

Complex Target Volume Delineation and Treatment Planning in Radiotherapy for Malignant Pleural Mesothelioma (MPM)

Aaron Innocent Bogmis^{1*}, Adrian Raducu Popa², Daniela Adam², Violeta Ciocâltei², Nicoleta Alina Guraliuc², Florin Ciubotaru², Ion-Christian Chiricuță²

¹Department of Electricity, Solid State Physics & Biophysics, Faculty of Physics, University of Bucharest, Bucharest, Romania

²Amethyst Radiotherapy Center, Otopeni, Romania

Email: *bogmis.ai@medphysics.fr

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Abstract

Introduction: Radiotherapy alone or combined with surgery and/or chemotherapy is being investigated in the treatment of malignant pleural mesothelioma (MPM). This study aimed to simulate a Volumetric Modulated Arc Therapy (VMAT) treatment of a patient with MPM. **Materials and Methods:** CT images from a patient with intact lungs were imported via DICOM into the Pinnacle³ treatment planning (TP) system (TPS) and used as a model for MPM to delineate organs at risk (OAR) and both clinical and planning target volumes (CTV and PTV) with a margin of 5 mm. Elekta Synergy with 6 MV photons and 80 leafs MLCi2 was employed. VMAT plans were generated using two coplanar arcs with gantry rotation angles of 178° - 182°, the collimator angles of each arc were set to 90°, Octavius[®] 4D 729 was employed for quality assurance while the calculated and measured doses were compared using VeriSoft. **Results:** A TP was achieved. The Gamma volume analysis with criteria of 3 mm distance to agreement and 3% dose difference yielded the gamma passing rate = 99.9%. The reference isodose was 42.75 Gy with the coverage constraints for the PTV D95 and V95 = 95.0% of 45 Gy. The remaining dosimetric parameters met the recommendations from the clinically acceptable guidelines for the radiotherapy of MPM. **Conclusion:** Using well-defined TV and VMAT, a consistent TP compared to similar ones from publications was achieved. We obtained a high agreement between the 3D dose reconstructed and the dose calculated.

Keywords

Malignant Pleural Mesothelioma, Radiation Therapy, Radiotherapy, Volumetric Modulated Arc Therapy, VMAT, Target Volume Delineation, Treatment Planning, CTV, PTV

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare locally invasive (malignant), asbestos-related cancer [1] [2] that arises from the pleural surfaces, which encapsulate the lung and thoracic cavity. But, non-asbestos-related mesothelioma has been reported [3]. The typical growth pattern is along the pleural surface; but, infiltration of the lung and/or mediastinal and chest wall structures can occur in a more advanced stage while distant metastases outside the chest can result also [4]. Video thoracoscopy is the standard procedure for confirming the disease and obtaining sufficient tissue for the diagnosis; and the complete and detailed staging is mandatory for MPM categorization and for therapeutic decision making [5].

MPM treatment may include systemic chemotherapy, surgery (extrapleural pneumonectomy, pleurectomy, decortication, thoracotomy, complete surgical resection), radiation therapy, trimodality therapy (combination of chemotherapy, definitive surgery, and radiation therapy), targeted and biologic therapies [6]. Technically, the radiotherapy treatment of MPM with intact lungs (*i.e.* no surgery) is very challenging not only due to the large size and the complex shape of the target volume (TV), but also because of the difficulty to distinguish the tumor from non-malignant radiographic abnormalities in addition to the need to spare organs at risk (OAR) within and in the vicinity including the ipsilateral lung to protect from ionizing radiation [7].

The accuracy of the set-up, tumor delineation, treatment plan generation and the treatment delivery itself are all conditioned by the ability to deliver a precise lethal dose of radiation to the tumor while minimizing dose to surrounding healthy structures. Thus, one of the most challenging aspects in this scenario is the accurate localization and delineation of the OAR and TV followed by the accurate development of a treatment planning (TP) prior to the actual radiation treatment delivery. Volumetric modulated arc therapy (VMAT) is a promising new treatment method which compared with conventional radiotherapy, has the potential to allow more effective sparing of normal tissues and OAR while providing conformal high-dose irradiation for improved target coverage and dose delivery [8]. However, there are limited reports available on VMAT.

The purpose of this study based on a simulation of a patient with MPM and intact lungs, was to manually delineate TV and OAR, then to plan an irradiation of TV around an OAR as the whole involved lung pleural space. A Volumetric Modulated Arc Therapy (VMAT) TP on a Pinnacle³ treatment planning system (TPS) was used.

2. Materials and Methods

2.1. Tumor Board Indication—Imaging for Target Volume Delineation

The chain of procedures in a modern radiation treatment process that must be followed to guarantee the safety of the patients by making sure they are pro-

tected from overexposure to ionizing radiation is the following (Figure 1).

