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# Radiotherapy of the pleural cavity in patients with primary and secondary malignancies of the pleura

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## ABSTRACT

**Background:** Although there have been various attempts to find appropriate treatment from best conservative care to multimodal treatments, curative outcomes remain poor.

**Materials and methods:** 30 patients with primary and secondary malignant tumors of the pleura were treated in the Radiotherapy Clinic of USHATO during the period from December 2016 to April 2023. Video-assisted thoracoscopic surgery (VATS) and talc pleurodesis was performed in 18 patients (60%). In all patients, radiotherapy for the pleura was performed on a helical tomotherapy machine. In 21 patients (70%), normal fractionated radiotherapy was performed at daily dose of 1.8–2 Gy to total dose of 40 Gy (5 times a week), and in 6 patients (20%), integrated surdosage to 50 Gy was also performed for visible lesions. Hypofractionated radiotherapy (10 fractions of 3 Gy and 4 fractions of 4 Gy) was performed in 3 (10%) patients.

**Results:** Patients were followed up from 1 month to 57 months (median 14 months) or until death. The observed median survival for all patients was 19.2 months [95% confidence interval (CI): 11.5–26.9] (Fig. 3). The 1-, 2- and 3-year survival rates were 40%, 23% and 7% of patients, respectively. Malignant mesothelioma patients had 1-, 2- and 3-year survival rates of 31%, 10% and 0%, respectively. The 1-, 2-, and 3-year survival rates for patients with secondary malignancies were 54%, 45%, and 18%, respectively.

**Conclusion:** Our results suggest that helical tomotherapy is a feasible therapeutic option for patients with malignant mesothelioma or malignant secondary pleural involvement with a reasonable toxicity profile relative to other unaffected lung.

**Key words:** malignant pleural mesothelioma; tomotherapy; secondary malignancies of the pleura

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## Introduction

Malignant diseases of the pleural cavity are rare diseases, representing 0.1% of all cancers with an incidence of 0.5 per 100,000 according to the National Cancer Register [1]. Malignant diseases of the pleura, primary or metastatic, are associated with a poor prognosis. In addition to the serious oncologic sequelae of pleural malignancy, these tumors can be highly symptomatic. Malignant pleural effusion can cause dyspnea secondary to lung compression. Pleural malignancies can cause severe pain with chest wall invasion or can cause a myriad of painful symptoms due to invasion of chest structures such as the heart, lung, or esophagus.

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The majority of malignant tumors of the pleura are either metastases or direct invasions of other primaries and not primary pleural tumors. The most frequent primaries involved are lung cancer, breast cancer, ovarian cancer and stomach cancer.

Approximately 15% of lung cancer patients have a pleural effusion at the time of initial diagnosis and 50% develop a pleural effusion later in the course of their disease [2,–4]. Patients with pleural effusion have a short life expectancy and are difficult to treat [5–7]. Treatment strategies include medical therapy, thoracocentesis, drainage with talc pleurodesis, placement of a permanent, cuffed or tunneled pleural catheter (ICTPC) with or without pleurodesis, or video-assisted thoracoscopic surgery (VATS) with pleurodesis, and radiation therapy for the pleural cavity [8–14].

Primary pleural malignancies are less common, although their incidence is increasing with the rise of malignant mesothelioma and there is evidence of its association with asbestos exposure. Other malignant primary tumors include localized fibrous tumor and pleural liposarcoma. Malignant pleural mesothelioma is an aggressive tumor arising from the pleural surface. Mesothelioma is a rare malignancy with an incidence of 14,200 cases worldwide per year [5, 15, 16].

The incidence of mesothelioma usually peaks and declines 20–30 years after asbestos use. For example, in Korea, the asbestos industry began in the 1960s, and the industry peaked in the 1990s. In 2009, the use of asbestos was banned. Therefore, the incidence of mesothelioma is expected to increase by 2045 [3, 6, 15].

Despite the increasing incidence, there is no consensus on the best treatment for malignant mesothelioma. Treatment of malignant mesothelioma is very challenging, and its overall prognosis is poor with a 2-year survival rate of 0–12% [17]. Although there have been various attempts to find appropriate treatment from best conservative care to multimodal treatments, curative outcomes remain poor [18, 19].

