



# Impact of Post-chemotherapy Radiotherapy on Survival Outcomes in Inoperable Malignant Mesothelioma: A Single-center Retrospective Analysis

Sila ÖKSÜZ, Uğur ÖZKERİM, Seval AY

University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Department of Medical Oncology, İstanbul, Türkiye

## ABSTRACT

**Objective:** Malignant pleural mesothelioma (MPM) is a rare and aggressive form of cancer with limited treatment options and a grim prognosis. While platinum-based chemotherapy remains the primary treatment for inoperable or metastatic disease, the role of radiotherapy (RT) in current treatment approaches remains incompletely defined. This study aimed to assess the effect of RT after first-line systemic chemotherapy on survival outcomes in patients with metastatic or inoperable malignant mesothelioma.

**Material and Methods:** We conducted a retrospective review of the medical records of 58 patients with unresectable or metastatic MPM who were treated from January 2022 through December 2024 at a tertiary oncology center. All patients received platinum-pemetrexed-based first-line chemotherapy followed by pemetrexed maintenance. Based on post-treatment management, patients were categorized into RT and non-RT groups. Kaplan-Meier analyses were conducted to assess progression-free survival (PFS) and overall survival (OS), and statistical significance was assessed using the log-rank test.

**Results:** RT was administered to 41.4% of patients after initial chemotherapy. The RT group showed a significantly longer median PFS (14.1 months) compared with the non-RT group (9.7 months) [hazard ratio (HR): 0.34; 95% confidence interval (CI): 0.16-0.73;  $p < 0.045$ ]. Similarly, median OS was notably longer in the RT group (24.6 months vs. 14.5 months; HR: 0.55; 95% CI: 0.31-0.72;  $p < 0.003$ ). Moreover, a greater proportion of RT patients received second-line immunotherapy. No grade  $\geq 3$  RT-related toxicities were observed.

**Conclusion:** RT after first-line chemotherapy may provide a survival advantage in certain patients with metastatic or inoperable mesothelioma, particularly when incorporated into sequential treatment plans that include immunotherapy. Further prospective studies are necessary to validate these results and improve patient selection.

**Keywords:** Malignant pleural mesothelioma; chemotherapy; radiotherapy; survival; multimodal treatment

## INTRODUCTION

Malignant mesothelioma is a rare, very aggressive cancer that arises from the mesothelial surfaces of the pleura, pericardium, peritoneum, or tunica vaginalis. Malignant pleural mesothelioma (MPM) is the most prevalent subtype, accounting for about 80% of cases. The disease is strongly associated with occupational or environmental exposure to asbestos fibers, with a latency period that can last more than 30-40 years.<sup>1,2</sup> Although asbestos has been banned

or regulated in many regions, it still poses health risks to countries. The global burden of mesothelioma remains high, especially in regions with ongoing or previous industrial exposure.<sup>3,4</sup>

MPM has an insidious onset and often presents with non-specific symptoms such as shortness of breath, chest pain, or pleural effusion, which can delay diagnosis and lead to poor clinical outcomes. Most patients are diagnosed when the disease is already at an advanced stage. and the median

**Correspondence:** Sila ÖKSÜZ MD,

University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Department of Medical Oncology, İstanbul, Türkiye

**E-mail:** sila.oksuz@gmail.com

**ORCID ID:** orcid.org/0000-0003-4721-0585

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overall survival (OS) remains poor, typically ranging from 12 to 18 months, depending on histologic subtype and performance status.<sup>5,6</sup> Epithelioid histology is associated with a better prognosis than that of the biphasic or sarcomatoid subtypes.<sup>7</sup>

The current standard of care for unresectable or metastatic MPM involves first-line platinum-based chemotherapy combined with pemetrexed, which has shown modest survival benefits since the pivotal phase III trial by Vogelzang et al.<sup>8</sup> in 2003. More recently, the addition of immune checkpoint inhibitors, such as nivolumab and ipilimumab, has demonstrated improved outcomes in selected patient populations, especially in the CheckMate 743 trial, where dual immunotherapy showed a significant survival advantage over chemotherapy in unresectable MPM.<sup>5</sup> Despite these advancements, therapeutic progress has been limited and prognosis remains poor.