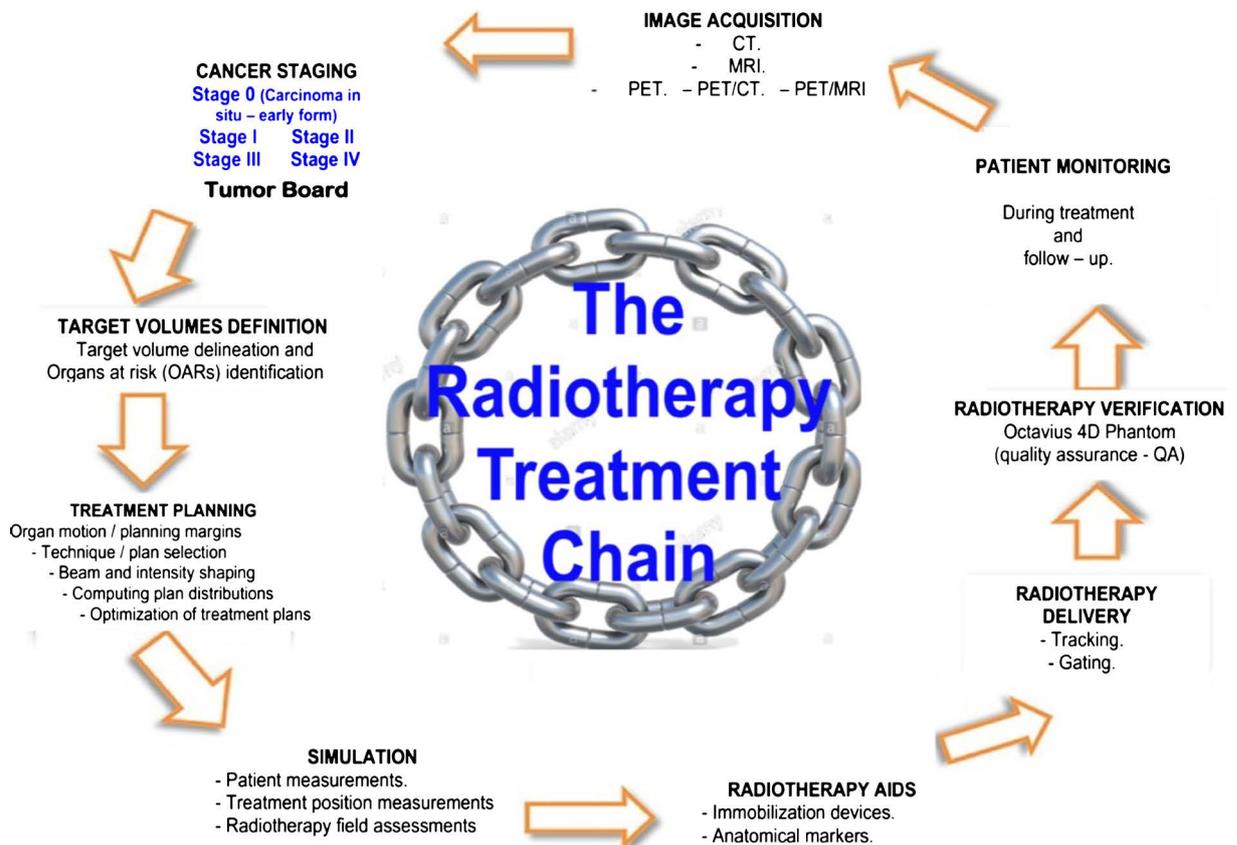


Figure 1. Sequential process of planning and delivery of radiotherapy as applied at AMETHYST Radiotherapy Center, Otopeni, Romania.

2.2. Materials

The Volumetric modulated arc therapy (VMAT) system used at AMETHYST Radiotherapy Center, Otopeni in Romania when carrying out this work included the Elekta Synergy linear accelerator (linac) 6 MV photons, 80 leafs MLCi2 with the IGRT-CBCT, the Pinnacle³ version 16.2 (Philips Medical Systems, Fitchburg, WI 53711-4910) treatment planning system (TPS), the MOSAIQ Oncology Information Management System (Elekta, Stockholm, Sweden) and Octavius[®] 4D phantom with a 2D-array 729 detector.

Elekta Synergy linear accelerator (linac) 6 MV photons, 80 leafs MLCi2 was employed. CT images from a 58-year old female patient with an ovarian cancer and intact lungs were imported via DICOM into the Pinnacle³ version 16.2 (Philips Medical Systems, Fitchburg, WI 53711-4910) treatment planning system and used as a model to simulate a patient with malignant pleural mesothelioma (MPM) in actual clinical conditions.

2.3. Methods

2.3.1. Target Volume Delineation

For the treatment of MPM with radiotherapy, there is no published delineation

guideline, thus, in this work, we followed target volume delineation (TVD) tips and instructions from the Target Volume Delineation Guidelines in Malignant Pleural Mesothelioma [9]. We delineated both lungs following the atlas for the delineation of OAR in thoracic RT proposed by the Radiation Therapy Oncology Group (RTOG) [10] [11] by using the pulmonary window. Thus, lungs considered as two distinct organs were delineated separately as right and left, and then both were combined as a single organ prior to the dose volume histogram (DVH) evaluation step. The chest wall and ribs were delineated by expanding 2 cm lateral, anterior, and posterior to the ipsilateral lung and excluding the lung itself starting 3 cm superior to the PTV and ending 3 cm inferior to it. The CTV included in the PTV was defined inside the chest wall and ribs contouring. That delineation (chest wall and ribs) includes intercostal muscles and nerves but excludes the vertebral bodies, sternum, skin, and other muscles. In addition to the CTV and PTV, both breasts and the OAR located inside the chest cavity: the heart, the esophagus, the spinal cord and of course the lungs were also contoured.

2.3.2. Radiation Therapy Planning

Organs at risk (OAR) and two target volumes (TV): clinical target volume (CTV) and planning target volume (PTV) were delineated manually on the TPS with a margin of 5 mm following instructions from the target volume delineation (TVD) Guidelines in MPM [9]. Using the inverse planning method, VMAT plans were generated employing two coplanar arcs with gantry rotation angles of 178° - 182° on the TPS. The collimator angles of each arc were set to 90° .

2.3.3. Plan Evaluation and Volume Analysis —Quality Assurance

The complexity associated with MPM treatment planning is due to the presence of radiosensitive structures with different dose prescriptions. The treatment plan evaluation was made by analyzing the dose distribution over the transverse section and by evaluating the dose volume histogram (DVH) which displays the radiation doses received by all structures/regions of interest (ROI) (PTV, CTV, OAR). Octavius[®] 4D phantom with a 2D-array 729 detector was used for the quality assurance (QA). The Volume Analysis displays the analysis of the Octavius[®] 4D measurements. The Gamma 3D method was used to calculate the 3%/3mm passing rates. To evaluate the deviation between the TP developed and the measured beam, the 3D Gamma Index method available in VeriSoft was employed. The Volumetric Gamma analysis provides a useful statistical overview of the 3D gamma calculation.

2.3.4. Dose Prescription

The prescribed dose was 45 Gy in the PTV for 25 fractions resulting to 1.8 Gy per fraction. The ipsilateral involved lung should be spared optimally.

2.3.5. Dose Constraints of Organs at Risk

For the treatment of malignant pleural mesothelioma for a patient with intact

lungs, the target volume for radiotherapy (RT) of one lung includes the entire visceral and parietal pleura which form a circumferential envelope around the lung, extend along fissures between lobes of the lung, and are attached to ipsilateral, pericardial, and diaphragmatic surfaces leading to a tumoricidal dose of RT for gross disease to be >60 Gy, while the normal tissue tolerance of the adjacent organs is much lower [12]. **Table 1** presents the whole organ tolerances for these structures.

Table 1. Treatment planning objectives for VMAT and IMRT plans, and doses constraints for OAR. (a) TP objectives for VMAT and IMRT plans [13]; (b) Doses constraints for OAR [14].

