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Impact of Neoadjuvant and Adjuvant Pleural Intensity-Modulated Radiotherapy in Multimodality Treatment for Malignant Pleural Mesothelioma

Berta Mosleh[1] | Stefan Schwarz[1] | Anna Cho[2] | Katharina Sinn[1] | Ariane Steindl[3] | Sabine Zöchbauer-Müller[3] | Wolfgang J. Köstler[3] | Karin Dieckmann[4] | Martin Heilmann[4] | Joachim Widder[4] | Daniela Gompelmann[5] | Clemens Aigner[1] | Thomas Klikovits[1] | Mir Alireza Hoda[1]

[1]Department of Thoracic Surgery, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria | [2]Department of Neurosurgery, Medical University of Vienna, Vienna, Austria | [3]Division of Oncology, Department of Internal Medicine I, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria | [4]Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria | [5]Division of Pulmonology, Department of Internal Medicine II, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

Correspondence: Berta Mosleh (berta.mosleh@meduniwien.ac.at)

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ABSTRACT

Background: Few malignancies provoke as many controversies about treatment as pleural mesothelioma. There is limited experience with novel radiotherapy techniques worldwide in adjuvant and particularly in neoadjuvant settings within multimodality treatment. The objective of the current study was to investigate the long-term outcome of neoadjuvant and adjuvant pleural intensity-modulated radiotherapy (IMRT) combined with macroscopic complete resection with or without chemotherapy.

Methods: We retrospectively analyzed a consecutive cohort of 59 patients who were diagnosed with pleural mesothelioma and underwent multimodality treatment including macroscopic complete resection and neoadjuvant or adjuvant IMRT between 2005 and 2019 at the Department of Thoracic Surgery, Medical University of Vienna, Austria.

Results: In total, 59 patients (median age 59 years; IQR 54–66, male, $n = 48$; 81%) were included. Forty-seven patients underwent trimodality treatment consisting of induction chemotherapy, extrapleural pneumonectomy, and adjuvant IMRT. Novel neoadjuvant IMRT with ($n = 9$) or without ($n = 3$) chemotherapy followed by extrapleural pneumonectomy was performed in 12 patients. Median overall survival (OS) of all patients was 23.2 months (95% CI; 18.1–28.2) and 3- and 5-year survival rates were 33% and 28%, respectively. Survival was comparable between therapies including neoadjuvant versus adjuvant IMRT (median OS 17.5 vs. 24.0 months, $p = 0.39$).

Conclusions: Neoadjuvant pleural IMRT has been investigated as a novel treatment option for highly selected cases in pleural mesothelioma. Neoadjuvant IMRT was effective and safe in patients treated in a high-volume institution but showed no relevant survival benefit compared to adjuvant IMRT within multimodality treatment.

1 | Introduction

Radiotherapy is a widely used treatment modality in many malignancies. Irradiation for malignant pleural mesothelioma has been mainly used as palliative and for local control. Only expert centers with sufficient radiation and surgical experience have utilized novel radiotherapy techniques as an integral part of multimodality treatment protocols. Detailed guidelines remain

still undefined due to the treatment-resistant nature of the disease with a wide spectrum of presentations often requiring individual treatment approaches. Clinical management is controversial but often multidisciplinary in selected patients since no single therapy has been able to achieve meaningful outcome alone throughout the course of the disease [1, 2].

Treatment for pleural mesothelioma may include chemotherapy, radiotherapy, surgery, as well as targeted therapy. The use of doublet chemotherapy with platinum and pemetrexed has been the standard systemic regimen, the addition of targeted therapies and immunotherapy represents new promising treatment options [3]. The two main radical surgical strategies performed in pleural mesothelioma are extrapleural pneumonectomy (EPP) and extended pleurectomy/decortication (EPD). The role of surgery and the surgical techniques are debated. There has been a notable shift from lung-sacrificing to lung-sparing surgery in recent years with reduced mortality and morbidity and comparable survival in expert centers [4–9]. Preeminently, the field of radiotherapy in the treatment of pleural mesothelioma is characterized by a significant variety of logistical, mechanistic, and clinical aspects [10].

Radiation in pleural mesothelioma is technically challenging. Over the past few decades, more advanced radiation techniques, such as intensity-modulated radiation therapy (IMRT), have led to better local control [11–14]. In MPM, radiotherapy in multimodality settings before and after EPP as well as after EPD may be applied. The use of IMRT has been recently investigated after pleurectomy and decortication (P/D) and has been shown feasible with acceptable risk of pneumonitis of the intact lung with encouraging survival [15–18]. However, this approach still requires further investigation and is currently not supported by mesothelioma expert guidelines [15, 17, 19, 20]. Removal of the lung allows for high-dose adjuvant irradiation and may represent one rationale for more aggressive resections in terms of EPP. The inherent risk of toxicity remains a primary concern in treating the entire hemithorax with a larger radiation field in patients with only one lung [21]. Several series suggest that the addition of radiotherapy to EPP yields superior overall and progression-free survival [22–29]. In selected patients, a well-established trimodality protocol including neoadjuvant chemotherapy, EPP, and adjuvant hemithoracic IMRT has been in practice with replicable results in large-volume centers worldwide [23–25, 27–29]. The randomized multi-institutional SAKK 17/04 trial, however, has brought the efficacy of hemithoracic radiation after neoadjuvant chemotherapy and EPP into question, wherein it failed to show significant differences in locoregional control in the radiation group [30]. A large propensity-matched national analysis still demonstrated benefits of radiotherapy in adjuvant settings in early stages [31].

Neoadjuvant radiotherapy has not been routinely employed in MPM due to technical difficulties and surgical challenges. However, encouraged by the long-term results of potentially improved local control achieved with adjuvant radiation after EPP, a novel protocol has been initiated by de Perrot et al. [32] This recently developed, Surgery for Mesothelioma After Radiation Therapy (SMART), approach involves a total of 25 Gy of radiation applied in five daily fractions over 1 week to the entire ipsilateral hemithorax with concomitant boost of 5 Gy to high-risk areas followed by EPP in 6 ± 2 days, and adjuvant chemotherapy in ypN2 disease [33]. The final results of this study on a large cohort of 102 patients showed impressive early and long-term results [34]. There are no randomized or multi-institutional prospective studies investigating the outcome of neoadjuvant radiation in MPM, therefore this regimen has been only performed in a few experienced high-volume centers worldwide [1, 35]. The role of radiation therapy in malignant mesothelioma continues to be a subject of investigation.

In this study, we present our single-center experience and long-term clinical outcome across two multimodality treatment groups receiving either neoadjuvant or adjuvant pleural intensity-modulated radiotherapy combined with EPP with or without chemotherapy in MPM. The aim of this investigation was to determine the efficacy and safety of neoadjuvant and adjuvant radiotherapy as part of multimodality treatment.

2 | Materials and Methods

2.1 | Patients and Methods

Our prospective, single-center database was reviewed for patients with histologically confirmed pleural mesothelioma who underwent multimodality treatment including EPP and IMRT with or without chemotherapy between 2005 and 2019 at the Department of Thoracic Surgery, Medical University of Vienna, Austria.

Demographic and clinical parameters including age, sex, ECOG status, histologic subtype, symptoms, tumor site, tumor stage, diagnostic methods, treatment strategies, and treatment-related adverse events were retrospectively reviewed.

