase II study evaluating pembrolizumab activity in various tumors, including relapsed MPM, were presented during the virtual World Conference on Lung Cancer (WCLC) 2020 [56]. With an ORR of 8.5%, independent of PD-L1 expression status, and a median duration of response (mDOR) of 14.3 months, pembrolizumab proves to be an attractive option for relapsing disease, considering its favorable toxicity profile and limited second-line treatment choices [56].

Moreover, a phase III randomized trial, CONFIRM, evaluated nivolumab versus placebo in 332 patients with MPM, who had progressed after platinum-based chemotherapy. In the experimental arm, the median OS was 10.2 months (95% CI, 8.5–12.1) versus 6.9 months (95% CI, 5.0–8.0) in those receiving placebo (HR, 0.69; 95% CI, 0.52–0.91). Serious adverse events were similar between the groups (41% for nivolumab vs. 44% for placebo) [59].

Despite the unquestionable benefits, immunotherapy has its limitations, primarily resistance and unclear progression phenomena. For this reason, it's essential to clearly define response criteria in MPM, taking into consideration the principles of iRECIST as applied to PD. This helps in better recognizing the potential for pseudo-progression and/or delayed response, allowing patients to continue ICI treatment even when a single imaging time point shows PD.

Studying immunological resistances becomes crucial to identifying biomarkers that could predict treatment response and considering combined therapies that work synergistically to overcome resistances.

While the predictive biological characteristics of response and resistance are not well established, evidence is emerging from the study of the tumor microenvironment and genetic drivers. This could pave the way for introducing new combinations of ICIs or targeted therapies.

Major factors contributing to resistance against immunotherapy treatments include mechanisms sustained by cancer-associated fibroblasts, T-lymphocytes, Tumor Associated Macrophages (TAMs), and Myeloid-derived suppressor cells (MDSCs). TAMs, a type of macrophages, significantly contribute to the development of a pro-tumor microenvironment, leading to tumor growth, invasion, metastasis, drug resistance, and, importantly, immunosuppression [61]. Additionally, the secretomes of mesothelioma are known to enhance the production of Granulocyte Colony Stimulating Factor (G-CSF), which promotes the formation of MDSCs, thereby inhibiting T-lymphocytes [62].

The Cancer Genome Atlas Study has demonstrated that MPM is the tumor type that most frequently expresses the V-domain Ig suppressor of T cell activation (VISTA). This type I transmembrane protein is encoded by the C10orf54 gene and functions as an immune checkpoint by suppressing T-lymphocytes. Consequently, VISTA becomes an attractive target for overcoming resistance to immunotherapy [63,64].

Exploring resistance mechanisms to ICIs in MPM has given impetus to chemotherapy, as it has been observed that anticancer drugs enrich the Tumor Microenvironment (TME) with CD3+ and CD8+ T lymphocytes [55]. This has opened avenues for chemo-immunotherapy strategies, much like what has been adopted in other pathologies [66].

Some instances of early death and rapid progression following ICI administration have cast doubt on the use of such treatments. Hyperprogressive disease (HPD) is characterized by the rapid development of tumors after exposure to immunotherapy agents, often leading to swift demise [67]. However, data about HPD in MPM are limited, with most information derived from studies on NSCLC, as immunotherapy was not a standard care for mesothelioma.

Specifically, HPD was primarily observed in retrospective studies where evaluation criteria were based on pre-ICI radiological imaging [68,69], or post-ICI detection of a rapid metastatic spread. Unfortunately, both assessments were not consistently available for every patient, resulting in highly heterogeneous data [70].

The MAPS-2 study was the sole trial that precisely conducted pre-ICI radiological evaluation to assess HPD [71]. In this non-comparative, double-arm study evaluating nivolumab or nivolumab in combination with ipilimumab in pre-treated MPM, Early Death (ED) rates within the first 5 months after randomization were 30% (19/63) and 21% (13/62) for nivolumab and nivolumab plus ipilimumab, respectively. Modified RECIST (mRECIST) PD rates for MPM were high for both nivolumab (60%) and nivolumab plus ipilimumab (48%). Notably, two patients from the study exhibited impressive Progressive Disease (PD) with a tumor burden increase measured by mRECIST of 160% compared to the baseline.

The Checkmate743 trial [50,51] showed that in the overall population and in patients with epithelioid or sarcomatoid histology ED rates were 10% (30/303), 10% (22/229) and 11% (8/74) in the immunotherapy arm vs. 11% (34/302), 10% (23/227) and 15% (11/75) in the chemotherapy arm, respectively.

The concept of tumor growth kinetics (TGK) had been previously applied to assess HPD in head and neck cancers, where HPD was defined as a doubling of the RECIST sum of the longest diameter (SLD) of target lesions on ICI compared to the pre-treatment period [72]. According to this definition, HPD was reported in 11 (9%) of 125 MPM patients in MAPS-2 (7 patients in the nivolumab arm and 4 patients in the nivolumab plus ipilimumab arm). It was significantly associated with negative PD-L1 expression (<1%) on tumor cells (8 of 11 HPD patients had negative PD-L1 expression) [73].