(a)		
Target	Dose-Volume Constraints	Weight
PTV	Min dose 50 Gy, to 98% volume	100
	Max dose 53 Gy	100
	Uniform dose 50.5 Gy	100
Normal Tissue	Dose-Volume Constraints	Weight
Spinal cord	No portion may receive 45 Gy	75
Contralateral lung	$V_5 < 40\%$	10
	$V_5 < 60\%$	15
Whole lung	$V_{20} < 28\%$	13
	$V_{30} < 20\%$	10
Heart	$V_{30} < 40\%$	10
Ring	Max dose < 51 Gy	10
(b)		
Target (Absorber)	Tumoricidal Radiation Dose	
Gross disease (MPM)	>60 Gy	
Organs at Risk (OAR)	Normal Tissue Dose Tolerance	
Lung	18 - 20 Gy	
Heart	40 Gy	
Liver	30 Gy	
Stomach	50 Gy	
Kidney	18 - 20 Gy	
Spinal cord	45 - 50 Gy	
Brachial plexus	50 Gy	

3. Results

Some of the CT images slices imported via DICOM and showing our manual delineation, the treatment plan developed and the dose distribution are presented in the three planes. The result of the treatment planning verification is also presented.

3.1. Results (1): Target Volume Delineation

Figure 2(a), **Figure 2(b)** show the result of the delineation performed from the Pinnacle³ treatment planning system.

3.2. Results (2): Treatment Planning and Dose Distribution

The planning goal was to deliver the prescription dose (4500 cGy) to 95% of the PTV ($95\% \times 4500 \text{ cGy} = 4275.0 \text{ cGy}$ which is the reference isodose while meeting the normal tissue constraints. The dose distribution is presented separately in the mediastinal window and in the lung (pulmonary) window for both target volumes (the PTV and CTV) for the clarity purpose. **Figure 3(a)**, **Figure 3(b)** and **Figure 4(a)**, **Figure 4(b)** show the result of the treatment planning developed and the dose distribution.

3.3. Results (3): Plan Evaluation and Volume Analysis—Quality Assurance

Figure 5 shows the dose volume histograms (DVH) obtained.

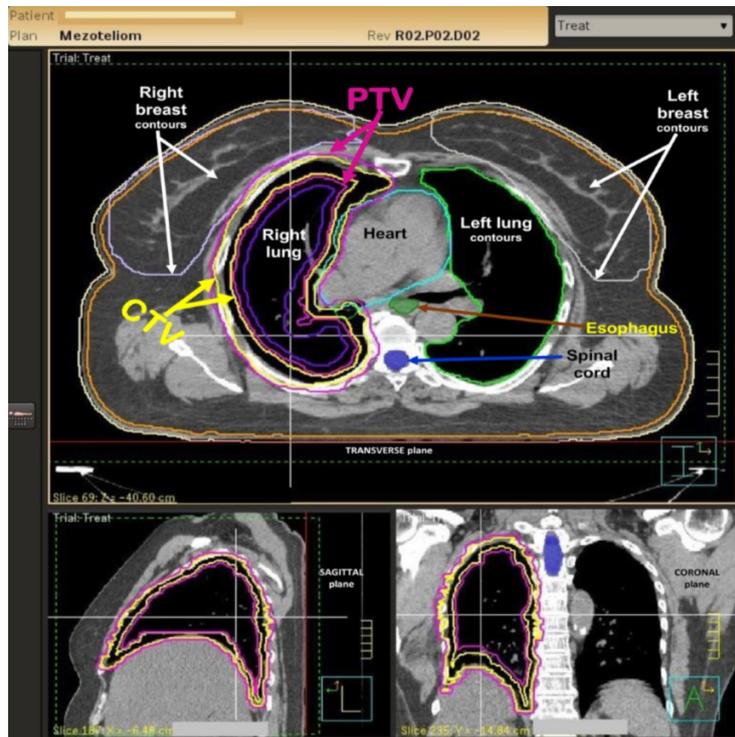
In the volume analysis of our result (**Figure 6**), we obtained the rate for gamma pass = 99.9%. By evaluating the dose distribution and the dose-volume histograms, it can be seen that VMAT plan offers a good coverage of the TV with avoidance of OAR. The reference isodose was 42.75 Gy with the coverage constraints for the PTV D95 and V95 = 95.0% of the prescribed dose (45 Gy).

3.4. Measured and Calculated Dose Distributions—Their Comparison

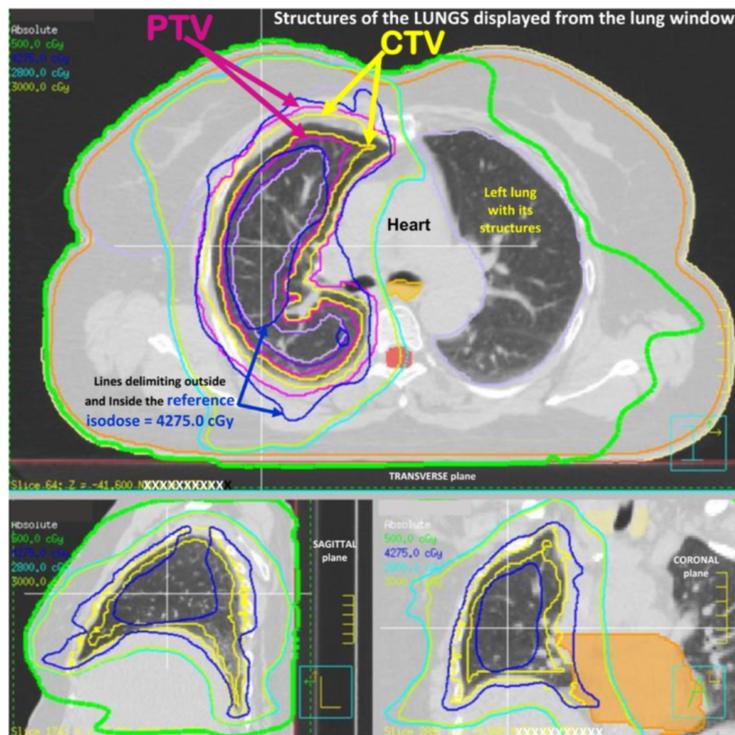
The measured doses (**Figure 7(a)**) in Octavius[®] 4D with a 2D-array 729 detector and the calculated Pinnacle³ doses (**Figure 7(b)**) compared using VeriSoft (**Figure 8(b)**) are presented together with the corresponding dose profiles (**Figure 8(a)**) created using Octavius[®] 4D.