All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients aged 27–75 years, had normal renal and hepatic function, and no major comorbidities. Pulmonary function tests, ventilation-perfusion scintigraphy as well as cardiac echography were mandatory and part of the preoperative assessment protocol in all patients. Histological confirmation was routinely obtained by tissue biopsy by video-assisted thoracoscopic surgery (VATS).

2.2 | Staging

Clinical stage was determined by brain magnetic resonance imaging (MRI) or cranial computed tomography (CT) as well as CT scan of the chest and abdomen before 2015 and by positron emission computed tomography scan (PET/CT) after 2015. All patients were (re)staged according to the eighth version of the TNM staging system established by the International Mesothelioma Interest Group (IMIG) and the International Association for the Study of Lung Cancer (IASLC) [36, 37]. Patients functionally suitable for multimodality therapy with clinical stage T1-3N0-2M0 with resectable disease were included. Preoperative lymph node biopsy with endobronchial ultrasound–transbronchial needle aspiration biopsy (EBUS-TBNA) was performed in patients with suspected lymph node involvement or suspected progression under neoadjuvant therapy for accurate (re)staging.

2.3 | Treatment Approaches

All patients were evaluated in thoracic oncology multidisciplinary tumor boards including oncologists, radiation oncologists, radiologists, pulmonologists, and thoracic surgeons to set the given sequence of treatment modalities. Patient stratification to treatment protocols was based on imaging results, disease stage, tumor volume, resectability as well as existing co-morbidities and performance status. Overall, patients aged 18–75 years with an ECOG performance status of 0–1, adequate pulmonary function (defined as a predicted postoperative forced expiratory volume in 1 s [FEV1] and a diffusing capacity for carbon monoxide [DLCO] > 45%), normal cardiac function (defined as an ejection fraction > 55% and no major heart valve disease), no major organ dysfunctions (normal kidney and liver functions), and no history of other malignancies were eligible for inclusion. Patients had previously untreated pleural mesothelioma judged as macroscopically completely resectable on the basis of CT and/or PET/CT scans assessed by a thoracic oncology tumor board including expert thoracic surgeons. Contralateral nodal disease was ruled out by mediastinoscopy or EBUS in case of clinical suspicion. Based on the inclusion criteria, all patients were carefully assessed as suitable for multimodality treatment. Other patient-related requirements included enhanced compliance and written consent forms to complete the planned treatment protocol to remove the radiated lung after neoadjuvant intensity-modulated radiotherapy (NIMRT).

In respect of radiation therapy, two treatment groups were identified (Figure 1).

2.3.1 | Neoadjuvant Intensity-Modulated Radiotherapy (NIMRT) group

In the NIMRT group ($n = 12$, 12/59; 20%), patients with confirmed disease and initial staging underwent neoadjuvant IMRT

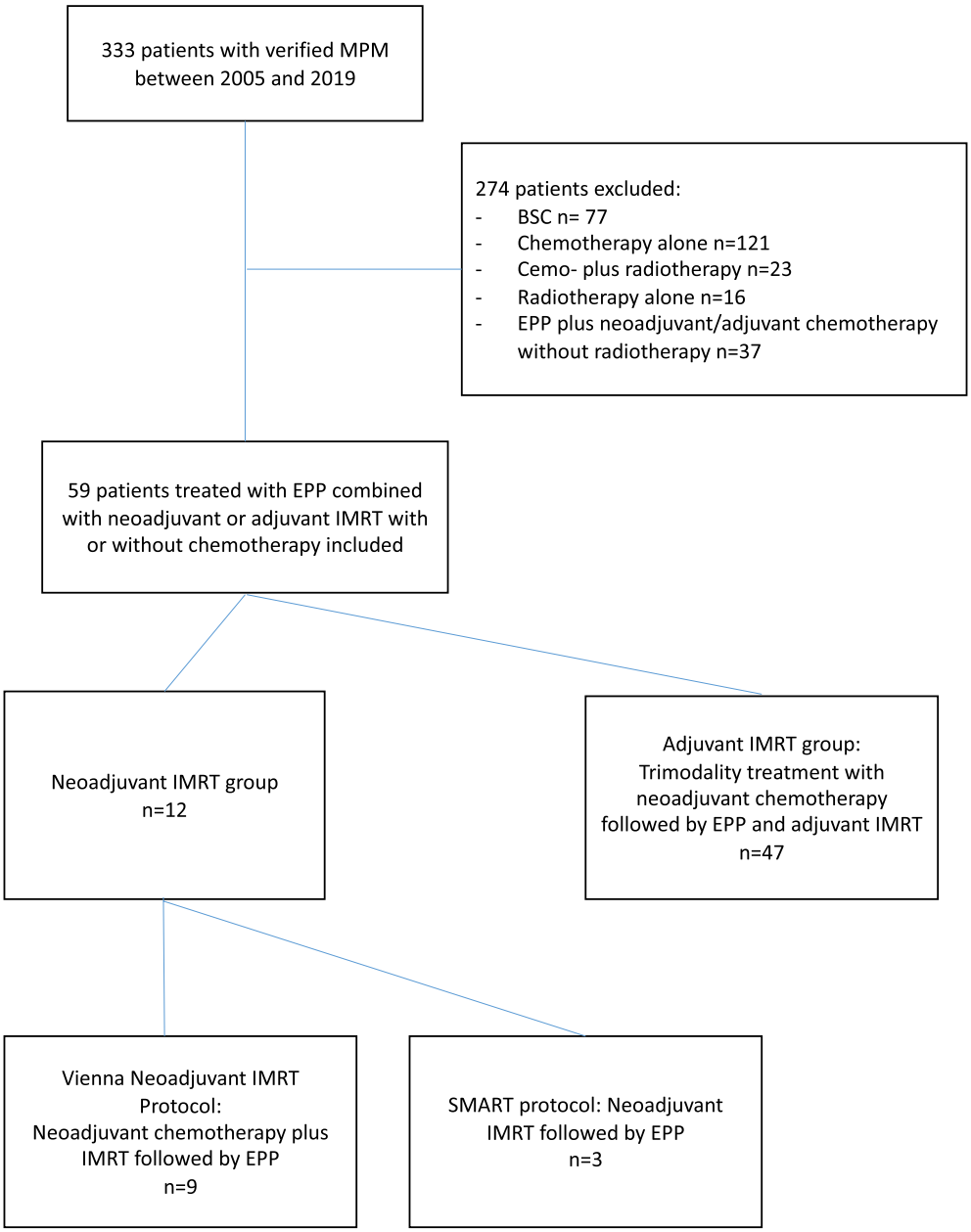

FIGURE 1 | Flow diagram showing the selection of patients throughout the analysis.

with or without chemotherapy followed by EPP. Most commonly ($n = 9$, 9/12, 75%), according to our "Vienna Neoadjuvant IMRT Protocol" (Figure 2), induction doublet chemotherapy with 3 cycles of cis- or carboplatin and pemetrexed was administered followed by a re-staging PET/CT scan at Day 7 of cycle 3. In response or in stable disease, neoadjuvant IMRT was delivered. To avoid fatal toxicity, an accelerated fractionation regimen of a total of 25 Gy in 5 × 5 Gy daily fractions along with a concomitant boost of 5 × 6 Gy to high-volume targets and tract sites was administered starting from Day 14 of cycle 3 over a period of 1 week (Figure 2). The radiation field involved the ipsilateral hemithorax from the thoracic inlet down to the thoracic outlet including the diaphragmatic insertion, as well as the ipsilateral mediastinal and upper retroperitoneal lymph node stations as well as high-tumor volume areas (Figure 3). Finally, planned EPP to remove the irradiated lung to avoid severe risk of post-radiation pneumonitis as well as to perform macroscopic complete resection was performed within 1 week after completing IMRT. In three cases ($n = 3$, 3/12, 25%), based on the SMART protocol [32, 34], the treatment plan included radical surgery in terms of EPP after neoadjuvant pleural IMRT without neoadjuvant chemotherapy.

