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**The role of radiotherapy in the treatment of malignant pleural mesothelioma – possibilities and controversy**

Улога радиотерапије у лечењу малигног мезотелиома плеуре – могућности и контроверзе

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## The role of radiotherapy in the treatment of malignant pleural mesothelioma – possibilities and controversy

### Улога радиотерапије у лечењу малигног мезотелиома плеуре – могућности и контроверзе

#### SUMMARY

Malignant pleural mesothelioma (MPM) is a rare malignancy with a poor prognosis. In recent years, significant progress has been made in the treatment of this disease, including surgical and radiotherapy techniques, systemic and immunotherapy. Due to the wide range of clinical presentations, lack of phase III randomized trials, and heterogeneity in treatment approach, the treatment of malignant pleural mesothelioma remains challenging regardless of available diagnostic and therapeutic guidelines.

The limited possibility to avoid critical healthy organs (particularly lungs) which can lead to severe, and even fatal radiation-induced toxicity, makes high-dose radical radiotherapy very demanding. Thus, the majority of patients in the era of conventional radiotherapy were mostly referred to no more than palliative radiotherapy only.

Technological development in radiotherapy such as respiratory gating, 4D computed tomography (4DCT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic techniques, and proton therapy, made a step forward in treating malignant pleural mesothelioma with this modality. Today, MPM radiotherapy can be considered in various indications, alone or in combination with surgery and systemic treatment.

However, many questions remain open, and further investigation is needed especially in dose escalation possibility and lung sparing.

**Keywords:** malignant pleural mesothelioma; radiotherapy; treatment

#### САЖЕТАК

Малигни мезотелиом плеуре (MPM) јесте редак малигнитет са лошом прогнозом. Последњих година постигнут је значајан напредак у лечењу ове болести, укључујући хируршке и радиотерапијске технике, као и системску и имунотерапију. Због широког спектра клиничке презентације, недостатка рандомизованих студија фазе III, хетерогености у терапијском приступу, лечење малигног мезотелиома плеуре остаје изазовно и поред доступних водича за дијагностику и терапију.

Ограничена могућност избегавања критичних здравих органа (посебно плућа) који могу довести до озбиљне, па чак и фаталне токсичности изазване зрачењем, чини радикалну радиотерапију високим дозама веома захтевном. Стога је већина пацијената са мезотелиомом у ери конвенционалне радиотерапије, упућивана само на палијативну радиотерапију.

Технолошки развој у радиотерапији укључујући респираторни гејтинг, 4D компјутеризовану томографију (4DCT), интензитетом модулисану радиотерапију (IMRT), волуметријски модулисану лучну радиотерапију (VMAT), технике стереотаксе и протонску терапију, је направио значајан искорак у лечењу малигног мезотелиома плеуре зрачењем. Данас се радиотерапија мезотелиома може разматрати у различитим индикацијама, сама или у комбинацији са хируршким и системским лечењем. Ипак, многа питања остају отворена, и даља истраживања су неопходна, посебно у смислу ескалације радиотерапијских доза и боље поштеде плућног паренхима.

**Кључне речи:** лечење; малигни мезотелиом плеуре; радиотерапија

## INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare malignancy [1], but the outcome remains poor with less than 5% of 5-year overall survival for all stages [2, 3]. It is to date of great oncological concern since it is correlated with significant morbidity and severe symptoms such as pleural effusion, dyspnea, pain, and fatigue [4, 5].

Due to various clinical presentations of MPM and challenging clinical scenarios, the treatment of MPM must be multidisciplinary decided, with an individually tailored strategy

concerning the stage of the disease, histology, performance status (PS), comorbidities, and patient preferences [6].

In the absence of clear data on the radiosensitivity of mesothelioma, clinical evidence point out that it is a rather radioresistant disease, needing a high dose of radiotherapy to the near proximity of critical healthy structures in order to obtain local control. With conventional radiotherapy (2D and 3D conformal radiotherapy), the treatment of MPM was mainly directed to surgery and systemic therapy, while radiotherapy was usually palliative or adjuvant in selected cases [4].

Technological development in radiotherapy including respiratory gating, 4D computed tomography (4DCT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic body radiotherapy (SBRT), and proton therapy, brought back the interest to radiotherapy alone or in combination with systemic therapy and/or surgery. The choice of radiotherapy technique depends on the clinical context, treatment intent (curative or palliative), localization and bulk of the target, organs at risk, and planned dose [7].