Although the dose distribution is presented in the three plans (transverse, sagittal, coronal), only the transverse section or view was employed because it relates most easily to the treatment plan isodose displayed on the transversal CT slices of the patient. This is because when the 3D dose reconstruction grid is set in the VeriSoft, the plane coordinates matches measurement and calculation dose distribution, but, this advantage vanishes if the coronal and sagittal view in which it is not an easy task to control the exact pixel positions in the calculated dose matrix exported from the TPS are used.

The analysis of the measured dose distribution (**Figure 7(a)**), calculated dose distribution (**Figure 7(b)**) and combined doses distributions (**Figure 8(b)**) shows that: 100% measured dose in the complete range = 2.015 Gy with LR = 91.6 mm and TG = 62.6 mm and 1.465 Gy. 100% calculated dose in the dose map = 2.141 Gy with LR = 91.6 mm and TG = 62.6 mm and mean = 1.447 Gy. The combined measured and calculated dose has an AbsDiff = 0.019 Gy and a Diff = 1.306% with Gamma 3D LR = 92.0 mm and TG = 62.0 mm. The dose line profiles (**Figure 8(a)**) of the measured and calculated doses show a good agreement

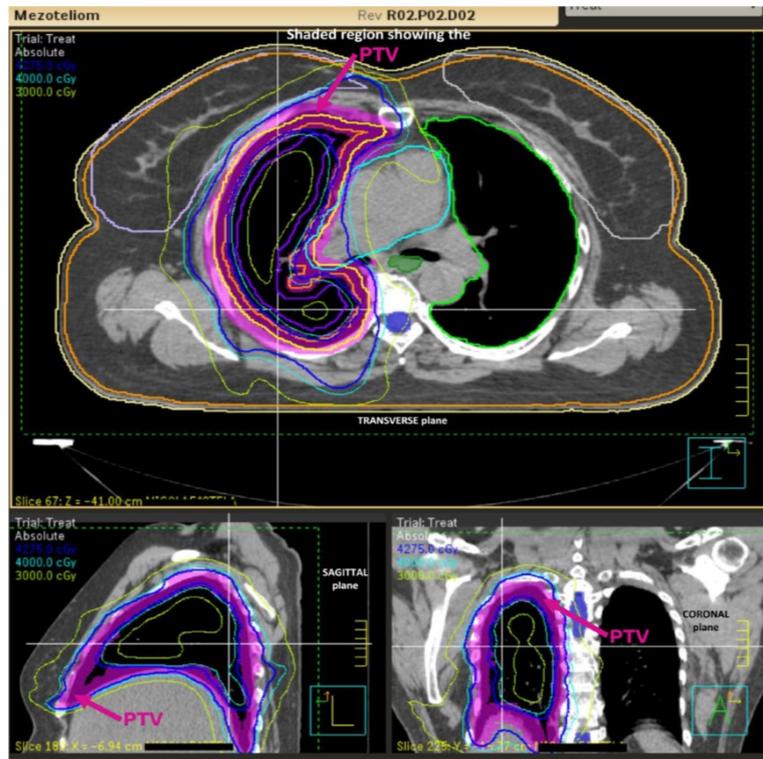


(a)

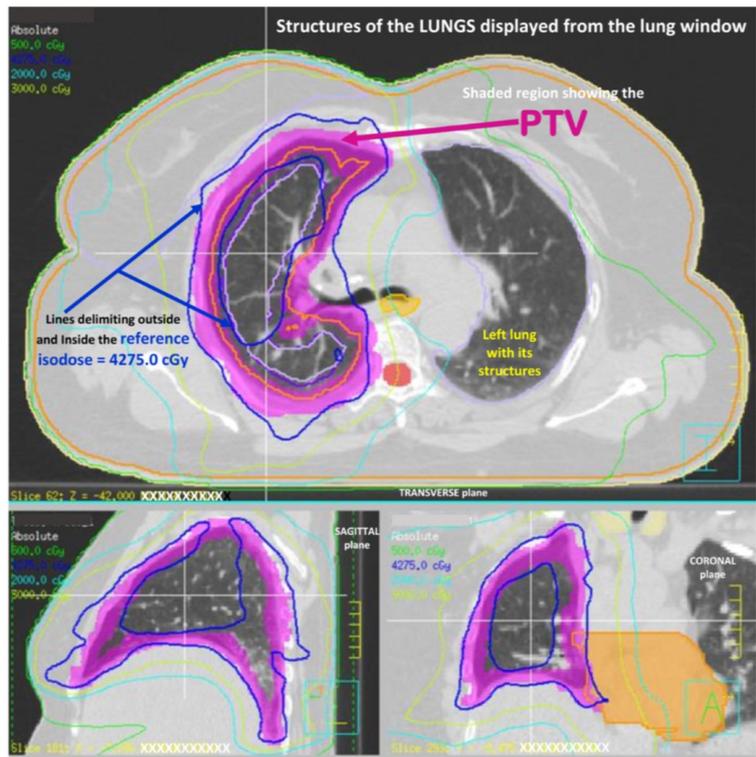


(b)

Figure 2. (a) TV and OAR delineation are displayed on one of the many CT slices showing the transverse, sagittal and coronal planes. The different colored lines indicate the delineated TV (PTV and CTV) and OAR (both lungs, both breasts, the Esophagus, the spinal cord and the heart); (b) The same result presented in the lung window. This in addition also shows the lines delimiting outside and inside the reference dose = 4275.0 cGy.