The purpose of this study was to present the experience of the Radiotherapy Clinic at the University Specialized Hospital for Active Treatment in Oncology-Sofia, Bulgaria (USHATO), in the radiotherapy of the pleural cavity of patients with primary and secondary malignancies of the pleura.

## Materials and methods

30 patients with primary and secondary malignant tumors of the pleura were treated in the Radiotherapy Clinic of USHATO during the period from December 2016 to April 23. The patients were aged from 42 to 78 years (mean age 61.9 years). Of these, 16 (53.3%) were men and 14 (46.7%), women. Table 1 shows the distribution depending on the histological variant or type of the tumor.

Patients with malignant mesothelioma who underwent radiotherapy for pleural cavity had locally advanced disease without distant hematogenous metastases. In patients with secondary pleural involvement, the only manifestation was pleural involvement by the direct

invasion or metastatic process. The distribution according to the primary localization of the tumor and histological type is shown in Table 1.

VATS and talc pleurodesis was performed in 18 patients (60%). In all patients, radiotherapy for the pleura was performed on a helical tomotherapy machine, and the examples of the anatomotopographic and dosimetric planning of radiotherapy are shown in Figures 1 and 2.

In 21 patients (70%), conventionally fractionated radiotherapy was performed at daily dose of 1.8–2 Gy to total dose of 40 Gy (5 times a week), and in 6 patients (20%), integrated boost to 50 Gy was also performed for visible lesions. Hypofractionated radiotherapy (10 fractions of 3 Gy and 4 fractions of 4 Gy) was performed in 3 (10%) patients. Overall survival (OS) was estimated by the Kaplan-Meier method and the rela-

**Table 1.** Distribution according to the primary location of the tumor and histological type

| Diagnosis | Number of patients | Percentage |
|---|---|---|
| Malignant mesothelioma | 19 | 63.3% |
| Papillary carcinoma of the breast | 1 | 3.3% |
| Squamous cell carcinoma of the cervix | 3 | 10% |
| Adenocarcinoma of the lung | 2 | 6.6% |
| Ductal carcinoma of the breast | 1 | 3.3% |
| Other primary | 4 | 13.3% |

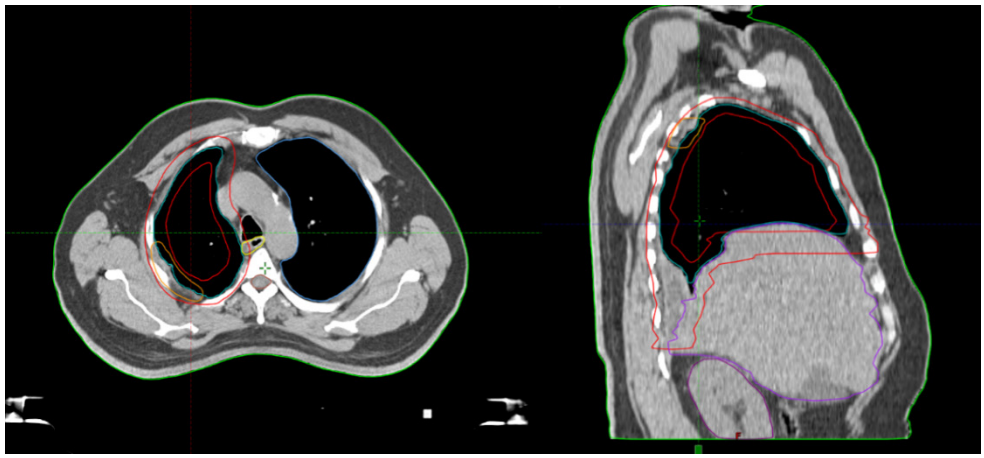

**Figure 1.** An example of the anatomotopographic treatment planning of radiotherapy in a patient with malignant mesothelioma