Clearly, delving into the mechanisms of HPD in MPM presents a future challenge. In NSCLC, available data indicate that M2 tumor-associated immunosuppressive macrophages (CD163+, CD33+, and PD-L1+) play a role in resistance to immunotherapic treatments. Some models suggest that when the immune microenvironment of MPM is dominated by macrophages, a high ratio of M2 to CD8+ T-lymphocytes seems to contribute to HPD and ED after ICI exposure, which is ultimately associated with a poor prognosis in MPM [74] (Figure 6).

Another phenomenon considered as an atypical response to immunotherapy is pseudo-progression (PsPD), where initial tumor size expansion or appearance of new lesions is followed by a subsequent decrease in tumor burden. Although this often accompanies clinical benefit, it frequently results in prematurely discontinuing immunotherapy due to an incorrect assessment of progression [35]. Several clinical trials showed that PsPD has also been observed in MPM, but at lower rates than HPD [75]. In the MERIT trial, which evaluated nivolumab in Japanese MPM patients, no PsPD was formally reported [58], and PsPD were not formally reported in trials testing anti-CTLA agents alone or in combination with PD-1/PD-L1 inhibitors. Data on this phenomenon, however, remain anecdotal [76].

One key objective is to molecularly characterize the mechanisms underlying both HPD and PsPD and to define common evaluation criteria. It is possible to speculate that the development of Artificial Intelligence (AI) algorithms based on radiomic techniques [42] -- in combination with blood and genomic data -- could assist clinicians and radiologists in better defining prognosis and predicting the response to therapy in patients with MPM, as observed in other contexts [77]. For example, in a recent study by *Basler et al.* [78], the authors were able to develop an AI model based on radiomics and blood sample data for early differentiation of PsPD in patients with melanoma treated with ICIs, achieving a very good accuracy (area under the curve = 0.82). A similar approach was applied by *Tunali et al.* [79] to predict HPD in patients with non-small-cell lung cancer undergoing ICI treatment, also achieving a very good accuracy (82.28%). Unfortunately, at present, available data, especially for diseases like MPM or its subpopulations, are limited, but it is reasonable to speculate that the development and validation of these models will represent a fundamental step in the direction of precision medicine, even for patients with MPM.

5) Discussion and Conclusions

In recent decades, ICIs have emerged as an effective therapeutic alternative for various solid tumors, including MPM. However, staging, radiological assessment, and response evaluation to immunotherapy are significantly complicated by the distinct growth patterns and unclear progressive phenomena characteristic of this tumor.

The primary staging modality is typically the CT scan, yet its effectiveness is limited due to the low contrast resolution between the tumor and the adjacent chest wall structures. MRI provides superior accuracy compared to CT in terms of contrast resolution and soft tissue differentiation. It offers better precision in identifying invasion into mediastinal fat, diaphragm, endothoracic fascia, and chest wall. Additionally, ^{18}FDG PET/CT exhibits higher sensitivity and specificity for N and M staging than CT alone, making their combined use recommended for TNM staging.

Despite the undeniable advantages, immunotherapy encounters numerous limitations, particularly resistance and unclear progressive phenomena. Consequently, it is crucial for response criteria in MPM to be clearly defined, alongside adherence to the principles of iRECIST for progressive disease scenarios. This ensures better identification of pseudo-progression and/or delayed responses, that may be observed frequently with immunotherapy after an initial progressive disease and should be confirmed, facilitating continued ICI treatment following a single imaging assessment indicating disease progression.

Following the NCI's 2019 guidelines regarding evaluation methodology for MPM response, mRECIST criteria are favored for treatment response assessment. For trials involving immunotherapy, the iRECIST principles are applied to the mRECIST criteria, enhancing the characterization of distinct patterns of PD response, encompassing concepts like pseudoprogression and delayed responses.

Assessment of metabolic response to treatment can be accomplished through ^{18}FDG PET/CT using either the EORCT criteria or PERCIST.

While these criteria are widely utilized in clinical practice for MPM response assessment, their application is not currently recommended in clinical trials due to insufficient validation of ^{18}FDG PET/CT as a response assessment tool within existing literature.

As of now, predictive biological traits influencing response and resistance to ICIs in MPM remain inadequately understood. However, evidence is gradually emerging from studies involving TME and genetic drivers. These findings may support the introduction of new combinations of ICIs or targeted therapies.

This review summarizes potential molecular mechanisms of immunological resistance. Further exploration into these mechanisms will aid in identifying new biomarkers capable of predicting treatment response, thereby facilitating the consideration of synergistic combination therapies to overcome resistances. In this context, our radio-immuno-oncology review on radiological response criteria in MPM and ICIs aims to provide valuable assistance to radiologists and clinicians involved in diagnosing and monitoring the treatment of pleural mesothelioma.

Declarations

Funding

No external funding was used in the preparation of this manuscript.