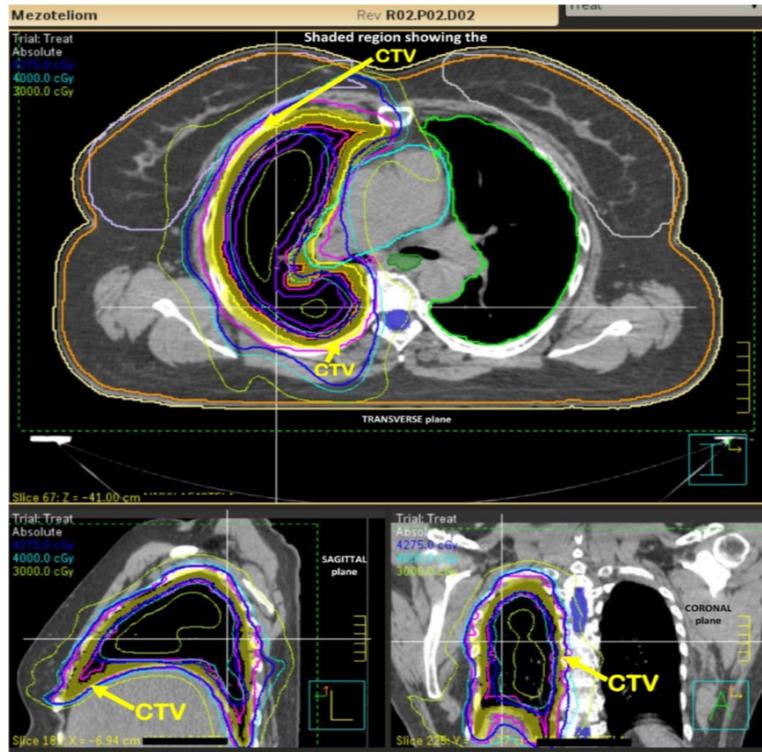


(a)

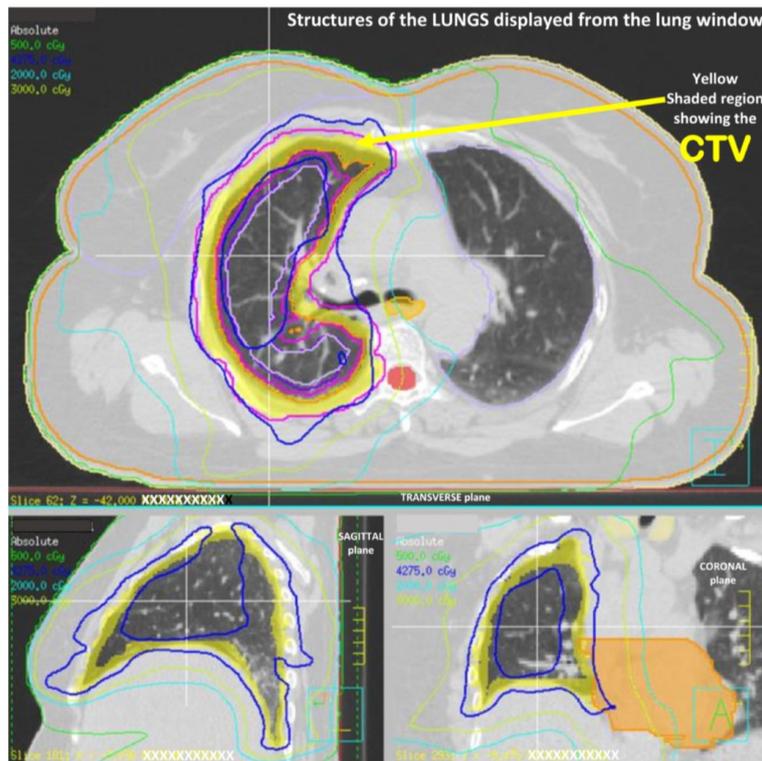


(b)

Figure 3. (a) The dose distribution within the PTV is presented here in the shaded region in magenta color filling its delineated region (volume). The 3 planes: transverse, sagittal and coronal are presented; (b) The same dose distribution within the PTV is presented in the lung window in the 3 planes.



(a)



(b)

Figure 4. (a) The dose distribution within the CTV is presented here in the shaded region in yellow color filling its delineated region (volume). The 3 planes: transverse, sagittal and coronal are presented; (b) The same dose distribution within the CTV is presented in the lung window in the 3 planes.

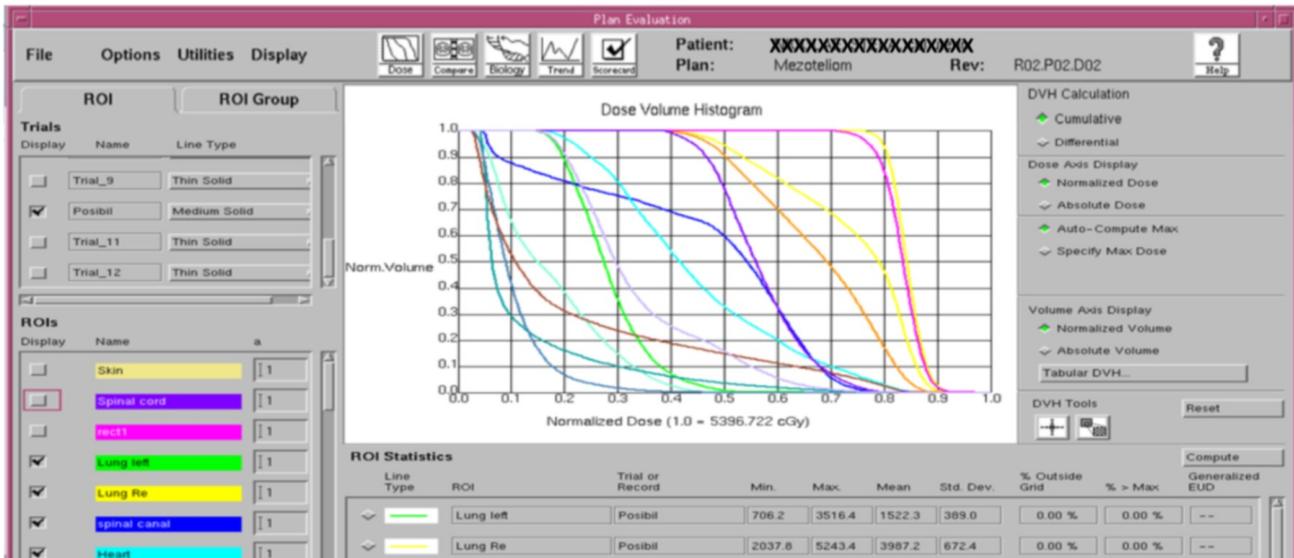


Figure 5. Dose Volume Histogram for VMAT for the PTV 45 and OAR obtained. The curves represent the percentage volumes which got a dose value. Below the DVHs is the associated ROI statistics fully presented in Figure 9 in the Discussion section.