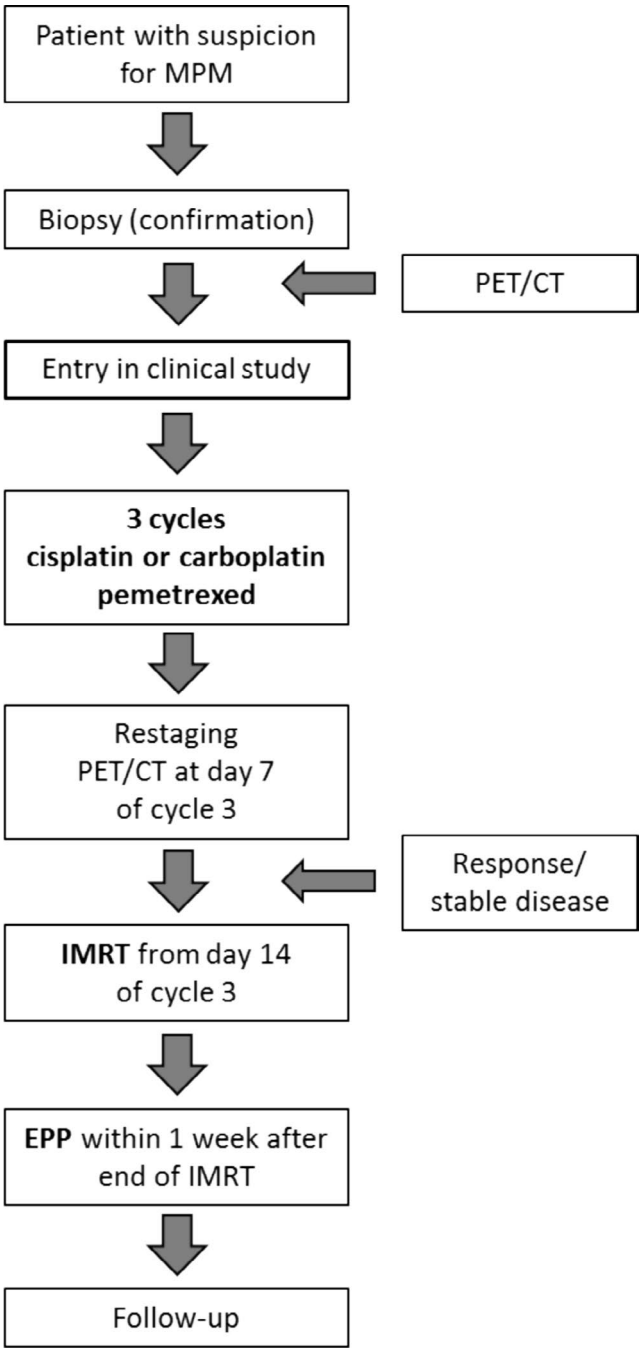

FIGURE 2 | Consort flowchart of the "Vienna Neoadjuvant IMRT Protocol."

Due to the substantial risk of potential pulmonary toxicity, we conducted a particularly careful patient selection for the neoadjuvant IMRT protocol to ensure that all these patients will be able to proceed to the planned surgery to remove the radiated lung.

2.3.2 | Adjuvant Intensity-Modulated Radiotherapy (AIMRT) group

In the adjuvant intensity-modulated radiotherapy (AIMRT) group ($n = 47$, 47/59; 80%), patients received neoadjuvant doublet chemotherapy with 3 cycles of cis- or carboplatin and pemetrexed and subsequent EPP and postoperative hemithoracic IMRT according to the "classical" trimodality treatment approach. The postoperative radiation field encompassed the entire ipsilateral pleural bed, the chest wall including the ribs and intercostal muscles to a total dose of 50–60 Gy with a safety margin to the mediastinal interface minimizing the dose to the heart and esophagus, anteriorly extending to the sternum and pleura, posteriorly extending to the vertebral body and inferiorly covering the lowest insertion point of the diaphragmatic reconstruction.

2.4 | Follow-Up

After completing therapy, patients were followed up with CT scans of the chest and abdomen or PET-CT images every 4 months up to 2 years and later every 6 months. Post-treatment follow-up images were consistently reviewed in tumor boards. Recurrences were diagnosed clinically based on imaging results and verified pathologically when feasible with emphasis on local therapy in terms of local resections or irradiation. Second-line chemotherapy was given in the absence of accessible local treatment or in the presence of systemic recurrence in eligible patients.

2.5 | Surgical Considerations

A maximal cytoreductive surgery in terms of EPP was systematically performed following a standard technique defined by resective and reconstructive steps including the radical en bloc resection of the entire lung, visceral and parietal pleura, pericardium and diaphragm, and subsequent reconstruction of the pericardium and diaphragm with prosthetic patches. As prosthetic materials, Gore-Tex Dual mesh and Vicryl mesh for diaphragmatic and pericardial reconstruction in single suture fashion were used, respectively. Emphasis was made on a low reconstruction of the diaphragm to facilitate the adjuvant radiation