Traditionally, radiotherapy (RT) has had a limited role in managing MPM, mainly due to concerns about lung toxicity and minimal survival benefits in the pre-modern RT era.<sup>9</sup> Historically, its role has been confined to the palliation of localized symptoms, such as pain, chest wall invasion, or dyspnea. However, as modern RT methods such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) become more common, interest in adding RT to multimodal treatment protocols has grown.<sup>10-12</sup> These advanced techniques enable safer delivery of higher doses with improved organ sparing, potentially offering local control without unacceptable toxicity.

Recent retrospective and prospective studies suggest that consolidative RT after systemic treatment may enhance local control and survival in certain patients, especially those with good performance status and limited disease burden.<sup>13-15</sup> Nevertheless, there is a paucity of high-level evidence supporting the routine use of RT for metastatic or inoperable MPM, and clinical guidelines remain inconclusive regarding its definitive role.

This study aims to explore whether RT offers a survival advantage after initial systemic chemotherapy in patients with metastatic or inoperable malignant mesothelioma. Given the limited literature in this context, our study seeks to provide further insight into optimizing treatment strategies and guiding the integration of RT into the therapeutic landscape of advanced MPM.

## MATERIAL AND METHODS

Patients diagnosed with metastatic and/or inoperable mesothelioma were retrospectively analyzed between January 2022 and December 2024 in the Medical Oncology

Department of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital. Of 72 patients diagnosed with mesothelioma, 58 were considered inoperable and received first-line metastatic treatment and maintenance therapy. Patients who received initial treatment for metastatic disease are included in this study. However, patients under 18 years old who had operable mesothelioma and those with secondary malignancies were excluded from the study.

Patients' medical records, including age at diagnosis, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), histology, first-line metastatic therapy, response to initial therapy, and second-line metastatic treatments were analyzed. Patients were categorized into two groups: those who received RT after first-line metastatic therapy and those who did not. This study aims to assess the effect of RT on metastatic or inoperable mesothelioma.

## Statistical Analysis

The Mann-Whitney U test is used to analyze quantitative variables, whereas chi-square analysis or Fisher's exact test is used for qualitative variables. Kaplan-Meier curves and log-rank tests are used to compare survival between groups. Progression-free survival (PFS) measures the time from the start of first-line metastatic treatment to disease progression. OS is the duration from the beginning of first-line treatment to death caused by cancer or to the last follow-up. A 95% confidence interval (CI) was used to assess statistical significance; p-values below 0.05 were considered significant.

All analyses were conducted using SPSS software (version 27.0, SPSS Inc., Chicago, IL).

This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital's Ethics/Institutional Review Board (date: 30.12.2025, no: 2025/010.99/23/33).

## RESULTS

Medical records of 58 patients diagnosed with unresectable mesothelioma from 2021 to 2025 were analyzed. Twenty-four patients (41.4%) were female and thirty-four (58.6%) were male; the median age was 58 (range 28-84). Among mesothelioma tumors, 86.2% were epithelioid and 13.8% were sarcomatoid. In the first-line metastatic setting, therapy distribution included 33 patients (56.9%) who received cisplatin and pemetrexed, and 25 patients (43.1%) who received carboplatin and pemetrexed. Additionally, if a response such as stable disease (SD), partial response (PR), or complete response (CR) was observed after the initial evaluation, pemetrexed maintenance therapy was continued.

Consequently, all patients in the study received maintenance pemetrexed therapy. Based on the first assessment, response rates were 12.1% for the CR group, 79.3% for the PR group, and 8.6% for the SD group. The median number of pemetrexed maintenance cycles was 8 (range 3-35). No drug discontinuation or interruption due to toxicity was observed. If disease progression was confirmed and the patient's performance status was deemed eligible, second-line metastatic therapies were planned. Follow-up treatments included gemcitabine (20.7%), a platinum-based combination with pemetrexed rechallenge (13.8%), nivolumab combined with ipilimumab (15.5%), nivolumab alone (17.2%), and no treatment (32.8%). Following initial therapy, patients were divided into two groups based on whether they received RT. The RT group accounted for 41.4% of participants, while the not receiving RT (non-RT) group accounted for 58.6%. Table 1 displays the baseline characteristics of the patients.