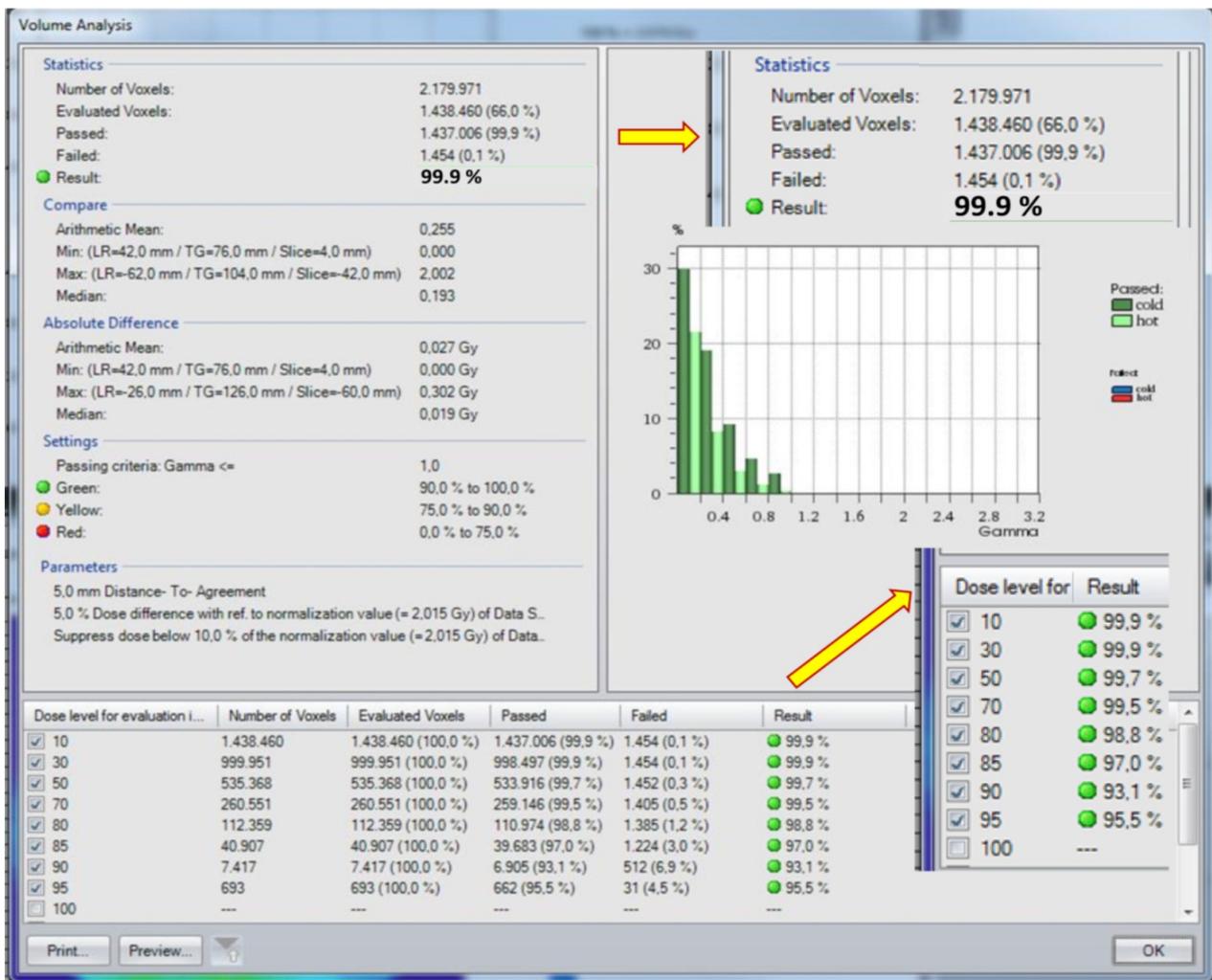
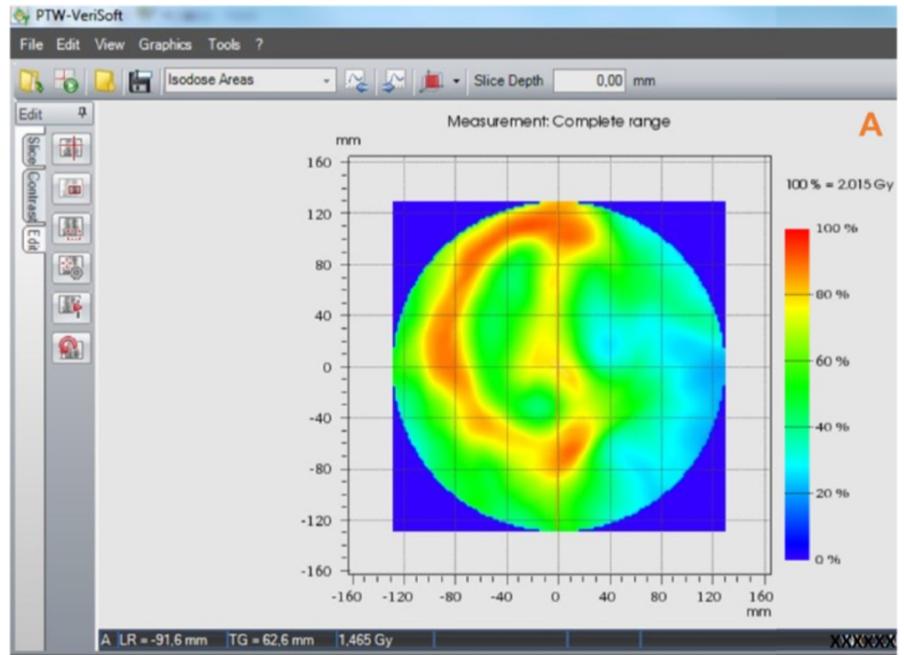
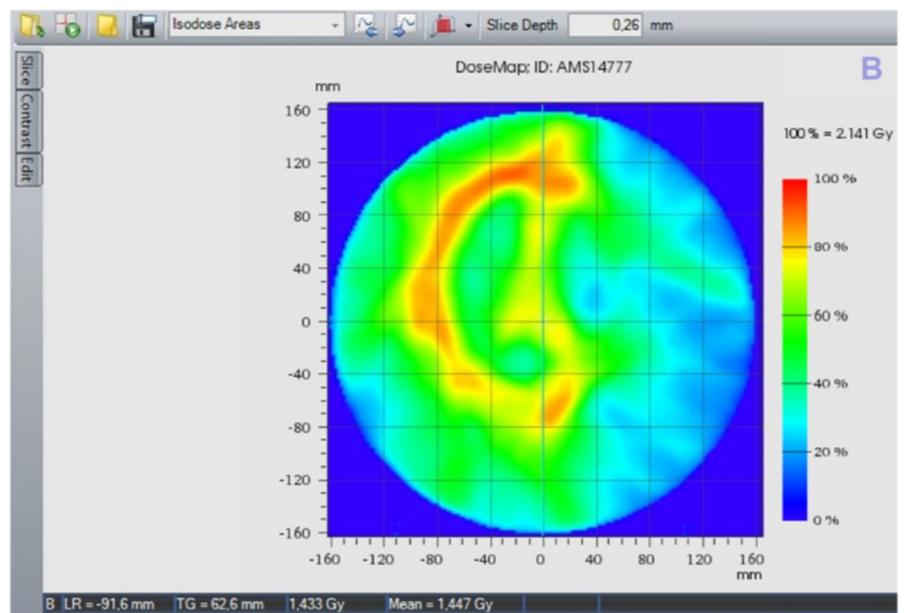