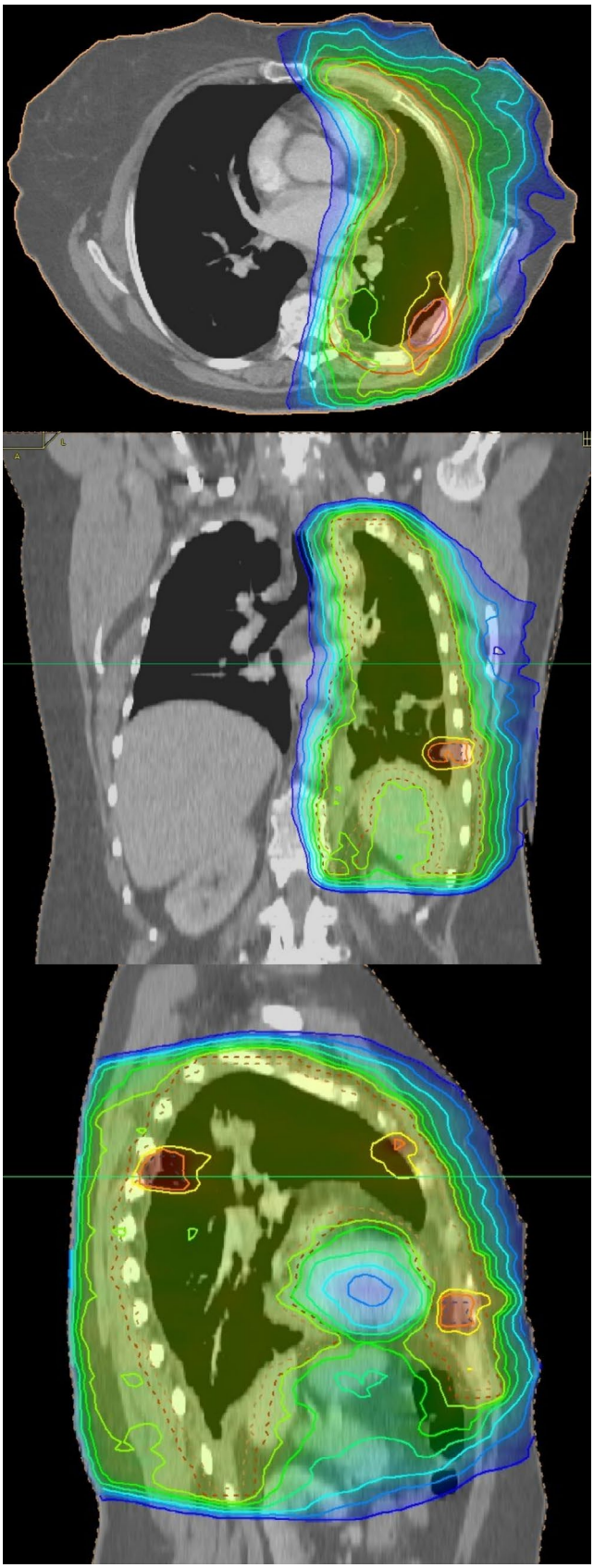

FIGURE 3 | Considerations for planning neoadjuvant hemithoracic IMRT to be delivered before extrapleural pneumonectomy for patients with resectable malignant pleural mesothelioma according to the "Vienna Neoadjuvant IMRT Protocol."

field when applicable. The bronchial stump was consistently covered with the posterior pericardium or mediastinal fat pad. The most technically challenging part is the diaphragmatic resection and reconstruction. We routinely used a standard sixth intercostal space, rib- and muscle-sparing thoracotomy. This approach is also feasible for excision of previous biopsy and chest tube sites of the recommended single-port diagnostic thoracoscopy in the sixth intercostal space. The rib-sparing thoracotomy leaves no localized chest wall defect. This approach also assures a comfortable view and access to the surgical field including the apex of the chest, the hilum as well as the diaphragm with exposure to the costophrenic and cardio-phrenic angles to facilitate radical resection of these conventionally high tumor mass areas. In taller individuals, a second lower thoracotomy might be required to enable the dissection of the diaphragm along its lateral and posterior attachments [38, 39].

2.6 | Statistical Analysis

Categorical data are displayed as counts and percentages and metric data are given as median and interquartile range (IQR), or, in case of survival, as median and corresponding 95% confidence interval (CI). To compare groups, Mann–Whitney U-tests, Kruskal–Wallis, or Chi-square-tests were performed as appropriate. The correlation of metric data was analyzed by Pearson's correlation coefficient. Overall survival (OS) was defined as the time between diagnosis and death or the last follow-up date. Survival was estimated by the Kaplan–Meier method and log rank or Breslow test was used to compare the group differences as appropriate. The Cox regression model was used for univariate and multivariate analyses of survival. Differences were considered statistically significant for p values <0.05. Statistical analyses were performed using the SPSS 27.0 software system (SPSS Inc., Chicago, IL, USA) and plots were generated with GraphPad Prism 8.

To minimize confounding differences between the two treatment groups, propensity score matching was performed with a 1:2 ratio using the following covariates: age at diagnosis, sex, side (left vs. right), histology (epithelioid vs. non-epithelioid), and pathological stage (early vs. non-early stage). A propensity score was assigned to each patient using a logistic regression model and greedy caliper matching with a caliper set at 0.3 was performed. Cases with missing values for any of the covariate parameters were excluded during the matching process. Covariate balance, density plots, and histograms illustrating the distribution of matched and unmatched patients in the two treatment groups are shown in Figures S1–S3. Propensity score matching was performed using R software (R Core Team. R: A language and environment for statistical computing, Vienna, Austria, R Foundation for Statistical Computing, 2019).

3 | Results

3.1 | Patient Characteristics and Overall Outcome

Demographics and clinical characteristics are described in Table 1.

TABLE 1 | Patient characteristics grouped by treatment groups.

				Pleural IMRT				
		Total		Neoadjuvant		Adjuvant		
		n	%	*n*	%	*n*	%	*p*
Age	< 65	48	81%	10	83%	38	81%	0.44
	> 65	11	19%	2	17%	9	19%	
Sex	Male	48	81%	9	75%	39	83%	0.41
	Female	11	19%	3	25%	8	17%	
Histology	Epithelioid	52	88%	12	100%	40	85%	0.16
	Non-epithelioid	7	12%	0	0%	7	15%	
Clinical stage	I/II	54	92%	12	100%	42	89%	0.24
	cT1N0M0			3		7		
	cT2N0M0			8		17		
	cT3N0M0			1		18		
	III/IV	5	8%	0	0%	5	11%	
	cT2N2M0			0		1		
	cT3N1M0			0		2		
	cT3N2M0			0		2		
Pathological stage	I/II	49	83%	11	92%	38	81%	0.38
	cT1N0M0			5		4		
	cT1N1M0			0		1		
	cT2N0M0			4		9		
	cT3N0M0			2		24		
	III/IV	10	17%	1	8%	9	19%	
	cT2N2M0			0		1		
	cT3N1M0			1		4		
	cT3N2M0			0		4		
Chemotherapy	Neoadjuvant	56	95%	9	75%	47	100%	0.21
	None	3	5%	3	25%	0	0%	
Side	Right	39	66%	6	50%	33	70%	0.19
	Left	20	34%	6	50%	14	30%	

A total of 59 patients with a median age of 59 years (IQR 54–66; male, $n = 48$, 81%) were included. Right-sided disease was observed in the majority of patients ($n = 39$, 66%). At the time of the diagnostic thoracoscopy, 41 patients (69%) received talc pleurodesis. Epithelioid histology counted for most cases ($n = 52$, 88%). Biphasic histology was confirmed on final pathology in six patients ($n = 6$, 10%) and one individual with sarcomatoid ($n = 1$, 2%) subtype was selectively included in multimodality treatment.

On final pathology, the majority of patients (49/59, 83%) had an early tumor stage (stage I/II, TNM eighth edition). A total of 11 patients (19%) had evidence of ypN+ disease. Concordance between clinical and pathological staging was reported in most cases in terms of the eighth TNM classification ($n = 51$, 86%). Discordance rate was 14% ($n = 8$). In the final pathological assessment compared to the initial clinical staging, seven patients (12%) were upstaged (six from stage I to III and one from stage I to II) and one (2%) patient was downstaged (from stage III to I).

3.2 | Treatment

Between 2005 and 2019, 47 patients (47/59, 80%) underwent trimodality treatment consisting of induction platinum-pemetrexed doublet chemotherapy followed by EPP within 3–10 weeks and adjuvant pleural IMRT within 4–14 weeks after surgery (adjuvant IMRT group, AIMRT).

Between 2016 and 2018, 12 patients (12/59, 20%) underwent the neoadjuvant IMRT (NIMRT) treatment plan. All patients completed their intended EPP. While 9/12 patients (75%) were treated according to the "Vienna Neoadjuvant IMRT Protocol" (neoadjuvant chemotherapy and subsequent neoadjuvant IMRT followed by EPP), 3/12 patients (25%) were treated according to the SMART protocol (neoadjuvant IMRT followed by EPP without chemotherapy due to node-negative disease) [32, 34].

In the NIMRT group ($n=12$), all patients had an initial early-stage disease (stage I/II). In the AIMRT cohort ($n=47$), most patients presented in early stages (stage I/II, $n=42$, 89%) while five patients (11%) in resectable stage III.