### Efficacy

Patients are divided into two groups: those receiving RT and those non-RT. Response rates for patients with RT were 25%

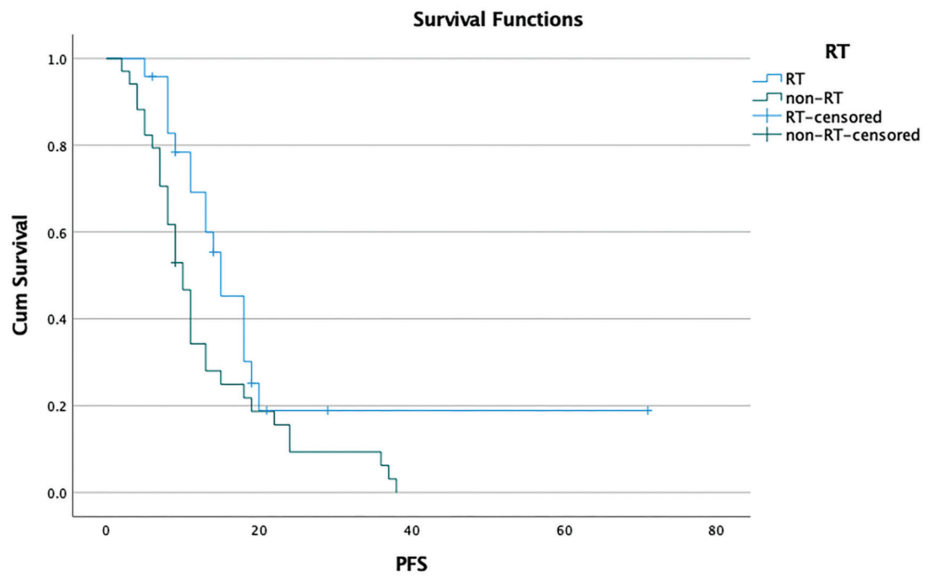
CR and 75% PR; no SD was observed. In the non-RT group, response rates were 2.9% CR, 82.4% PR, and 14.7% SD.

The RT group experienced significantly higher survival rates. The median PFS was 12.1 months [RT group: 14.1 vs. non-RT group: 9.7; hazard ratio (HR): 0.34; 95% CI: 0.16-0.73;  $p < 0.045$ ] (Figure 1); the median OS was 20.5 months (RT group: 24.6 vs. non-RT group: 14.5; HR: 0.55; 95% CI: 0.31-0.72;  $p < 0.003$ ) (Figure 2).

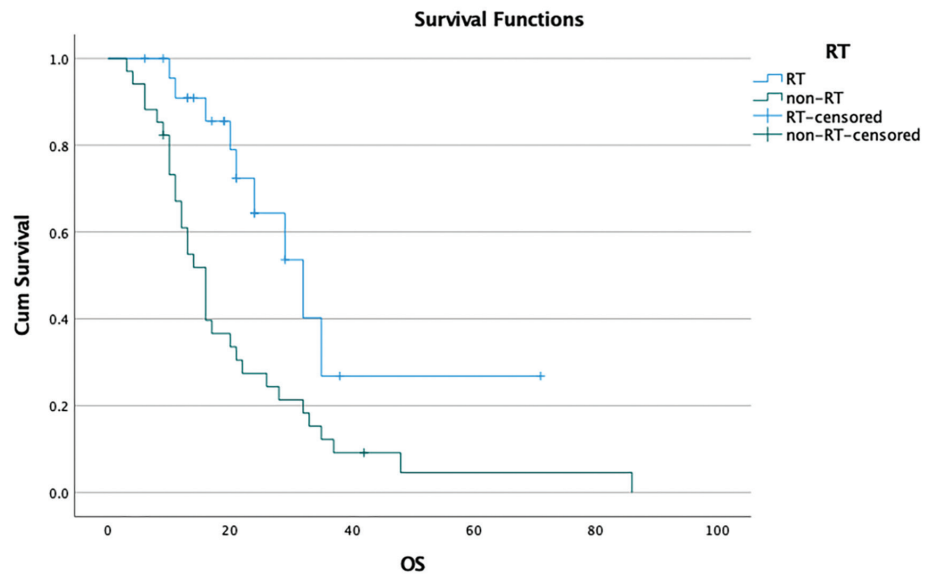
As shown in Table 2, in multivariate Cox proportional hazards analysis, RT remained independently associated with OS (HR: 2.36, 95% CI: 1.07-5.21,  $p = 0.032$ ). ECOG PS was also identified as a strong, independent prognostic factor (HR: 5.15, 95% CI: 2.25-11.78,  $p < 0.001$ ). In contrast, age (HR: 0.99, 95% CI: 0.96-1.03,  $p = 0.592$ ), histology (HR: 1.27, 95% CI: 0.69-2.34,  $p = 0.426$ ), and gender (HR: 0.87, 95% CI: 0.40-1.89,  $p = 0.698$ ) were not significantly associated with OS.