Figure 6. Octavius® 4D Measurements analysis—the Volume Analysis.



(a)



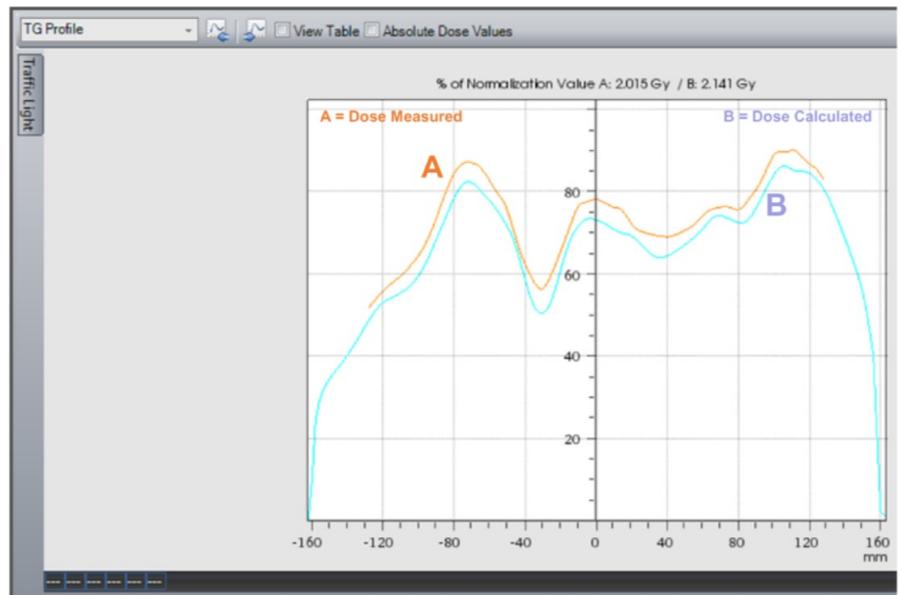
(b)

Figure 7. (a) Measured dose distribution—PTV 45; (b) Calculated dose distribution—PTV 45.

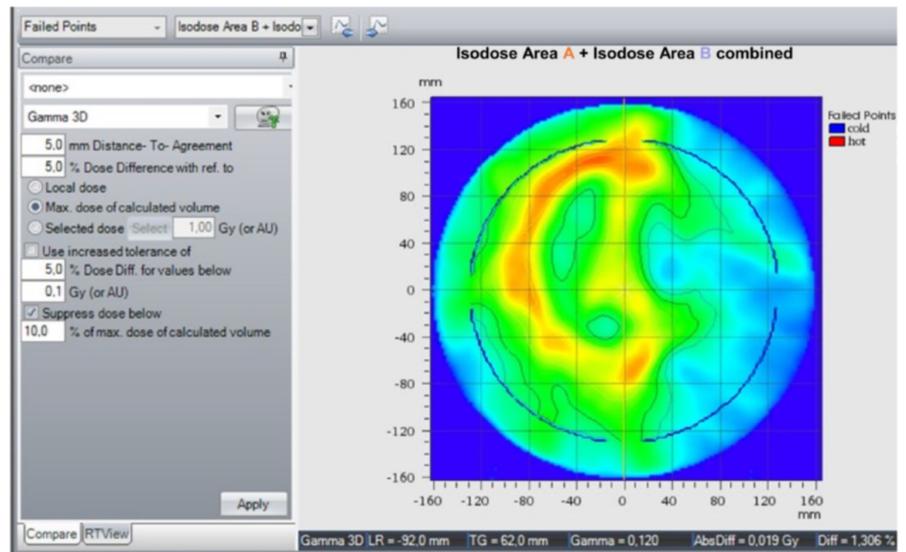
that confirms the other results.

4. Discussion

We have compared our results (Figure 9) with others from different publications to show how consistent was the TP developed and the protection of the involved lung realized (Table 2).



(a)



(b)

Figure 8. (a) Dose profile lines taken across both the measured and calculated dose distributions at TG direction for VMAT treatment planning—PTV 45; (b) Evaluation (Combined) measured and calculated dose distribution—PTV 45.

This study used only one patient as a model for malignant pleural mesothelioma (MPM). It was a 58-year old female patient with an ovarian cancer and intact lungs. The choice for that particular patient was based on the fact that MPM and ovarian/peritoneal serous carcinoma have a lot of features in common. They are two of the most common tumours affecting the serosal cavities, they share a common histogenesis, they are difficult to differentiate morphologically, and they co-express many of the diagnostic markers used by cytopathologists in effusion diagnosis [18]. Therefore, we believed that the said patient was a perfect candidate to use as a model to simulate the VMAT treatment of a patient

ROI Statistics										Compute
Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max	Generalized EUD	
◇	Lung left	Posibil	706.2	3516.4	1522.3	389.0	0.00 %	0.00 %	--	
◇	Lung Re	Posibil	2037.8	5243.4	3987.2	672.4	0.00 %	0.00 %	--	
◇	spinal canal	Posibil	244.1	4440.6	1485.9	1513.4	40.27 %	0.00 %	--	
◇	Heart	Posibil	816.7	4723.8	2402.8	894.2	0.10 %	0.00 %	--	
◇	Kidney R	Posibil	209.5	4399.1	168.3	459.7	74.31 %	0.00 %	--	
◇	Bowel	Posibil	108.6	2486.4	33.4	153.9	94.01 %	0.00 %	--	
◇	Liver	Posibil	120.0	4797.9	891.0	1178.2	21.98 %	0.00 %	--	
◇	R Lung	Posibil	2037.8	5145.1	3641.0	649.1	0.00 %	0.00 %	--	
◇	CTV pleura RIM	Posibil	3431.3	5243.4	4548.7	156.6	0.00 %	0.00 %	--	
◇	PTV	Posibil	2957.7	5253.3	4497.3	192.8	0.00 %	0.00 %	--	
◇	R Lung-7mm	Posibil	2037.8	4575.4	3053.4	445.3	0.00 %	0.00 %	--	
◇	Whole lung	Posibil	706.2	4497.9	1817.7	713.2	0.00 %	0.00 %	--	

Figure 9. The ROI statistics of our results extracted from the Plan Evaluation section in **Figure 5**.

