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CURRENT TOPIC / АКТУЕЛНА ТЕМА

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

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SUMMARY

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

The limited possibility to avoid critical healthy organs (particularly lungs), overexposure of 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.

Technological development in radiotherapy such as respiratory gating, 4D computed tomography, intensity-modulated radiotherapy, volumetric modulated arc therapy, stereotactic techniques, and proton therapy, made a step forward in treating MPM 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

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare malignancy, but the outcome remains poor with less than 5% of the five-year overall survival for all stages [1, 2, 3]. To date, it is 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 decided by a multidisciplinary approach, with an individually tailored strategy concerning the stage of the disease, histology, performance status, comorbidities, and patient preferences [6].

In the absence of clear data on the radiosensitivity of mesothelioma, clinical evidence points 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 developments 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 the 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 MPM today, radiotherapy has five major indications: 1) hemithorax irradiation prior to extrapleural pneumonectomy (EPP); hemithorax irradiation after extrapleural pneumonectomy; 3) hemithorax irradiation after lung spearing therapy (pleurectomy/decortication and/or systemic therapy); 4) prophylactic (procedural path) irradiation, and 5) palliation.

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

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

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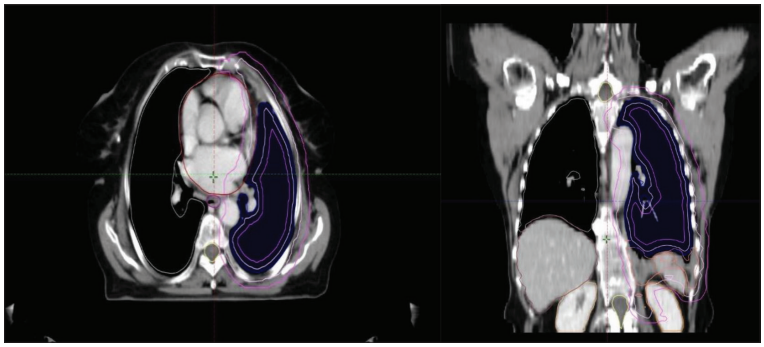

Figure 1. 4D computed tomography of the thorax; target volume delineation and organs at risk; gross tumor volume – orange contour at coronal slice; clinical target volume – light pink contour; planning target volume – purple contour; organs at risk: spinal column – yellow contour; esophagus – brown contour;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

overhead, the procedural scar marked with led markers. Standard 3D or 4DCT is performed in free breathing, from the lung apex to the third lumbar vertebrae due to low diaphragm insertions, with 2.5–3 mm thick slices. Prior diagnostic positron emission tomography – computed tomography is advisory for better gross tumor volume (GTV) delineation. The clinical target volume encompasses the entire thoracic cavity, as well as mediastinal lymph nodes. Planning target volume (PTV) is an additional margin of 5–10 mm in all directions for respiratory and set-up uncertainties. Organs at risk 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. [9] in 2016 as a trial resembling standard hypofractionated preoperative radiotherapy approach in other malignant tumor localization, predominantly rectal cancer. A high radiotherapy dose of 25 Gy in five fractions was delivered to the whole hemothorax, with a simultaneous integrated boost of 5 Gy to GTV, aiming to inhibit reimplantation of malignant cells after surgery. Significant risk of high-grade cardiopulmonary toxicity was avoided by immediate surgery, six days after completion of radiotherapy. Overall survival in the whole group of patients was 36 months, but almost 30% of the 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].

To date, 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 is 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 54 Gy 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 55.9 Gy 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 the reduction of 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 45–54 Gy with a boost to R1 or R2 residual disease up to 54–60 Gy.