All extrapleural pneumonectomies were performed with resection and reconstruction of the diaphragm and pericardium. Macroscopic complete resection was achieved in all patients. No incomplete macroscopic resection was reported on final pathology. Postoperatively, the median length of hospital stay was 13 days (IQR 10–18, range 5–65 days).

3.3 | Adverse Events

The postoperative complication rate was 42% for the entire cohort (25/59, Table 2). The most common postoperative morbidity (grade 2) was atrial fibrillation (9/59, 15%). A total of 13 patients (13/59, 22%) developed grade 3+ adverse events with postoperative haematothorax (4/59, 7%) as the most frequent operative complication. Treatment-related death (grade 5 toxicity) occurred in 1 patient who developed fatal radiation pneumonitis during adjuvant IMRT and passed 1.5 months after completing treatment with a survival time of 8.4 months after diagnosis. Perioperative mortality was nil.

Between the neoadjuvant or adjuvant IMRT groups, no significant differences were observed with respect to complications ($p=0.14$). OS for patients who suffered grade 2, 3, 4, and 5 adverse events were 28.8, 33.9, 11.2, and 8.4 months, respectively. Patients with treatment-related morbidities in the neoadjuvant and adjuvant IMRT groups had a median OS of 11.2 and 25.8 months, respectively ($p=0.49$).

In the AIMRT cohort, postoperative events were seen in 21/47 patients (45%). Major operative complications affected three cases including diaphragmatic patch dehiscence in two patients with a survival time of 20.9 and 24.2 months as well as a bronchopleural fistula development in one case requiring revisions with a survival time of 75.2 months after diagnosis.

In the NIMRT group, the postoperative morbidity rate was 33% (4/12) with one major event of a postoperative pulmonary embolism treated with extracorporeal membrane oxygenation (ECMO) support with a survival time of 11.2 months after diagnosis.

3.4 | Survival

Postoperative 30- and 90-day survival was 100% in the entire cohort.

Median OS of all patients was 23.2 months (95% CI; 18.1–28.2), while 3- and 5-year survival rates were 33% and 28%, respectively. The median follow-up time was 97.4 months. There was no significant survival difference between patients receiving neoadjuvant versus adjuvant IMRT, however, OS was slightly prolonged in patients with adjuvant IMRT (median OS 17.5 vs. 24.0 months, $p=0.39$), (Figure 4).

TABLE 2 | Adverse events—measured prevalence of morbidity type (morbidity rates for individual domains of morbidity type do not sum to overall morbidity as several patients had more than one type of morbidity).

		Complications (*n*, [%])							
		Grade 2		Grade 3		Grade 4		Grade 5	
Complication type	Total	NIMRT	AIMRT	NIMRT	AIMRT	NIMRT	AIMRT	NIMRT	AIMRT
Atrial fibrillation	9 (15.3)		9						
Pneumonia	4 (6.8)	2	2						
Hemothorax	4 (6.8)				4				
Recurrent nerve palsy	2 (3.4)		1	1					
Wound dehiscence	2 (3.4)				2				
Diaphragmatic patch dehiscence	2 (3.4)						2		
Acute kidney injury	1 (1.7)						1		
Plexus injury	1 (1.7)		1						
Pulmonary embolism	1 (1.7)					1			
Bronchopleural fistula	1 (1.7)						1		
Fatal radiation pneumonitis	1 (1.7)								1

Abbreviations: AIMRT: adjuvant intensity-modulated radiotherapy; NIMRT: neoadjuvant intensity-modulated radiotherapy.

Disease-free survival (DFS) of all patients was 13.2 months (95% CI; 7.7–18.9) with no significant differences between the neoadjuvant and adjuvant IMRT groups (7.9 vs. 13.7 months, $p = 0.37$), (Figure 5).

The OS was 23.2 months in patients with epithelioid subtype compared to 20.9 months in patients with non-epithelioid histology ($p = 0.91$). Among patients with epithelioid histology, the DFS reached 13.6 months compared to 5.6 months in patients with non-epithelioid mesothelioma ($p = 0.21$), (Figure 6).

A total of 32/59 patients (54%) developed recurrence during the follow-up time. The primary site of recurrence was the ipsilateral thoracic wall (16/59, 27%). Contralateral chest recurrence in terms of parenchymal lung nodules occurred in 4/59 (7%) patients. Abdominal recurrence was characterized by peritoneal carcinosis in 8/59 (14%) patients as well as kidney and liver metastasis in 1/59 (2%) patient. Paravertebral recurrence was seen in 4/59 (7%) cases. Recurrences were treated with chemo- plus radiotherapy in 13/59 (22%), and with chemotherapy in 9/59 (15%) patients. Local treatment was feasible in terms of local resection as well as local irradiation in 5/59 (8%) and 3/59 (5%) patients, respectively. Best supportive care was provided to 3/59 (5%) patients.

To minimize confounding differences between the two treatment groups, we performed propensity score matching to reduce the confounding bias in each group. After 1:2 propensity score matching, we matched 24 patients in the adjuvant IMRT group

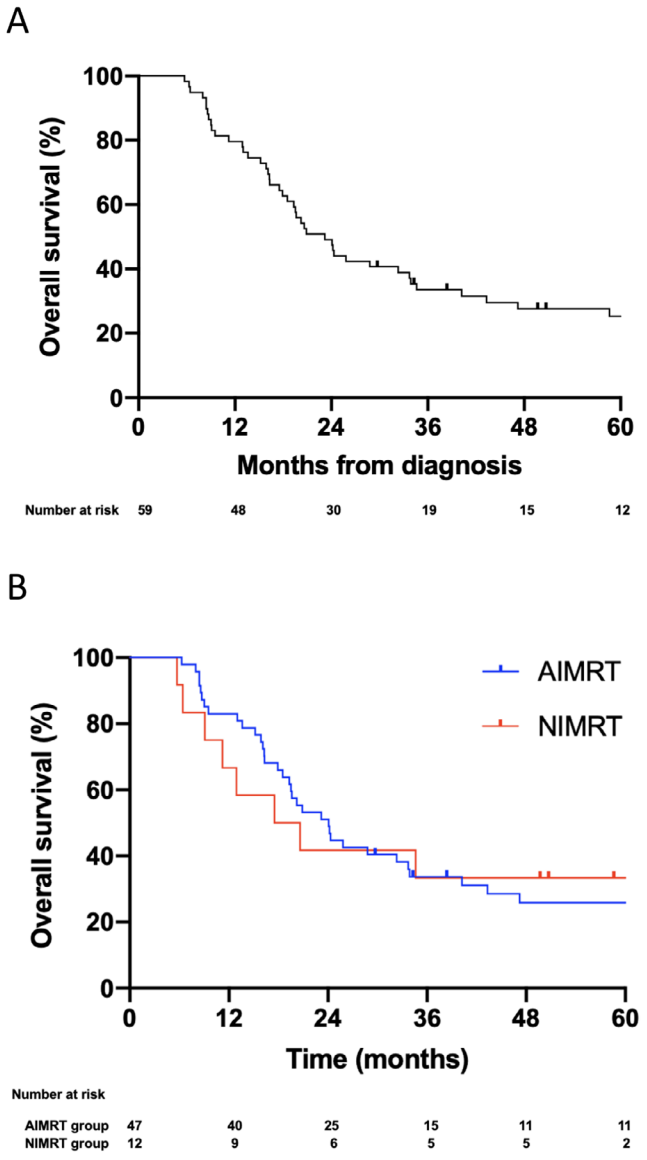

FIGURE 4 | Kaplan–Meier curve demonstrating overall survival for the entire cohort (A) and between treatment groups (B). No significant survival difference between patients receiving neoadjuvant versus adjuvant IMRT was observed (OS for the entire cohort 23.2 months; OS 24.0 vs. 17.5 months in the adjuvant vs. neoadjuvant IMRT group, $p = 0.39$). AIMRT: adjuvant intensity-modulated radiotherapy; NIMRT: neoadjuvant intensity-modulated radiotherapy.