Table 2. Dose Volume Histograms (DVH) details comparing dosimetric factors for VMAT, IMRT, 3D-CRT, Tomotherapy and Proton therapy plans in the treatment of MPM.

Parameters	Our results	Comparison with other results and techniques from external authors				
		VMAT 02 arcs	3D-CRT	IMRT	VMAT 02 arcs	Tomotherapy
PTV receiving 95% of the prescribed dose	95.5	85 ± 5.9	94.8 ± 3.0	96.4		
Prescribed dose (Gy) to the PTV	45	45.5	45.5	45.5	56	52.6
Max dose to Spinal cord (<45 Gy)	44.406	42.9	43.0	44.1		
Mean dose to ipsilateral kidney	1.683 ± 4.597	11.0 ± 5.7	12.4 ± 6.1	6		
Mean dose to liver	8.91 ± 11.78	5.2 ± 6.5	14.8 ± 6.4	16.7		
Mean dose to heart	24.02 ± 8.94	17.1 ± 10.5		11.4		
Mean dose to lung	18.17 ± 7.13	1.2 ± 0.9	5.2 ± 0.9	5.1		
<i>Sources:</i>	(¹)	[14] (²)	[15] (³)	[15] (³)	[16] (⁴)	[17] (⁵)

⁽¹⁾No surgery, *i.e.* MPM model for a case of a patient with intact lungs. ⁽²⁾Surgery: Radiotherapy adjuvant treatment after pleuropneumectomy [14].

⁽³⁾Surgery: Radiotherapy after extrapleural pleuropneumectomy [15]. ⁽⁴⁾Pilot study: Different types of surgery and chemotherapy for different patients [16]. ⁽⁵⁾Trimodality treatment = surgery included [17].

with MPM and intact lungs while using in clinical conditions the same VMAT system employed in the treatment of the ovarian cancer of our model. The clinical and sociodemographic characteristics of that patient were not relevant to be mentioned in this study.

The choice to use VMAT in this work in addition was motivated by its multiple advantages. VMAT can achieve highly conformal dose distributions with improved target volume coverage and sparing of normal tissues compared with conventional radiotherapy techniques [19]. VMAT allows for dynamic modulation of the speed of gantry rotation, the position and movement speed of multi-leaf collimators (MLC) and the rate of dose delivery. It can deliver a treatment that would require 7 - 9 Intensity modulated radiation therapy (IMRT) fields in one or two arcs, reducing treatment delivery time [20]. However, there are also disadvantages associated with VMAT. VMAT requires more extensive quality

assurance (QA) of machines and plans than conventional IMRT. This includes testing field flatness and dose distribution for different dose rates and testing of MLC positioning and movement. Therefore, the optimal treatment plan generally depends on the planner's devoted time and experience to translate the clinical goals into optimization parameters accounting for the relation among three competing priorities: planning target volume (PTV) coverage, PTV dose homogeneity, and sparing of the adjacent OAR [21].

Our model for malignant pleural mesothelioma is related to a case of a patient with intact lungs (*i.e.* no surgery). For that, the irradiation is focused on the pleura (where the PTV and CTV were defined). Organs at risk and both lungs are spared. So, the prescribed dose is intended to treat the cancer within the pleura only, while for the other cases presented for comparison, radiotherapy (with boost in few cases) was combined with surgery and in some cases chemotherapy.

In our model, we care more for example about the ipsilateral lung to protect from radiation while focusing the dose on the pleura. The cases with surgery present a different scenario regarding the lung(s) to protect, *e.g.* there is no ipsilateral lung to spare from radiation in case the later was removed. All that explains some noticeable differences on the table. But definitely, our treatment planning developed is consistent compared to these other results presented.

The reference isodose was 42.75 Gy with the coverage constraints for the PTV D95 and V95 = 95.0% of the prescribed dose (45 Gy). Thus, as it is the case for the other published results, our dose to the PTV receiving 95% of the prescribed dose and the remaining dosimetric parameters including the dose to organs at risk met the recommendations from the clinically acceptable guidelines for the radiotherapy treatment of malignant pleural mesothelioma.

The gamma passing rate (99.9%) of our results and the succeeded voxels for the VMAT planning can be explained by the effect of rotating the collimator angle because the collimation angle used in VMAT increases the detector array space and the resolution [22].

5. Conclusions

In this work, we were concerned with the delineation of complex target volume for malignant pleural mesothelioma (MPM) in radiotherapy using a model for MPM and the development of a treatment planning for Volumetric-Modulated Arc Therapy (VMAT) with associated quality assurance employing Octavius® 4D phantom. Using a well-defined TV and an adequate irradiation technique as VMAT, a consistent TP with the protection of the involved lung parenchyma was achieved.

By evaluating the dose distribution and the dose-volume histogram, it can be seen that VMAT plan offers a good coverage of the target volume with avoidance of organs at risk. The coverage of PTV was more than 95% of prescribed dose for 95% of the volume. The Volumetric Gamma analysis provides a useful statistical overview of the 3D gamma calculation. In the volume analysis of our

result, we obtained the rate for gamma pass = 99.9%. The dose lines profiles of our results show a high agreement between the calculated dose from the Pinnacle³ treatment planning system and the measured dose by the Octavius[®] 4D. The Octavius[®] 4D phantom with its detector array is well equipped for the verification of the dose distribution for VMAT plans in the three transverse, sagittal and coronal planes.

Our results compared to similar ones from the literature show that the treatment planning we developed is consistent.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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