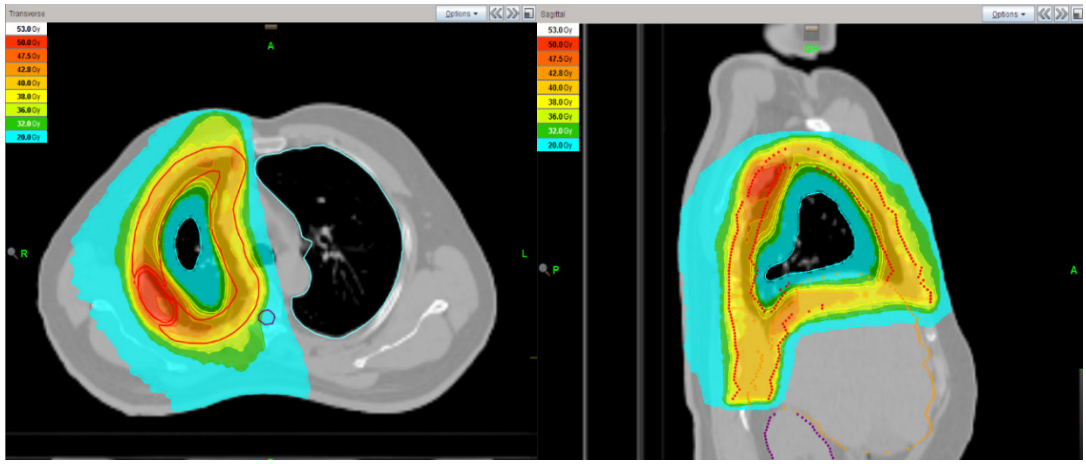

**Figure 2.** An example of dosimetric treatment planning of radiotherapy in a patient with malignant mesothelioma

tion between potential prognostic factors and OS was studied by means of Cox regression analyses and log-rank test.

## Results

Patients were followed up from 1 month to 57 months (median 14 months) or until death. The observed median survival for all patients was 19.2 months (95% CI: 11.5–26.9) (Fig. 3).

The 1-, 2- and 3-year survival rates were 40%, 23% and 7% of patients, respectively. Malignant mesothelioma patients had 1-, 2- and 3-year survival rates of 31%, 10% and 0%, respectively. The 1-, 2-, and 3-year survival rates for patients with secondary malignancies were 54%, 45%, and 18%, respectively.

In patients with malignant mesothelioma, the observed median survival was 10.1 months (95% CI: 6.2–14.1), whereas in those with secondary malignancies, the median survival was 34.7 months (95% CI: 19.2–50) (Fig. 4).

Univariate analysis of patient-, disease-, and treatment-related factors showed that histological variant or type (MMes 10.7 versus other 19.2 months, p = 0.005) and age, older or younger than 61 ( 9.4 versus 26.9 months, p = 0.033) were independent prognostic factors for shorter OS, whereas gender, administration of neoadjuvant chemotherapy, and fractionation did not show a statistically significant influence on OS (Tab. 2).

Acute reactions were seen in all patients and included: cutaneous erythema, radiation pneumo-

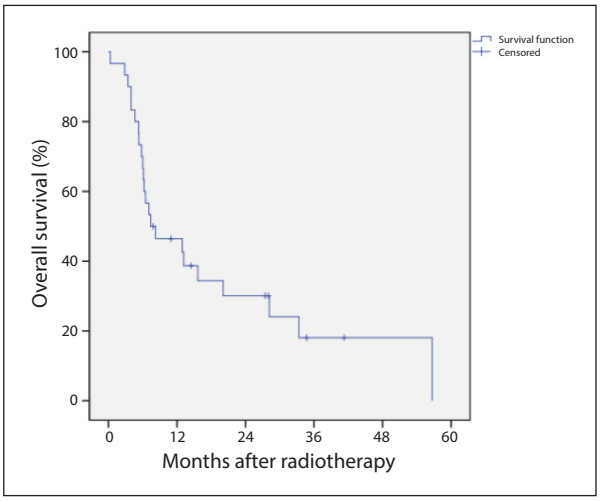


**Figure 3.** Kaplan-Meier distribution curve of overall survival of patients with primary and secondary malignant pleural tumors in months

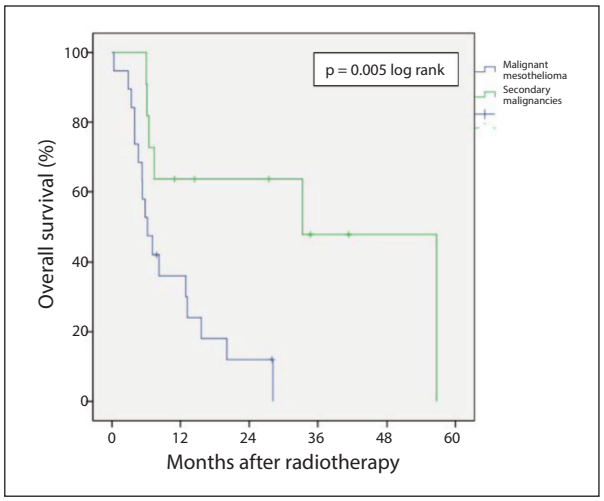


**Figure 4.** Kaplan-Meier distribution curve of overall survival of patients with mesothelioma and secondary malignant pleural tumors in months