In the treatment of malignant pleural mesothelioma today, radiotherapy has five major indications: 1) hemithorax irradiation prior to extrapleural pneumonectomy (EPP); hemithorax irradiation after extrapleural pneumonectomy; 3) hemithorax irradiation after lung sparing therapy (pleurectomy/decortication and/or systemic therapy); 4) prophylactic (procedural path) irradiation, and 5) palliation.

In 2019, Gomez et al. published detailed guidelines for radiotherapy target delineation and treatment delivery for all the above-mentioned indications [8].

All five indications will be discussed focusing on novel radiotherapy technique possibilities, current practice, and open questions.

## **MPM RADIOTHERAPY PLANNING**

Every radiotherapy treatment planning starts with the patient immobilization. For MPM patients it is usually a wing board, with arms overhead, the procedural scar marked with led markers. Standard 3D or 4D CT is performed in free breathing, from lung apex to 3rd lumbar vertebrae due to low diaphragm insertions, with 2,5 to 3 mm thick slices. Prior diagnostic PET/CT is advisory for better gross tumor volume (GTV) delineation. The clinical target volume (CTV) encompasses the entire thoracic cavity, as well as mediastinal lymph nodes. Planning target volume (PTV) is an additional margin of 5-10mm in all directions for

respiratory and set-up uncertainties. Organs at risk (OAR) include both lungs, heart, kidneys, spinal cord, liver, and esophagus (Figure 1).

### **HEMITHORAX RADIOTHERAPY PRIOR TO EPP**

Surgery for mesothelioma after IMRT radiation therapy was introduced by de Perrot et al. in the year 2016. as a trial designed resembling standard hypofractionated preoperative radiotherapy approach in other malignant tumor localization, predominantly rectal cancer. A high radiotherapy dose of 25Gy in 5 fractions was delivered to whole hemothorax, with a simultaneous integrated boost of 5Gy to gross tumor volume, aiming to inhibit reimplantation of malignant cells after surgery. Significant risk of high-grade cardiopulmonary toxicity was avoided by immediate surgery, 6 days after completion of radiotherapy. Overall survival in the whole group of patients was 36 months, but almost 30% of patients had grade 3 or higher complications, including three treatment-related deaths. SMART trial in 2020. provided promising outcomes with this technique, but due to significant treatment-related morbidity it was not widely adopted [4, 5, 8, 9, 10].

Up to now, no randomized prospective trial results have supported this approach, suggesting that it can only be considered in highly experienced centers and clinical trials for obtaining more data [8, 11].

### **HEMITHORAX RADIOTHERAPY AFTER EPP**

Malignant pleural mesothelioma spreads over the pleural surface, making it very difficult to achieve R0 resection at surgery [4]. The rationale for hemithorax radiotherapy after EPP is the reduction of local recurrence after the surgery which is higher than 30%. Still, there are very little randomized trial data to support this approach [2].

One of the first trials in 2011. (MARS) testing EPP followed by classic 3D conformal 54Gy postoperative radiotherapy versus standard oncological care (no pneumonectomy) failed to reach feasibility. The trial showed that surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients [12]. The latter IMRT technique Swiss trial (SAKK 17/04) in 2015. randomized patients who achieved complete remission due to induction chemotherapy (cisplatin/pemetrexed) and EPP to the group receiving up to 55.9Gy IMRT hemothorax radiotherapy and the group set to only follow up. The trial was closed prematurely showing no significant differences between the groups regarding local relapse-free survival

and overall survival, on cost of grade 5 pneumonitis in the radiotherapy group. It was concluded that the addition of hemithorax radiotherapy brings an additional treatment burden, with no patient benefits [4, 13]. Although this was the largest international multicenter phase 2 randomized trial, multiple institutional studies pushed forward with modern radiotherapy techniques after EPP and reported significant improvement in locoregional control rates as well as overall survival rates [7, 14, 15]. On the other hand, lung toxicity was still of major concern leading to significant treatment-related morbidity and mortality due to grade 5 radiation pneumonitis which in some series was up to 46% [7, 15]. In the years that came, greater experience with novel radiotherapy techniques (IMRT, VMAT, helical tomotherapy, etc) and treatment planning, developed strict dose constraints to organs at risk (mainly lungs) lead to reducing toxicity of grade 3 or higher to less than 10% [7, 8].

The postoperative radiation field includes the entire pleural bed and the treatment dose is 45-54Gy with a boost to R1 or R2 residual disease up to 54-60Gy.