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]. However, the cytoreductive approach imposed a question of adjuvant therapy for reducing the risk of local recurrence. Delivering a high dose of radiotherapy to both

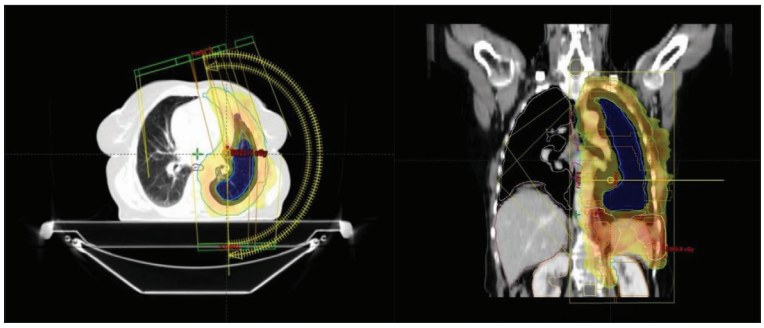

Figure 2. Radical hemithorax irradiation with 50.4 Gy to the whole hemithorax (orange color wash) and boost to gross tumor volume up to 60 Gy (red color wash); lung sparing procedure; RapidArc technique (two hemi arcs – yellow calibrated arcs) (Institute for Oncology and Radiology of Serbia)

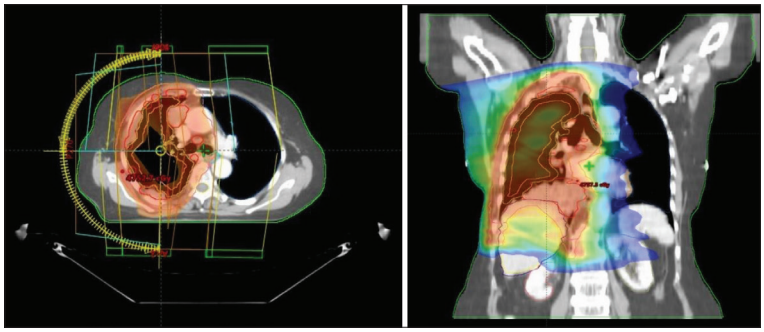

Figure 3. Palliative radiotherapy; multiple infiltrations of the right chest wall and mediastinum (red contour – gross tumor volume); RapidArc technique (Institute for Oncology and Radiology of Serbia)

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 multicenter phase 2 trial that used 50.4 Gy with the 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 > 45 Gy of modern technique radiotherapy can be delivered with acceptable toxicity levels [7].

In the target volume delineation GTV is delineated. The clinical target volume 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 50.4 Gy in 28 fractions with a boost to GTV up to 60 Gy (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 the 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 8 Gy in a single fraction, through 20 Gy in five fractions, to 30–39 Gy in 10–13 fractions or higher (Figure 3). Novel trials suggest that a higher dose per fraction (≥ 4 Gy per fraction) is associated with better outcome introducing 36 Gy in six 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 high-precision radiotherapy modalities such as 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 improvements in normal tissue sparing and PTV covering, with no greater than grade 3 toxicity due to its physical phenomenon of rapid dose fall-off (Bragg peak) [21].

The concept of adaptive radiotherapy is the creation of new radiotherapy treatment plans during the course of treatment to adapt to changes in target volumes detected by image-guided radiation therapy. 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 MPM 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 the 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.

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Улога радиотерапије у лечењу малигног мезотелиома плеуре – могућности и контроверзе

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САЖЕТАК

Малигни мезотелиом плеуре је редак малигнитет са лошом прогнозом. Последњих година постигнут је значајан напредак у лечењу ове болести, укључујући хируршке и радиотерапијске технике, као и системску терапију и имунотерапију. Због широког спектра клиничке презентације, недостатка рандомизованих студија III фазе, 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), чије прекомерно излагање зрачењу може довести до озбиљне, па чак и фаталне токсичности, чини радикалну радиотерапију високим дозама веома захтевном. Стога је већина болесника са мезотелиомом у ери конвенционалне радиотерапије упућивана само на палијативну радиотерапију.

Технолошки развој у радиотерапији, укључујући респираторни гејтинг, 4*D* компјутеризовану томографију, интензитетом модулисану радиотерапију, волуметријски модулисану лучну радиотерапију, технике стереотаксе и протонску терапију, направио је 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 неопходна су даља истраживања, посебно у смислу ескалације радиотерапијских доза и боље поштеде плућног паренхима.

Кључне речи: лечење; малигни мезотелиом плеуре; радиотерапија