Conflicts of interest/Competing interests

Mario Scartozzi declares potential conflict of interests as speaker bureau & advisory board for MSD, BMS and GSK. Nerina Denaro declares potential conflict for speaker honoraria for BMS, Novartis, and MSD. Serafina Martella, Marco Maria Aiello, Valentina Bertaglia, Riccardo Cau, Andrea Cadoni, Silvia Novello, Giuseppe Novello, Hector Josè Soto Parra, Luca Saba, Cinzia Solinas, and Michele Porcu declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Not applicable

Code availability

Not applicable

Figure legends

- **Figure 1**: Simplified resume scheme of MPM development [16]. When mesothelial cells come into contact with asbestos fibers, the subsequent secretion of CCL2 chemokines triggers the phagocytosis of asbestos fibers by macrophages; this, in turn, activates pro-inflammatory pathways mediated by TNF-α, culminating in carcinogenesis and the survival of tumor cells.
- **Figure 2**: Contrast-enhanced CT of a 74-year-old patient with malignant pleural mesothelioma located in the left hemithorax. A) Axial image at the level of the heart reveals involvement of the mediastinal pleura (white arrow) and non-transmural involvement of the pericardium (black arrow). B) Axial image at the level of the diaphragm demonstrates involvement of the parietal pleura (white arrowheads), diaphragmatic pleura (white arrowhead), and extension into the mediastinal fat (black arrow). No nodal or distant metastases were identified. The tumor was classified as T3 N0 M0 and staged as IIIB according to the AJCC Cancer Staging Manual [20-23].
- **Figure 3**: Practical example of tumor burden assessment according to the mRECIST 1.1 criteria in a contrast-enhanced CT of a 69-year-old patient with malignant pleural mesothelioma of the left hemithorax treated with Nivolumab plus Ipilimumab. The axial images (1, 2, and 3) in which the pleural target lesions (≥ 7 mm) are measured are marked in the coronal (A) and axial (B) reconstructions. All measurements were performed perpendicular to the mediastinum and the chest wall. A total of 4 measurements were taken. The tumor burden, calculated as the sum of the measurements (10 mm in axial section 1, 36 mm in axial section 2, and 11 mm in two different measurements in axial section 3), amounts to 68 mm.
- **Figure 4**: Practical example of tumor response assessment using the mRECIST 1.1 criteria in the same patient as shown in Figure 2, who was treated with Nivolumab plus Ipilimumab. A comparison between the baseline and follow-up scans (performed two months after the start of treatment) revealed an increase in tumor burden of approximately 30% compared to the nadir (97 mm in the follow-up CT scan versus 68 mm in the baseline CT scan). Additionally, new unequivocal pleural lesions (white arrows) are evident in the follow-up scan. The assigned response was classified as "progressive disease".
- **Figure 5**: Practical example of tumor response assessment using the mRECIST 1.1 criteria in a 73-year-old patient with malignant pleural mesothelioma of the right hemithorax, treated with Nivolumab. The baseline tumor burden was 71 mm, and the tumor burden at the follow-up was 72 mm, without any unequivocal new non-pleural lesions or pleural thickening exceeding the minimum measurable size (i.e., ≥ 7 mm). The same imaging findings observed in the follow-up CT scan of October 2020 were confirmed in a subsequent follow-up CT performed four weeks later (November 2020 – not shown in the figure). The assigned response was classified as “stable disease”.
- **Figure 6**: Simplified resume scheme of microenviromental mechanisms that seem to be contribute to HPD [74]. A high ratio of M2 to CD8+ T-lymphocytes seems to contribute to HPD and ED after ICI exposure.

Table legends

- **Table 1**: TNM classification for malignant pleural mesothelioma according to the 8th edition of the American joint Committee on Cancer (AJCC) Cancer Staging Manual [20-23].
- **Table 2**: Staging system according to the 8th edition of the American joint Committee on Cancer (AJCC) Cancer Staging Manual [20-23].
- **Table 3**: Summary table of the main acquisition parameters for each imaging technique 14andomized14 for MPM TNM staging and follow-up [15,19,27,28].
- **Table 4**: mRECIST 1.1 response classification criteria for malignant pleural mesothelioma [18, 20, 34, 35, 36].
- **Table 5**: Major clinical trials in malignant mesothelioma [50-60]. OS: overall survival; PFS: progressione free survival; ORR: objective response rate; NR: not reached.

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TNM classification for malignant pleural mesothelioma	
T category	
TX	Primary tumor not assessable
T0	Absence of the primary tumor
T1	Tumor involving ipsilateral parietal pleura (mediastinal and diaphragmatic included) with or without involvement of visceral pleura
T2	Tumor involving ipsilateral parietal surface (visceral, parietal, mediastinal and/or diaphragmatic), with at least one of the following features: • Confluent visceral pleural tumor (including the fissures) • Involvement of diaphragmatic muscle • Invasion of the lung
T3	Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: • Invasion of the endothoracic fascia • Extension into the mediastinal fat • Solitary, completely resectable focus invading soft tissues of the chest wall • Non-transmural involvement of the pericardium
T4	Tumor involving all of the ipsilateral pleural surfaces with at least one of the following features: • Diffuse or multifocal invasion of soft tissues of the chest wall • Any rib involvement • Invasion of the peritoneum through the diaphragm • Invasion of any mediastinal organ • Direct extension to the contralateral pleura • Invasion of the spine or brachial plexus • Transmural invasion of the pericardium (with or without pericardial effusion) or myocardium invasion
N category	
NX	Regional lymph nodes not assessable
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal lymph nodes (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes)
N2	Metastases in the contralateral bronchopulmonary, hilar, or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes
M category	
MX	Presence of distant metastases not assessable
M0	No evidence of distant metastases
M1	Evidence of distant metastases

Table 1: TNM classification for malignant pleural mesothelioma according to the 8th edition of the American joint Committee on Cancer (AJCC) Cancer Staging Manual [20-23]. TNM = Tumor, Node, and Metastasis; T = Tumor; N = Nodes; M = Metastasis.