In the absence of definitive data that support the evidence, EPP postoperative hemithorax radiotherapy can be considered for operable MPM patients stage I-III but only in centers of excellence with experience in this modality for mesothelioma according to current recommendations [6, 11, 16].

### **HEMITHORAX RADIOTHERAPY AFTER LUNG-SPARING PROCEDURES**

Given the high risk of perioperative mortality after EPP, the trend in surgical approach is switched to less aggressive (lung-sparing) procedures such as pleurectomy/decortication. It is believed that this management has no negative impact on overall survival with lower treatment-related risks [17]. But, the cytoreductive approach imposed a question of adjuvant therapy for reducing the risk of local recurrence. Delivering a high dose of radiotherapy to both intact lungs is one of the most challenging scenarios in radiation oncology due to the high risk of severe and even life-threatening treatment-related toxicity (pneumonitis).

In 2016, the results of a multicentre phase 2 trial that used 50.4Gy with IMRT technique in the lung-sparing multimodality treatment of MPM (IMPRTIN trial) have shown that it can be administered safely with no grade 4 or 5 pneumonitis and improved disease-free and overall survival [18]. Comparable following studies of radical radiotherapy in the lung-sparing approach brought emerging evidence that >45Gy of modern technique radiotherapy can be delivered with acceptable toxicity levels [7].

In the target volume delineation GTV is delineated. CTV includes all GTV sites and the entire virtual space around the pleura. An additional 10 mm margin is added for PTV. The treatment dose is 50.4Gy in 28 fractions with a boost to GTV up to 60Gy (Figure 2).

To date, several ongoing studies are testing the safety and outcomes of this multimodality lung-sparing approach (NGR-LU006, NCT00715611, etc). Until we obtain more detailed data, it is recommended that this demanding technique is to be considered and performed in highly experienced centers preferably within clinical trials.

### **PROPHYLACTIC (PROCEDURAL PATH) RADIOTHERAPY**

The rationale for radiotherapy of intervention sites is seen in the risk reduction of chest wall infiltration and subcutaneous spread following biopsy, thoracoscopy, or thoracotomy in patients with MPM. However, despite several single-center encouraging results, no large, prospective trial or meta-analysis so far has demonstrated a statistically significant reduction of the risk for procedural path dissemination [19, 20]. Thus, this procedure is not recommended upfront according to current protocols but can be considered on case-to-case bases.

### **PALLIATIVE RADIOTHERAPY**

Radiotherapy is the symptom-relieving treatment of choice in MPM patients. The choice of radiotherapy technique and treatment dose depends on the clinical presentation, performance status of the patient, and stage of the disease. In the current protocols, palliative radiotherapy doses range from 8Gy in single fraction, 20Gy in 5 fractions, and 30-39Gy in 10-13 fractions or higher (Figure 3). Novel trials suggest that a higher dose per fraction ( $\geq 4$ Gy per fraction) is associated with better outcome introducing 36Gy in 6 fractions (SYSTEMS-2 trial) and SBRT [5, 7].

### **FUTURE OF MPM RADIOTHERAPY**

The high local recurrence rate and high risk of radiation-induced toxicity focused the interest on other highly precision radiotherapy modalities such as stereotactic body radiotherapy (SBRT), proton therapy, and adaptive radiotherapy. Also, the combination of radiotherapy and advanced surgical techniques, immuno, and/or target therapy is evolving [2].

SBRT aims to deliver high, ablative, radiotherapy dose to a limited target, making it suitable for low tumor burden patients or oligoprogressive disease.

Although there is a very limited amount of data regarding proton beam therapy for MPM, results of recent studies suggest that it can bring improvement in normal tissue sparing and PTV covering, with no greater than grade 3 toxicity due to its physical phenomenon of rapid dose fall of (Bragg's peak) [21].

The concept of adaptive radiotherapy is the creation of new radiotherapy treatment plans during the course of treatment to adapt changes in target volumes detected by image guidance (IGRT). This concept may be favorable for MPM where dose constraints are difficult to meet due to large target volumes. Definitive conclusions are lacking, though [7].

## CONCLUSION

The treatment of malignant pleural mesothelioma remains challenging, especially in the field of radiation oncology. Though there are many concerns and open questions, it seems that novel radiotherapy techniques have promising possibilities for local treatment of this disease. That being said, a more radical radiotherapy approach can be considered for the treatment of MPM patients in highly experienced radiotherapy centers preferably within clinical trials.