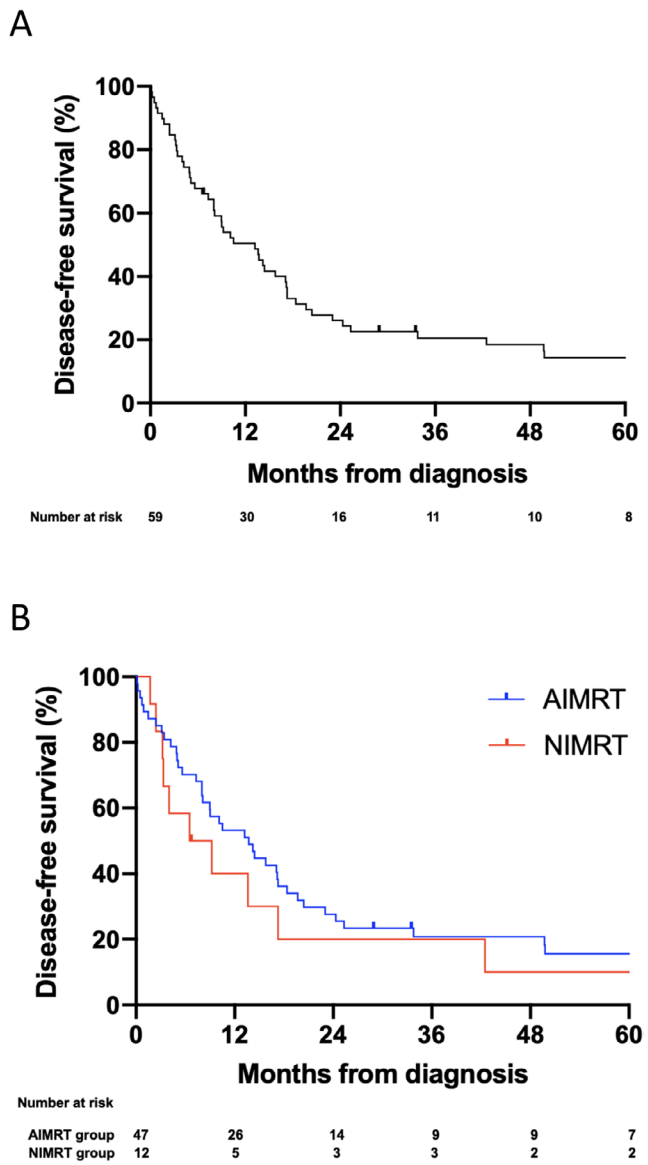

FIGURE 5 | Kaplan–Meier curve demonstrating disease-free survival (13.2 months, 95% CI; 7.7–18.9) for the entire cohort (A) and between treatment groups (B). No significant differences in disease-free survival between neoadjuvant and adjuvant IMRT treatment groups were found (7.9 vs. 13.7 months, $p = 0.37$). AIMRT: adjuvant intensity-modulated radiotherapy; NIMRT: neoadjuvant intensity-modulated radiotherapy.

to 12 patients in the neoadjuvant IMRT group and found no significant differences compared to the baseline analysis.

In the matched study cohort, median OS of patients was 23.2 months (95% CI; 17.6–28.7), while 3- and 5-year survival rates were 34% and 24%, respectively. There was no significant survival difference between patients receiving neoadjuvant versus adjuvant IMRT (median OS 17.5 vs. 24.2 months, $p = 0.40$), (Figure 7).

DFS after propensity score matching was 13.6 months (95% CI; 6.3–21.0) with no significant differences between the NIMRT and AIMRT groups (6.5 vs. 15.8 months, $p = 0.34$), (Figure 8).

4 | Discussion

This recent analysis in pleural mesothelioma involves a novel and sporadically applied treatment paradigm utilizing preoperative irradiation in comparison with the long-established trimodality treatment protocol utilizing postoperative radiotherapy in resectable malignant pleural mesothelioma.

This innovative treatment approach developed by the Toronto group was able to achieve improved results, especially in epithelioid histology, when compared to the "classical" trimodality treatment protocol showing that accelerated hemithoracic intensity-modulated radiotherapy followed by EPP is feasible.

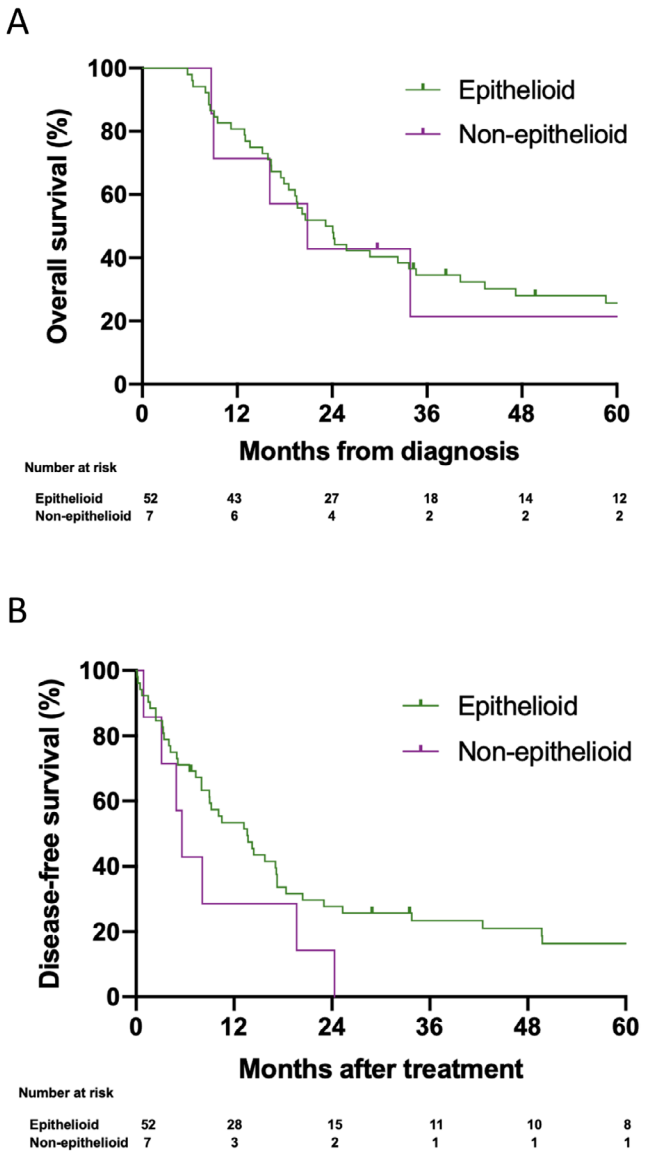

FIGURE 6 | (A) Kaplan–Meier curve demonstrating overall survival according to histology. Overall survival was 23.2 months in patients with epithelioid subtype compared to 20.9 months in patients with non-epithelioid histology ($p = 0.91$). (B) Among patients with epithelioid histology, the disease-free survival reached 13.6 months compared to 5.6 months in patients with non-epithelioid mesothelioma ($p = 0.21$).