**Table 2.** Factors associated with overall survival (OS) in patients with primary and secondary malignant tumors of the pleura

| Factor (n) | OS [months] | p-value |
|---|---|---|
| **Age** | | |
| ≤ 61 (14) | 26.9 | **0.033** |
| > 61 (16) | 9.4 | |
| **Sex** | | |
| Male (16) | 23.4 | 0.808 |
| Female (14) | 15.9 | |
| **Histology** | | |
| Mesothelioma (19) | 10.1 | **0.005** |
| Other (11) | 34.7 | |
| **Neoadjuvant chemotherapy** | | |
| Yes (24) | 17.9 | 0.168 |
| No (6) | 12.7 | |
| **Fractionation** | | |
| Standard fractionated radiotherapy (21) | 18.4 | 0.926 |
| Integrated boost (6) | 17.1 | |
| Hypofractionated radiotherapy (3) | 15.7 | |

nitis grade 2–3, esophagitis grade 1–2 and grade 2–3 tracheitis. More severe acute reactions were not observed. Late reactions that have been observed and followed are as follows: grade 1 pulmonitis, grade 1–2 pulmofibrosis, grade 2 chest wall fibrosis.

Figures 5 and 6 show the effect of radiotherapy of the pleura.

The mean dose received from the contralateral lung averaged 5.4 Gy. The mean dose received to the ipsilateral lung located outside the target volume at a distance of 0.5 cm was 24.1 Gy.