**Ethics:** This article was written in accordance with the ethical standard of the institutions and the journal.

**Conflicts of interest:** None declared.

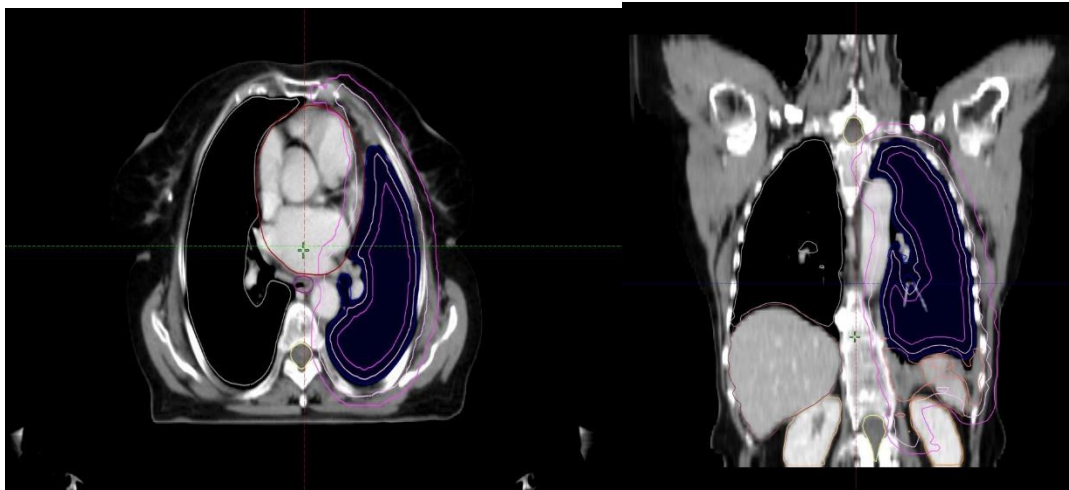
## REFERENCES

1. Alpert N, van Gerwen M, Taioli E. Epidemiology of mesothelioma in the 21st century in Europe and United States, 40 years after restricted/banned asbestos use. *Trans Lung Cancer Res.* 2020;9(1):S28-S38. PMID:32206568; PMCID:PMC7082259; DOI:10.21037/tlcr.2019.11.11
2. Davis A, Ke H, Kao S, Pavlakakis N. An update on emerging therapeutic options for malignant pleural mesothelioma. *Lung Cancer (Auckl).* 2022;13:1-12. PMID:35264891; PMCID:PMC8900635; DOI:10.2147/LCTT.S288535
3. Cimen F, Agackiran Y, Düzgün S, Aloglu M, Senturk A, Atikcan S. Factors affecting the life expectancy in malignant pleural mesothelioma: Our 10 years of studies and experience. *Medicine (Baltimore).* 2022;101(39):e30711. PMID:36181042; PMCID:PMC9524951; DOI:10.1097/MD.00000000000030711
4. Hanna GG, John T, Ball DL. Controversies in the role of radiotherapy in pleural mesothelioma. *Transl Lung Cancer Res.* 2021;10(4):2079-2087. PMID:34012816; PMCID:PMC8107768; DOI:10.21037/tlcr-20-583
5. Cramer G, Simone CB 2nd, Busch TM, Cengel KA. Adjuvant, neoadjuvant, and definitive radiation therapy for malignant pleural mesothelioma. *J Thorac Dis.* 2018;10(21):S2565-S2573. DOI:10.21037/jtd.2018.07.65; PMID:30206500; PMCID:PMC6123183
6. Popat S, Baas P, Faivre-Finn C, Girard N, Nicholson AG, Nowak AK, et al. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2022;33(2):129-142. PMID:34861373; DOI:10.1016/j.annonc.2021.11.005
7. Luna J, Bobo A, Cabrera-Rodriguez JJ, Pagola M, Martin-Martin M, Gonzalez Ruiz MA, et al. GOECP/SEOR clinical guidelines on radiotherapy for malignant pleural mesothelioma. *World J Clin Oncol.* 2021;12(8):581-608. PMID:34513595; PMCID:PMC8394157; DOI:10.5306/wjco.v12.i8.581
8. Gomez DR, Rimner A, Simone CB 2nd, John Cho BC, de Perrot M, Adjei AA, et al. The Use of Radiation Therapy for the Treatment of Malignant Pleural Mesothelioma: Expert Opinion from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. *J Thoracic Oncol.* 2019;14(7):1172-1183. PMID:31125736; DOI:10.1016/j.jtho.2019.03.030
9. de Perrot M, Feld R, Leigh NB, Hope A, Waddell TK, Keshavjee S, et al. Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg.* 2016;151:468-473. PMID:26614413; DOI:10.1016/j.jtcvs.2015.09.129