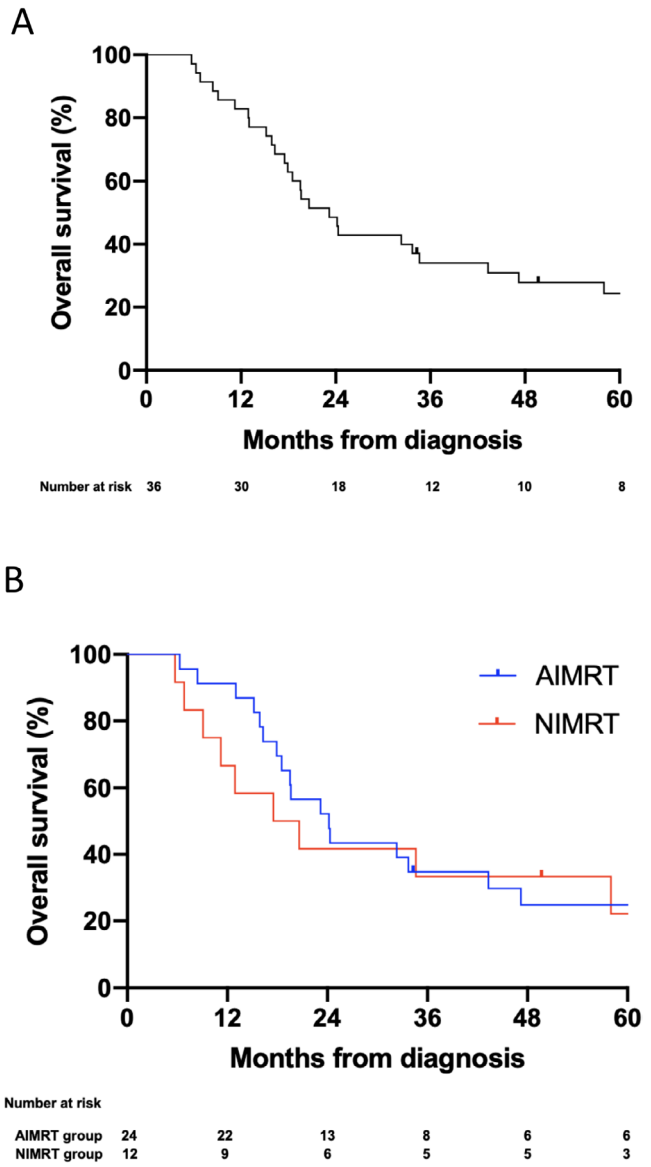

FIGURE 7 | Kaplan–Meier curve demonstrating overall survival for all patients (A) and between treatment groups (B) after propensity score matching. Median overall survival for the matched study cohort was 23.2 months (95% CI; 17.6–28.7). No significant survival difference between patients receiving neoadjuvant versus adjuvant IMRT was observed (OS 17.5 vs. 24.2 months in the neoadjuvant vs. adjuvant IMRT group, $p = 0.40$). AIMRT: adjuvant intensity-modulated radiotherapy; NIMRT: neoadjuvant intensity-modulated radiotherapy.

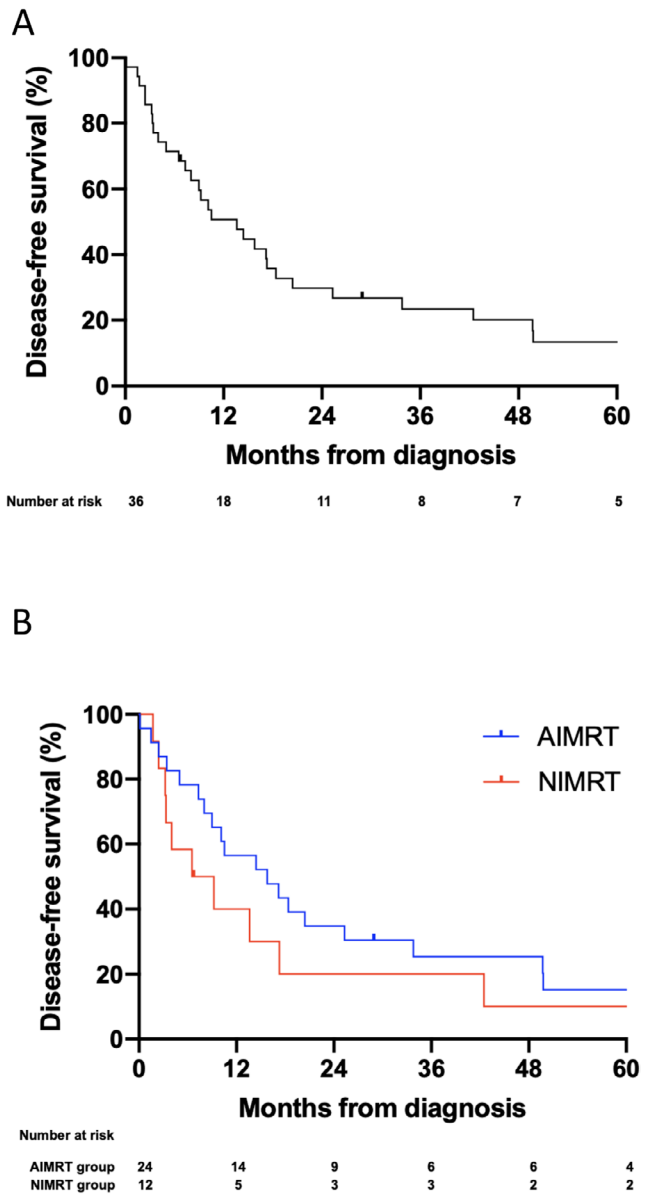

FIGURE 8 | Kaplan–Meier curve demonstrating disease-free survival after propensity score matching; (A) for all patients (13.6 months, 95% CI; 6.3–21.0) and between treatment groups (B). No significant differences in disease-free survival between neoadjuvant and adjuvant IMRT treatment groups were found (6.5 vs. 15.8 months, $p = 0.34$). AIMRT: adjuvant intensity-modulated radiotherapy; NIMRT: neoadjuvant intensity-modulated radiotherapy.

The authors also concluded that despite the achieved survival benefit, the potential treatment-related adverse events may influence overall outcome beyond the post-operative period [32, 34].

Rationale for neoadjuvant radiotherapy in pleural mesothelioma includes the potential of the radiation-first approach to induce a tumorostatic effect to delay distant metastasis and to prevent tumor spreading into the chest cavity at the time of surgery reducing the incidence of metastatic remnants. It also allows for patients with node-negative findings on final pathology to omit chemotherapy as a third major and consuming treatment modality after preoperative radiation and radical surgery preserving quality of life. In contrast, on the classical trimodality protocol, a significant drop-out of patients has been reported who presented in reduced condition after neoadjuvant chemotherapy and EPP and were ineligible to complete their planned adjuvant radiotherapy to improve local control of the disease [32, 40]. Poor response or disease progression under neoadjuvant chemotherapy has been also documented precluding patients with originally resectable disease from surgery, thereby altering the sequence of treatment modalities to begin with neoadjuvant IMRT to address the risk of disease progression during induction chemotherapy might represent a reasonable approach in patients with resectable tumors [32, 41–43].