Staging system for malignant pleural mesothelioma				
Stage		**T**	**N**	**M**
I	IA	T1	N0	M0
	IB	T2 or T3	N0	M0
II	-	T1 or T2	N1	M0
III	IIIA	T3	N1	M0
	IIIB	T1, T2 or T3	N0, N1 or N2	M0
IV	-	T4	N0, N1 or N2	M0
		Any T	Any N	M1

Table 2: Staging system according to the 8th edition of the American joint Committee on Cancer (AJCC) Cancer Staging Manual [20-23]. T = Tumor; N = Nodes; M = Metastasis.

Imaging technique	Staging (TNM)	Acquisition parameters
CT	Local staging (T)	• Contrast medium administration: 50-75 ml at a rate of 3-4 ml/s. • FOV, voltage (80-130 kVp), and tube current (100 to 200 mA) tailored to the patient's physique. • Axial images with 1- to 3-mm thickness, reconstructed using a soft-tissue kernel.
MRI	Local staging (T)	• 1.5 or 3 T scanners. • T1-weighted and T2-weighted single-shot acquisitions on both coronal and axial planes with the following parameters; slice thickness = 5 mm, interslice gap = 1.5 mm; FOV = 400 mm, matrix size = 320 x 224. • 3D T1-weighted volume interpolated gradient echo acquisitions to cover the entire chest and diaphragm in a single breath-hold. • DWI with 3 to 6 b-values ranging from 0 to 1000 s/mm^2, and ADC maps. • Multiplanar T1 sequences following administration of gadolinium-based contrast medium (0.1 mmol/kg). • Free-breathing DCE 3D gradient echo sequence during contrast medium administration (optional – whether available).
^{18}FDG PET/CT	Systemic staging (N, M)	• ^{18}FDG dose according to dose calculator charts • Imaging performed 60 minutes following ^{18}FDG administration. • Non-contrast low-dose CT scan from the head to the proximal thighs. • PET scan encompassing the same FOV of CT, performed immediately after the CT scan, with each bed position acquired over approximately 3 minutes.

Table 3: Summary table of the main acquisition parameters for each imaging technique reccomended for MPM TNM staging and follow-up [15,19,27,28].

mRECIST 1.1 response classification criteria for malignant pleural mesothelioma		
Type of response	*Therapeutic protocol*	*Description*
Complete Response (CR)	No immunotherapy/Immunotherapy	Disappearance of all the "pleural" and measurable "non-pleural" target lesions, and any of the "pathological" lymph nodes (whether target and non-target) must have reduction to short axis < 10 mm in the imaging follow-up*.
Stable Disease (SD)	No immunotherapy/Immunotherapy	A decrease of at least 30% of the tumor burden in the imaging follow-up, taking the baseline tumor burden as reference*.
Stable Disease (SD)	No immunotherapy/Immunotherapy	A shrinkage <30% of the tumor burden when compared to the baseline, or an increase <20% of the tumor burden when compared to the nadir**, in absence of unequivocal new either non-pleural lesion or pleural thickening that exceeds the minimum measurable size (i.e. ≥ 7 mm).
Progressive Disease (PD)	No immunotherapy	An increase of at least 20% of the tumor burden (with an absolute increase ≥ 5 mm), using the nadir** as reference. The detection of an unequivocal new either non-pleural lesion or pleural thickening that exceeds the minimum measurable size (i.e. ≥ 7 mm) would be considered as PD.

	Immunotherapy	When a PD is evidenced in a follow-up imaging, it is considered as immunotherapy unconfirmed PD (iUPD) and a further imaging assessment between 4-8 weeks must be performed, with the following scenarios:
		• The response will be classified as immunotherapy Confirmed PD (iCPD) whether we observe at least one of this conditions:
		  ○ Further increase of the tumor burden ≥ 5 mm
		  ○ Further increase of non-target lesions
		  ○ Appearance of new target or non-target lesions when compared to the previous imaging assessment.
		• If response pattern in the subsequent imaging assessment results to meet the criteria of SD, PR or CR when compared to baseline tumor burden, the response will be classified as SD, PR or CR.

*This pattern of response can be claimed only at a subsequent time point as specified in the protocol (usually 4 weeks later). **nadir = the smallest tumor burden on study		

Table 4: mRECIST 1.1 response classification criteria for malignant pleural mesothelioma [18,20,34,35,36]. mRECIST 1.1 = mesothelioma-specific modified Response Evaluation Criteria In Solid Tumors version 1.1.