TABLE 1: Patients' characteristics.				
	All	RT group	Non-RT group	p-value
<b>Gender</b>				
Male	58.6%	58.3%	41.2%	
Female	41.4%	41.7%	58.8%	0.060
Median age	58			0.062
<b>Histology</b>				
Epiteloid	86.2%	79.2%	91.2%	
Sarcomatoid	13.8%	20.8%	8.8%	0.068
<b>ECOG PS</b>				
0	51.7%	70.8%	38.2%	0.020
1	48.3%	29.2%	61.8%	
<b>First line metastatic setting therapy</b>				
Carboplatin+pemetrexed	43.1%	12.5%	14.7%	
Cisplatin+pemetrexed	56.9%	87.5%	85.3%	0.064
<b>Response rates of initial therapy</b>				
CR	12.1%	25%	2.9%	
PR	79.3%	75%	82.4%	0.072
SD	8.6%		14.7%	
<b>Metastatic second line therapies</b>				
None	32.8%	20.8%	41.2%	
Gemcitabine	20.7%	8.3%	29.4%	0.030
Nivolumab	17.2%	37.5%	23.5%	
Nivolumab+ipilumab	15.5%	33.3%	5.9%	

RT: Radiotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; CR: Complete response; PR: Partial response; SD: Stable disease.



**FIGURE 1:** Kaplan-Meier curve of PFS between RT versus non-RT.  
PFS: Progression-free survival; RT: Radiotherapy.



**FIGURE 2:** Kaplan-Meier curve of OS between RT group versus non-RT group.  
RT: Radiotherapy; OS: Overall survival.

**TABLE 2:** Multivariate cox regression analysis for overall survival.

Variable	HR (95% CI)	p-value
ECOG PS	5.15 (2.25-11.78)	<0.001
Age	0.99 (0.96-1.03)	0.592
Radiotherapy	2.36 (1.07-5.21)	0.032
Histology	1.27 (0.69-2.34)	0.426
Gender	0.87 (0.40-1.89)	0.698

HR: Hazard ratio; ECOG PS: Eastern Cooperative Oncology Group performance status; CI: Confidence interval.

## DISCUSSION

In this retrospective cohort, incorporating RT following first-line systemic therapy was associated with notable gains in both PFS and OS for patients with metastatic or inoperable malignant mesothelioma. Specifically, the RT group showed a median PFS of 14.1 months and a median OS of 24.6 months, which were notably better than those in the non-RT group: 9.7 and 14.5 months, respectively. These results emphasize a potential role for RT as a consolidative or disease-modifying treatment in advanced mesothelioma - a concept that remains underexplored in modern therapeutic approaches.