10. Breen WG, Garces YI, Olivier KR, Park SS, Merrell KW, Nichols FC, et al. Surgery for Mesothelioma After Radiation Therapy (SMART): A Single Institution Experience. *Front Oncol.* 2020;10:392. DOI:10.3389/fonc.2020.00392
11. Kindler HL, Ismaila N, Armato SG 3rd, Bueno R, Hesdorffer M, Jahan T, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2018;36(13):1343-1373. PMID:29346042; PMCID:PMC8058628; DOI:10.1200/JCO.2017.76.6394
12. Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwistle J, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomized feasibility study. *Lancet Oncol.* 2011;12(8):763-772. PMID:21723781; PMCID:PMC3148430; DOI:10.1016/S1470-2045(11)70149-8
13. Stahel RA, Reisterer O, Xyrafas A, Opitz I, Beyeler M, Ochsenbein A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomized, international, multicenter phase 2 trial. *Lancet Oncol.* 2015;16(16):1651-1658. PMID:26538423; DOI:10.1016/S1470-2045(15)00208-9
14. Simon M, Shochat T, Peled N, Zer A, Kramer MR, Eldanet O, et al. Intensity-modulated radiotherapy is a safe and effective treatment for localized malignant pleural mesothelioma. *Thorac Cancer.* 2018;9(11):1470-1475. DOI:10.1111/1759-7714.12860; PMID:30240138; PMCID:PMC6209784
15. Arrieta O, Lozano-Ruiz F, Blake-Cerda M, Catalan R, Lara-Mejia L, Salinas MA, et al. Locoregional control and toxicity after pleurectomy/decortication and intensity-modulated pleural radiation therapy in patients with malignant pleural mesothelioma. *Thoracic Canc.* 2020;11(12):3448-3455. DOI:10.1111/1759-7714.1366; PMID:33030313; PMCID:PMC7705616
16. Scherpereel A, Opitz I, Berghmans T, Psallidas I, Glatzer M, Rigau D, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. *Eur Respir J.* 2020;55(6):1900953. DOI:10.1183/13993003.00953-2019; PMID:32451346
17. Danuzzo F, Maiorca S, Bonitta G, Nosotti M. Systematic Review and Meta-Analysis of Pleurectomy/Decortication versus Extrapleural Pneumonectomy in the Treatment of Malignant Pleural Mesothelioma. *J Clin Med.* 2022;11(19):5544. DOI:10.3390/jcm11195544; PMID:36233416; PMCID:PMC9571799
18. Rimner A, Zauderer MG, Gomez DR, Adusumilli PS, Parhar PK, Wu AJ, et al. Phase II study of hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) as part of lung-sparing multimodality therapy in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2016;34(23):2761-2768. PMID:27325859; PMCID:PMC5019761; DOI:10.1200/JCO.2016.67.2675