Name study and year	Phase	Number of patients	Drugs	Line	Median OS (months)	Median PFS (months)	ORR (%)
Combination therapy							
Checkmate743 (2021) (50,51)	III	605	Nivolumab + Ipilimumab vs CHT	First line	18.1 vs 14.1	6.8 vs 7.2	40 vs 44
NIBIT-MESO 1 (2018) (52)	II	40	Tremelimumab + Durvalumab	Second and third line	16.6	5.7	28
INITIATE (2019) (53)	II	34	Nivolumab + Ipilimumab	Second and more line	NR	6.2	29
MAPS2 (2019) (54)	II	125	Nivolumab +/− Ipilimumab	Second and more line	Nivo arm 11.9 Ipi-Nivo arm 15.9	Nivo arm 4.0 Ipi-Nivo arm 5.6	Nivo arm 19.0 Ipi-Nivo arm 28.0
Monotherapy							
KEYNOTE-028 (2017) (55)	Ib	35	Pembrolizumab	Second and more line	18	5.4	20
KEYNOTE-158 (2021) (56)	II	118	Pembrolizumab	Second and more line	10.0	2.1	8
NIVO MES (2018) (57)	II	34	Nivolumab	Second and third line	11.8	2.6	24
MERIT (2019) (58)	II	34	Nivolumab	Second and third line	17.3	6.1	29
CONFIRM (2021) (59)	III	332	Nivolumab vs placebo	Second line	10.2 vs 6.9 (p=0.0090)	3.0 vs 1.8 (p=0.0012)	11.0 vs 1.0 (p=0.00086)
JAVELIN (2019) (60)	Ib	53	Avelumab	Second and more line	10.7	4.1	9

Table 5: Major clinical trials in malignant mesothelioma [50-60]. OS: overall survival; PFS: progressione free survival; ORR: objective response rate; NR: not reached.