The potential mechanisms behind the survival benefit observed in the RT group are complex. First, RT may enhance local disease control, particularly in cases of residual or bulky thoracic disease following systemic therapy. Improved locoregional control has been associated with longer survival in various solid tumors and may similarly benefit mesothelioma when employing curative-intent or high-precision techniques such as IMRT or VMAT.<sup>16,17</sup>

Secondly, the immune-modulating effects of RT may have played a synergistic role in patients who later received immune checkpoint inhibitors as part of second-line therapy. RT can alter the tumor microenvironment and promote antigen presentation through immunogenic cell death, thereby boosting systemic immune responses—a phenomenon known as the abscopal effect. In our cohort, a larger proportion of patients in the RT group received second-line immunotherapy, particularly programmed cell death protein 1/programmed death-ligand 1 or cytotoxic T-lymphocyte associated protein 4 blockade. This sequence may have enhanced durable responses, as suggested by recent trials studying the combination of RT and immunotherapy in thoracic cancers.<sup>18-21</sup>

Patient selection may have influenced outcomes. The RT group had a higher proportion of patients with an ECOG PS of 0, possibly reflecting better baseline functional status and treatment tolerance. While this introduces selection bias, the survival benefit persisted even after adjusting for these differences, suggesting that RT may contribute intrinsically to disease control.

Notably, in multivariate analysis, RT remained an independent predictor of improved OS despite baseline imbalances between groups. This finding indicates that the observed survival benefit is not solely due to selection bias or differences in baseline characteristics, although residual confounding cannot be entirely ruled out given the retrospective design.

The role of RT in mesothelioma has historically been limited due to concerns regarding pulmonary toxicity and the diffuse, often unresectable nature of the disease. However, accumulating evidence supports its reconsideration within multimodal treatment algorithms. A prospective phase II

study (IMPRINT trial)<sup>22</sup> demonstrated the safety and efficacy of hemithoracic IMRT after chemotherapy, showing promising local control and tolerability. Similarly, retrospective series have suggested a role for consolidative RT in prolonging survival when integrated into sequential strategies.<sup>23-25</sup>

Although some data suggest that hemithoracic IMRT after pleural decortication or extrapleural pneumonectomy may not confer additional survival benefit, our findings support the view that RT should not be entirely excluded from the treatment paradigm. In appropriately selected patients—particularly in the current era, where systemic therapies are increasingly prioritized—RT may still be a valuable component of multimodal management.<sup>26</sup>

### Study Limitations

This study has some limitations. One limitation is the lack of detailed RT planning information. Due to limited access to archived RT planning records in this retrospective dataset, specific treatment parameters such as radiation dose, fractionation schedules, target volumes, and treatment techniques could not be systematically obtained for all patients. Additionally, the intent of RT (consolidative versus palliative) could not be uniformly categorized. As a result, the potential impact of different RT approaches on clinical outcomes could not be assessed.

Taken together, these findings support the integration of RT as a feasible and potentially synergistic treatment option for selected patients with advanced mesothelioma, particularly when used in combination with or following immunotherapy. However, further randomized prospective studies are necessary to verify these findings and define optimal timing, dosage, and patient selection criteria for RT in this setting.

## CONCLUSION

Mesothelioma generally has a low incidence rate and limited treatment options. Although surgery has been phased out as a primary treatment option in recent years and immunotherapy has yielded effective results and increased survival rates, rapid progress is not yet evident. The role of RT in mesothelioma remains controversial. RT combined with immunotherapy is known to be more effective than expected. We observe this particularly in studies of locally advanced lung cancer.

Our results indicate that RT following first-line chemotherapy may offer a survival benefit for patients with metastatic or inoperable mesothelioma. While our findings are encouraging, this study has a small sample size and a retrospective design; further prospective studies are necessary to determine the optimal timing, appropriate patient selection, and the best approach for integrating RT into standard treatment protocols for mesothelioma.

## Ethics

**Ethics Committee Approval:** This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital's Ethics/Institutional Review Board (date: 30.12.2025, no: 2025/010.99/23/33).

**Informed Consent:** Retrospective study.

## Footnotes

### Authorship Contributions

Concept: S.Ö., S.A., Design: S.Ö., S.A., Data Collection or Processing: S.A., U.Ö., Analysis or Interpretation: S.Ö., S.A., Literature Search: S.A., U.Ö., Writing: S.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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