Our Vienna Neoadjuvant IMRT Protocol was designed to deliver both chemo- and radiotherapy preoperatively in a short course with prompt re-staging and with a short interval between the end of neoadjuvant chemo- and radiotherapy and subsequent surgery limiting the disease from progression over the usually long period between induction therapy and resection. Systemic therapy is still the cornerstone of mesothelioma management and a pivotal treatment modality that has consistently demonstrated a survival benefit [44]. Our neoadjuvant IMRT treatment approach ensures the administration of systemic treatment as well as eliminating the potential drop-out of patients from completing chemotherapy postoperatively as a third treatment modality with a missed opportunity of the associated survival benefits.

The perspective of IMRT as adjuvant therapy has been validated in several trials with reported benefits on OS by improved locoregional control rates ranging from 40% to 81% [14, 22, 24–29, 45–48]. Moreover, improved local failure rates have been confirmed by several studies [13, 21, 23, 25, 49]. Based on the results, the use of adjuvant hemithoracic IMRT remains the standard of care after induction chemotherapy and EPP for patients with stage I-III pleural mesothelioma. In conclusion, adjuvant hemithoracic IMRT is recognized as effective and safe with lower recurrence rates and acceptable toxicity and continues to be recommended according to several recent guidelines such as the National Comprehensive Cancer Network (NCCN) guidelines, the American Society of Clinical Oncology Clinical Practice Guidelines (ASCO), the ERS/ESTS/EACTS/ESTRO guidelines (European Respiratory Society [ERS]/European Society of Thoracic Surgeons [ESTS]/European Association for Cardio-Thoracic Surgery [EACTS]/European Society for Radiotherapy and Oncology [ESTRO]), and the ESMO Clinical Practice Guidelines (European Society for Medical Oncology). Neoadjuvant IMRT before EPP as well as adjuvant IMRT after EPD may be considered in experienced centers and preferably in the context of clinical trials, while neoadjuvant radiotherapy before lung-sparing surgery (EPD, P/D) is solidly disfavored and not supported with the currently available radiation and operative techniques [1, 2, 50–53].

Over the past years, the role of lung-removing EPP in pleural mesothelioma has been a growing topic for debate and the lung-sparing form of macroscopic complete resection with EPD has gained increasing significance [5, 6, 54–58]. To evaluate the

long-term results of EPP with neoadjuvant or adjuvant radiotherapy with sufficient follow-up time in this rare and aggressive disease that generates as many controversies about treatment as pleural mesothelioma does, is pivotal.

Our single-center experience across two multimodality treatment groups supports the efficacy and safety of the use of neoadjuvant hemithoracic IMRT followed by EPP in eligible patients with resectable disease in pleural mesothelioma. Our results were comparable to those of the trimodality protocol with adjuvant IMRT in terms of survival and safety. Thereby, we implicate that a multimodality treatment approach with neoadjuvant radiotherapy and subsequent EPP might be a valuable variation in a sub-group of selected patients. After our initial positive experience with neoadjuvant IMRT in MPM between 2016 and 2018, we started to implement lung-sparing radical resection as the preferred surgical approach at our institution that does not support the preoperative administration of radiation. Following the international tendency of transitioning from lung-sacrificing EPP to lung-sparing EPD, we adopted EPD as a standard practice in surgically-treated patients within a multimodality approach preserving EPP for the fittest patients in younger age groups in selected cases.

The merits of multimodality treatment protocols have been heavily discussed with limited evidence from prospective trials. As previously described, the prospective SMART trial was able to prove benefit of radical treatment modalities in eligible patients [34]. The highly anticipated results from the only two randomized clinical trials, the Mesothelioma and Radical Surgery (MARS) and MARS 2 trials, evaluating the feasibility of surgery showed no benefit in survival in patients who underwent surgery compared to patients treated with systemic chemotherapy [41, 56]. Due to several significant study flaws, it appears the controversy about treatment decisions will continue. Critics focus on patient selection including unfair distribution of patient characteristics between groups with a higher proportion of patients with comorbidities and major risk factors as well as higher tumor volume and also higher parenchymal lung involvement in the surgical arm. Critics also noted the lack of standard staging. Moreover, nearly half of the patients who underwent surgery were treated at low-volume centers with questionable experience as well as macroscopic complete resection was not achieved in all patients. In our study, we could conclude that macroscopic complete resection was achieved in all patients. Histological subtypes showed major imbalances as well. According to pleural mesothelioma guidelines, surgery may be recommended only for patients with epithelioid histology. In the MARS 2 trial, about 2.6 times as many sarcomatoid patients with well-researched treatment resistance and the poorest prognosis were included in the surgery arm as in the chemotherapy group. In our analysis, we reported 6 patients with biphasic histology who were initially diagnosed with epithelioid histology in referral hospitals with lack of expertise with regard to mesothelioma diagnosis and treatment. Biphasic histology in these patients ($n = 6$, 10%) was confirmed on final pathology by expert pathologists in the resected specimen after surgery. We selectively included one young individual who was 38 years old at the time of diagnosis with sarcomatoid ($n = 1$, 2%) subtype in multimodality treatment who had a survival time of 28 months after surgery. In studies evaluating treatment protocols including surgery, epithelioid histology consecutively has been and should be the main histologic subtype in resected mesothelioma with respect to the latest guidelines. Given the debatable results of the only randomized prospective studies directly evaluating the effect of surgery, it may be too soon to retire the concept of surgery within multimodality treatment in eligible patients with pleural mesothelioma.

We acknowledge that there is also limited evidence in the literature in terms of randomized and multi-institutional prospective studies supporting neoadjuvant IMRT as well as matched-comparison analyses between outcome in treatment arms utilizing neoadjuvant and adjuvant radiotherapy in resectable MPM. The limitations of this study are the retrospective single-center design and the relatively small number of patients that may limit the generalizability of our findings. For completeness, a long-term patient follow-up was pursued. Due to the rarity of the disease with a significant number of undiagnosed cases with only a limited proportion of patients eligible for multimodality treatments, building large-scale studies on multimodality protocols in pleural mesothelioma is difficult. Particularly, the use of neoadjuvant IMRT has been underreported as only a few centers worldwide have accumulated sufficient experience with meaningful case volume to safely and effectively offer this treatment approach. The only large-scale phase 2 trial is the SMART trial by the Toronto group in which Cho et al. established and reported the novel neoadjuvant IMRT protocol in pleural mesothelioma including 96 patients between 2008 and 2019 [34]. Another study from a Korean group by Hong et al. reporting the safety and efficacy of neoadjuvant IMRT within multimodality treatment for malignant pleural mesothelioma included 11 patients between 2016 to 2018 [35]. To the best of our knowledge, no other studies with significant case volume on neoadjuvant IMRT in pleural mesothelioma have been conducted. Herein, we were able to show that this approach is safe and represents a treatment strategy in experienced mesothelioma centers.

The recent advances in mesothelioma treatment should encourage future research and multi-center prospective large-volume trials investigating the sequence of treatment modalities and the impact of combining systemic and novel targeted therapy options as well as radiotherapy with different radical surgical approaches in the context of multimodality therapy protocols in pleural mesothelioma.

Author Contributions

Conceptualization: B.M., T.K., M.A.H. Investigation: B.M., A.C., K.S., A.S., T.K., M.A.H. Data curation: B.M., A.S., K.S. Formal analysis: B.M., S.S., A.C., M.H. Writing – original draft preparation: B.M., A.C., T.K., M.A.H. Writing – review and editing: All authors. Visualization: B.M., T.K., J.W., M.A.H. Supervision: T.K., M.A.H. All authors have read and agreed to the published version of the manuscript.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the Medical University of Vienna (EK 2137/2022).

Consent

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.