Figure 1

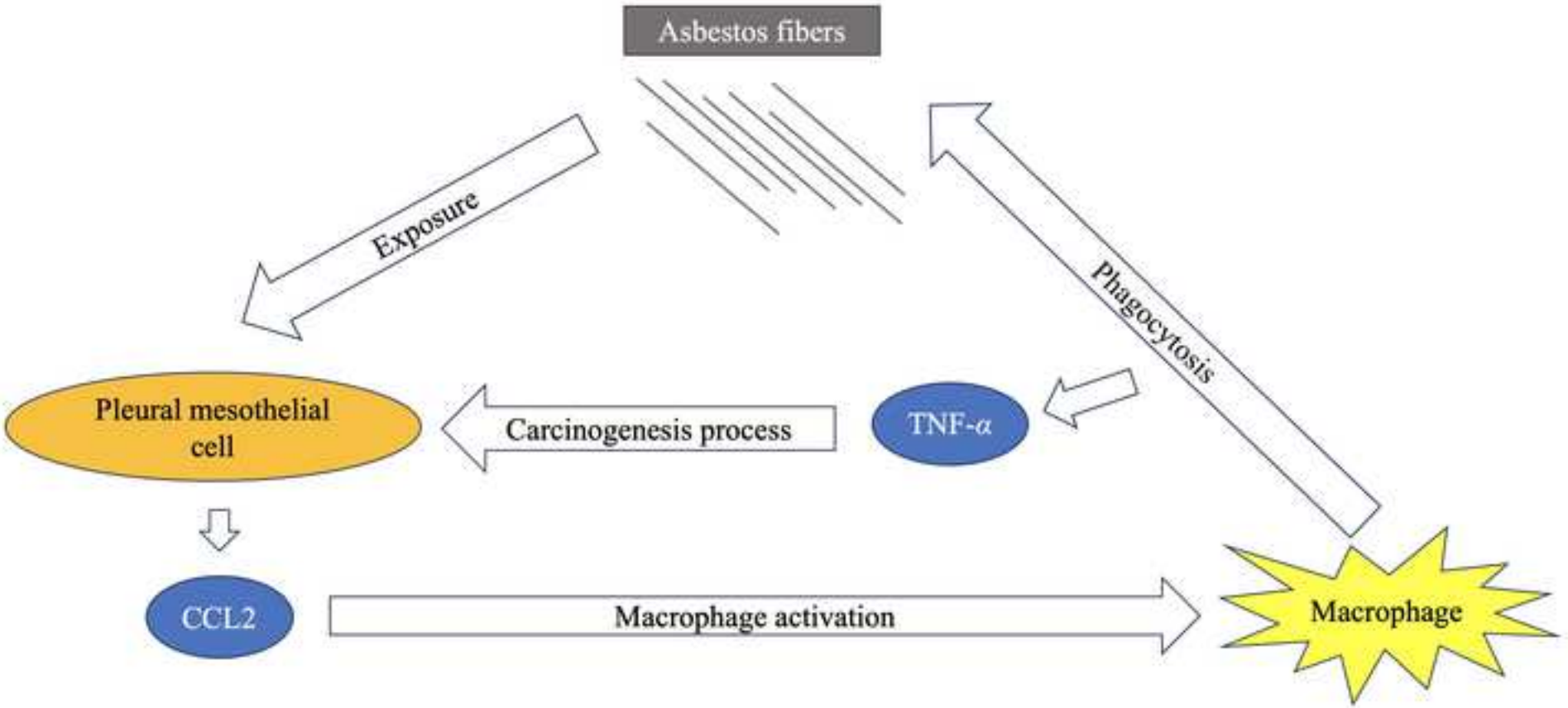

Figure 2

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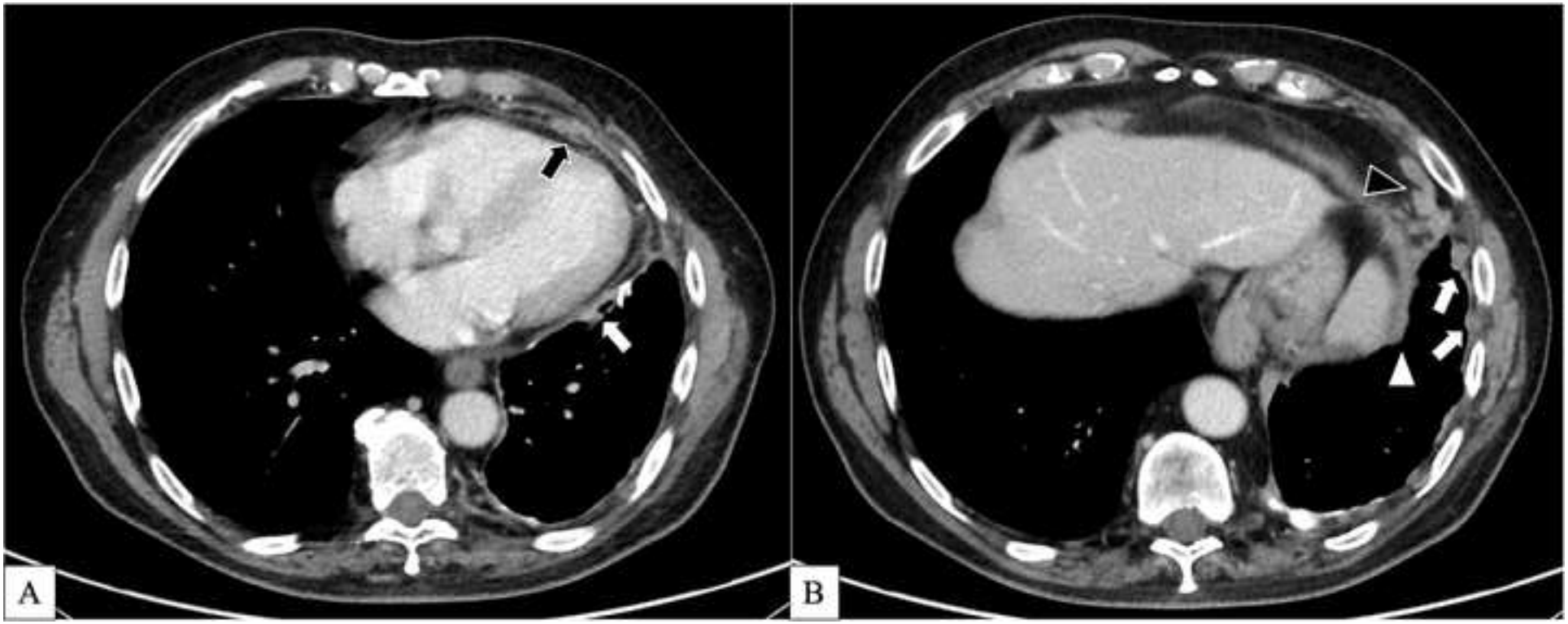