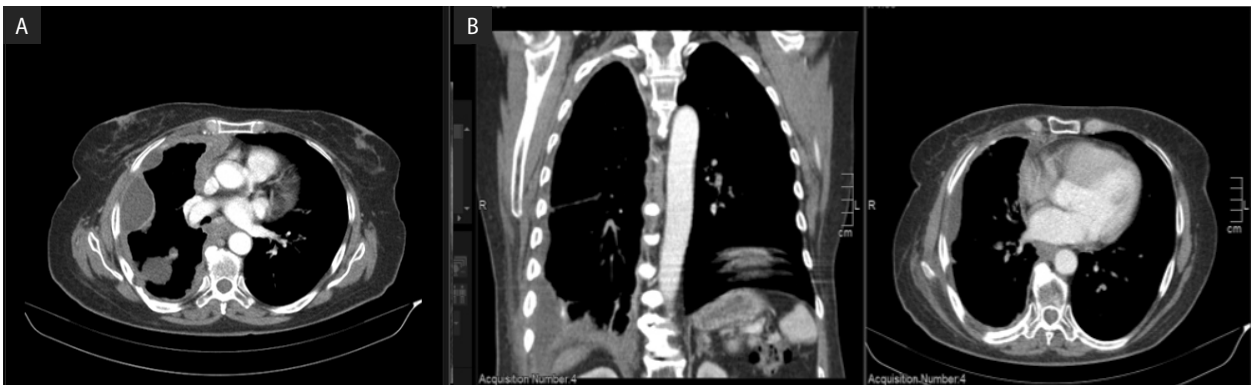


**Figure 5.** Patient with mesothelioma (**A**) before and (**B**) after radiotherapy

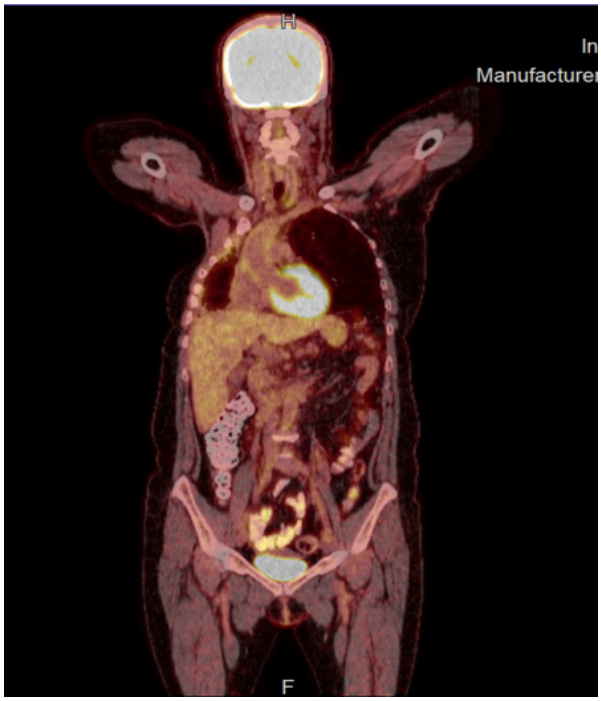


**Figure 6.** Fibrosis with chest wall retraction 24 months after treatment

## Discussion

Treatment of malignant mesothelioma is usually at best conservative care with a low median survival, ranging between 6 and 8 months [20]. Systemic chemotherapy with pemetrexed plus cisplatin extends median survival from 12 to 16 months. However, a multimodal approach (induction chemotherapy, surgery and adjuvant radiotherapy for the pleural cavity) resulted in improved survival outcomes, with a median survival of more than 20 months [18]. One study achieved a median survival of 59 months in patients with ypN0 disease who completed all multimodality treatments [19].

Kostron et al. [21] analyzed the outcomes of patients treated with induction chemotherapy and surgery. Since local recurrence remains the most common type of failure after treatment, radiotherapy plays a role in improving local control. De Perrot et al. [19] in 2009 demonstrated that patients who received adjuvant radiotherapy had fewer local recurrences than patients who underwent surgery alone (19% *vs.* 47%, respectively; p = 0.003). In addition, the development of new radiotherapy techniques influences radiotherapy outcomes and toxicities. Intensity-modulated radiotherapy allows delivery of the desired highly conformal radiotherapy dose with maximum sparing of normal tissues [4, 22, 23]. Jhavar et al. [22] reported good outcomes using intensity modulated radiation therapy (IMRT) postoperatively with a median survival of 38.2 months. Shiakh et al. [23] compared IMRT with conventional radiotherapy and demonstrated that IMRT improved overall survival (mean survival 20.2 months versus 12.3 months) with less toxicity such as esophagitis.

Because the multimodal approach has a long treatment period and is an aggressive treatment, the application of adjuvant radiotherapy to the pleural cavity is so difficult that only half of patients can complete treatment with all three methods [19]. Furthermore, approximately 25% of patients show disease progression during induction chemotherapy. Development of distant metastases is also common (69%) [21]. Therefore, whenever possible, the radiotherapy for pleural cavity should be started as soon as possible as we did in our patients.

The risk of radiation pneumonitis in terms of mean lung dose can be estimated using existing QUANTEC data [24]. With V20 Gy limited to less than 30–35% and mean lung dose to 20–23 Gy. This way, the risk of higher grade radiation pneumonitis does not exceed 20%. Our recommendation is to limit the mean dose to the contralateral lung to no more than 15% of the prescribed dose and the mean dose to a volume of the affected lung located 0.5 cm from the target volume to no more than 75%.

However, the extraordinarily high doses received from the underlying intact lung remain undisputed. On the other hand, the dose-volume relationship is not the sole determinant of the occurrence of therapy-related toxicity. It is possible that the role of dose distribution is greater than previously suggested. Figure 2 shows that, as determined from the anatomy, the high-dose area is concentrated predominantly on the peripheral areas of the lung and decreases rapidly as a result of the steep dose gradient achieved. Consistent with Timmerman et al. [25], we observed an exaggerated increase in toxicity with treatment of central lung tumors, defined as a 2-cm perimeter around the bronchial tree. The risk of radiation pneumonitis may be lower in the case of pleural tumors because of a predominantly peripheral dose distribution.

Due to the rarity of these diseases, available studies are limited and further in-depth studies in this area are needed.

## Conclusion

Our results suggest that helical tomotherapy is a feasible therapeutic option for patients with malignant mesothelioma or malignant secondary pleural involvement with a reasonable toxicity profile relative to the unaffected lung. Adjuvant irradiation of the pleural cavity offers another effective therapeutic option with potential that has yet to be reached. Further technical advances as well as standardization of treatment concepts are needed to ensure that patients with this rare disease are offered the best available therapy.

### Competing interest

The authors declare that they have no competing interests.


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