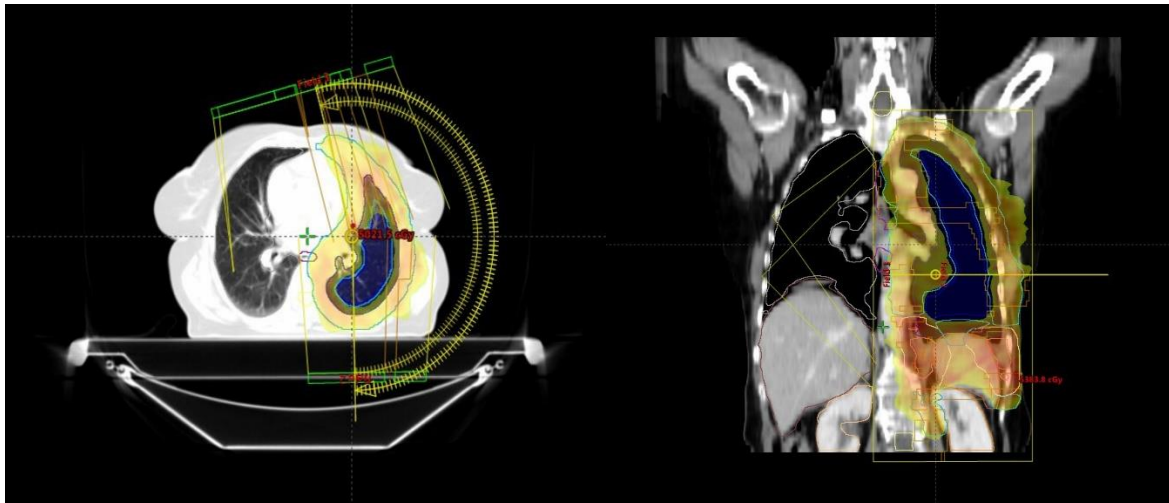


19. Bayman N, Appel W, Ashcroft L, Baldwin DR, Bates A, Darlison L, et al. Prophylactic Irradiation of Tracts in Patients With Malignant Pleural Mesothelioma: An Open-Label, Multicenter, Phase III Randomized Trial. *J Clin Oncol.* 2019;37(14):1200-1208. DOI:10.1200/JCO.18.01678; PMID:30920878.
20. Bergamin S, Tio M, Stevens MJ. Prophylactic procedure tract radiotherapy for malignant pleural mesothelioma: A systematic review and meta-analysis. *Clin Transl Radiat Oncol.* 2018;13:38-43. DOI:10.1016/j.ctro.2018.09.004; PMID:30302406; PMCID:PMC6174826
21. Cramer GM, Simone CB 2nd, Busch TM, Cengel A. (2023). Advances in Radiation Therapy for Malignant Pleural Mesothelioma. In: *Medical Radiology*. Springer, Berlin, Heidelberg. DOI.org/10.1007/174\_2022\_333

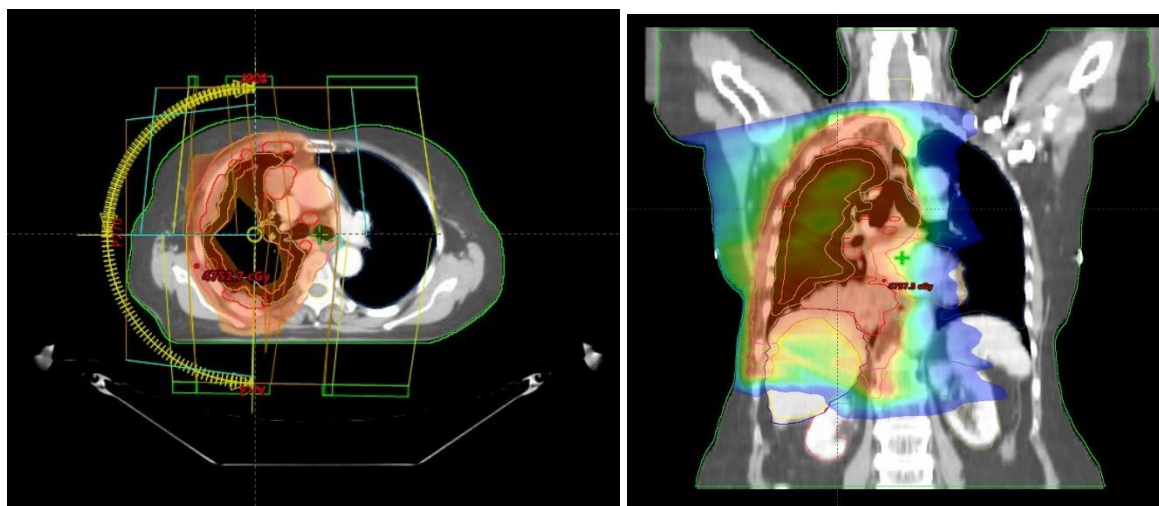
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**Figure 1.** 4DCT of the thorax; target volume delineation and organs at risk; gross tumor volume – orange contour at coronal slice; clinical target volume – light pink contour; planning target volume – purple contour; organs at risk: spinal column – yellow contour; esophagus – brown contour; heart – red contour; both lungs delineated, both kidneys and liver (Institute for Oncology and Radiology of Serbia)



**Figure 2.** Radical hemithorax irradiation with 50.4 Gy to the whole hemithorax (orange color wash) and boost to gross tumor volume up to 60 Gy (red color wash); lung sparing procedure; RapidArc technique (two hemi arcs-yellow calibrated arcs) (Institute for Oncology and Radiology of Serbia)



**Figure 3.** Palliative radiotherapy; multiple infiltrations of the right chest wall and mediastinum (red contour – gross tumor volume); RapidArc technique (Institute for Oncology and Radiology of Serbia)