Figure 3

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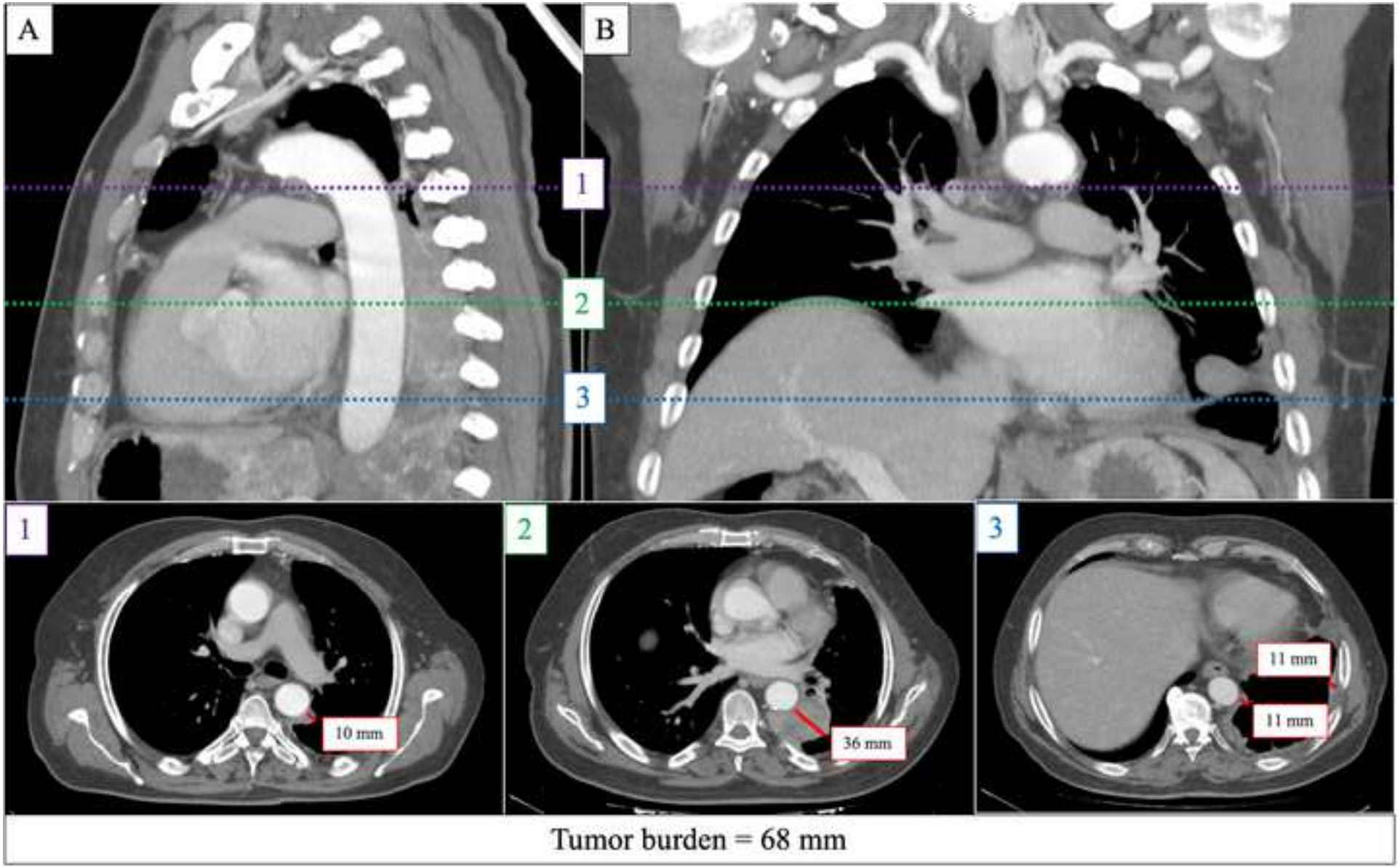

Figure 4

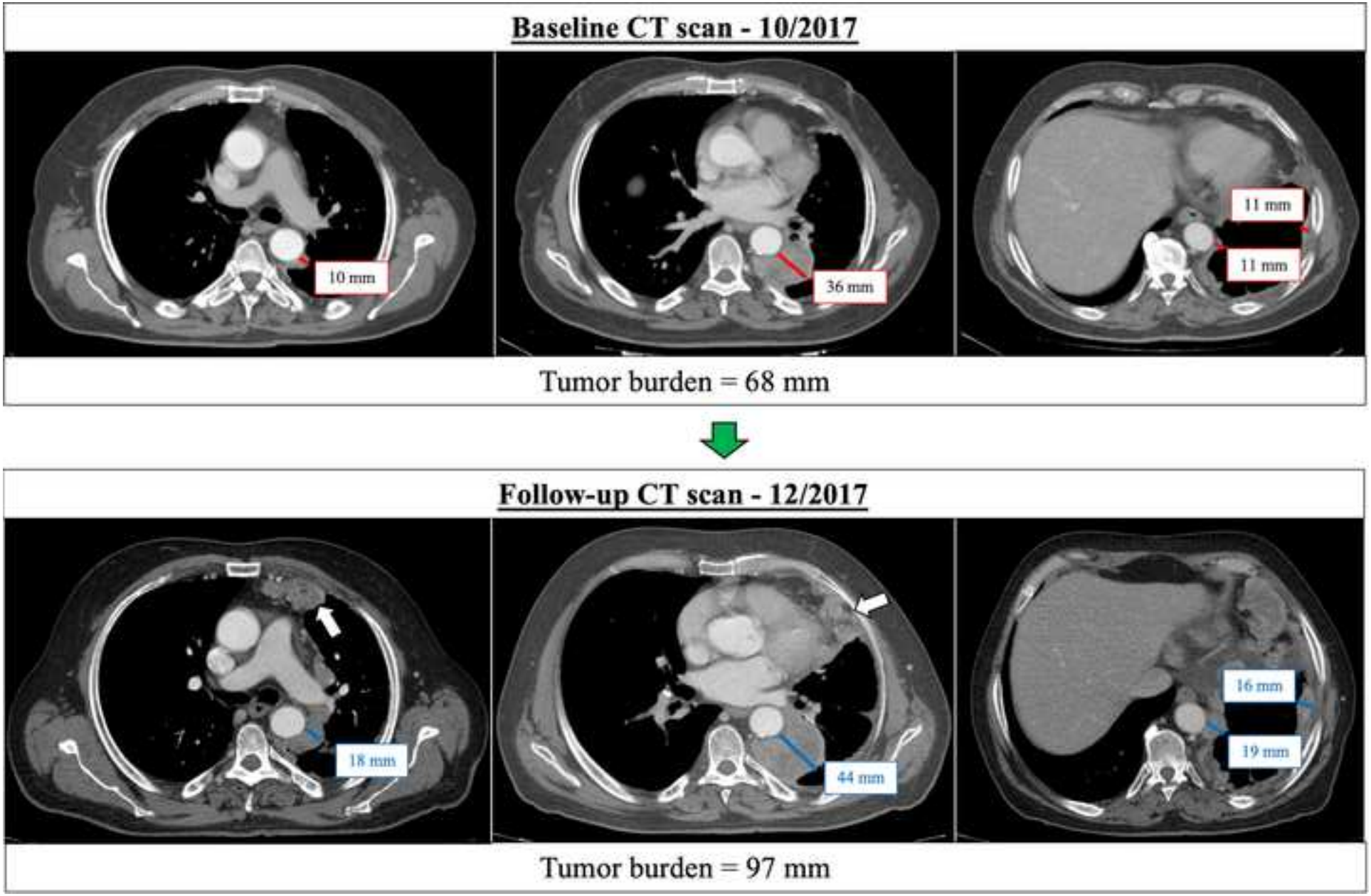

Figure 5

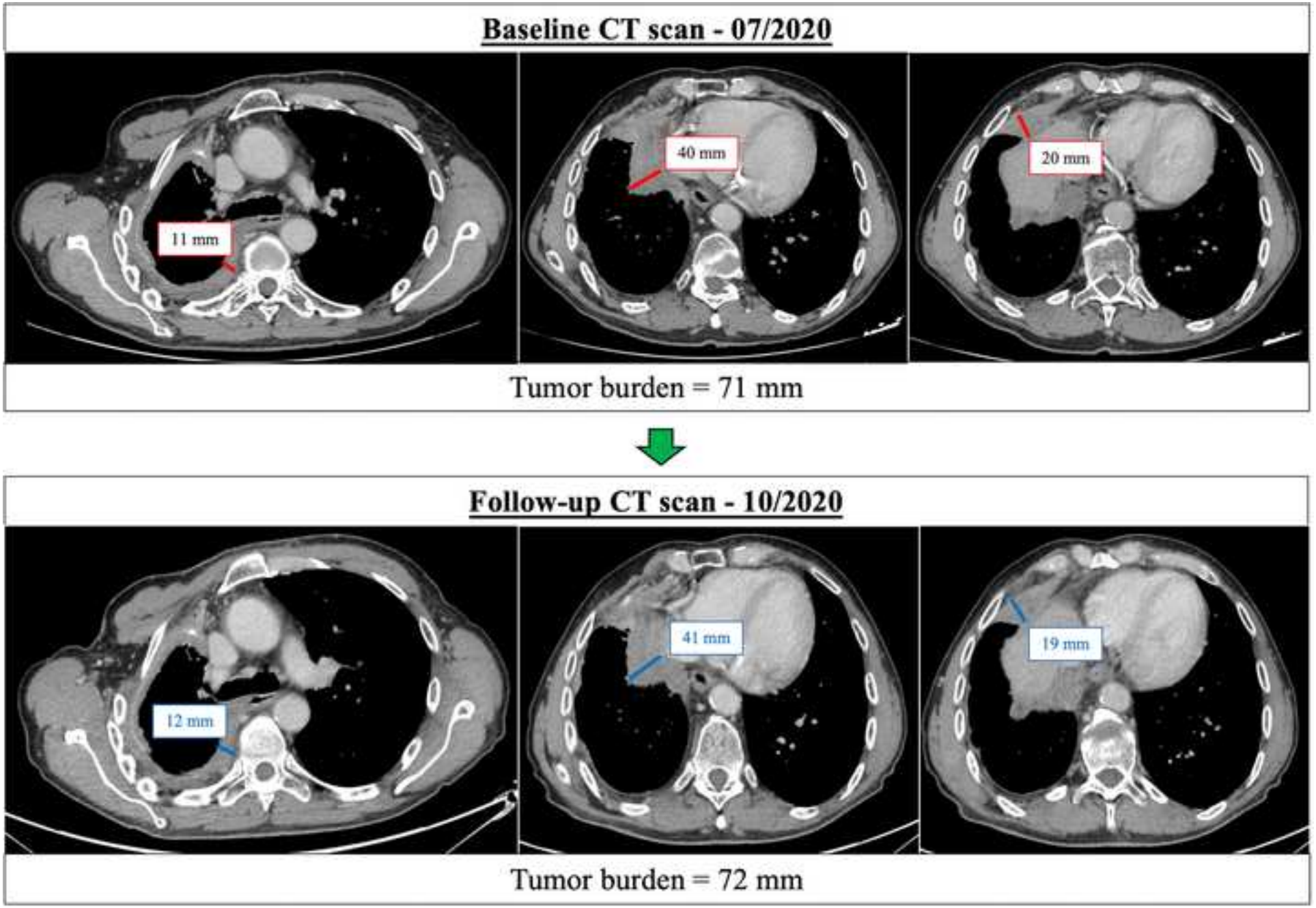

Figure 6