

ONCOLOGICAL OUTCOMES OF RADICAL SURGERY WITH AND WITHOUT INDUCTION AND ADJUVANT CHEMOTHERAPY IN MESOTHELIOMA PATIENTS – 8-YEAR EXPERIENCE IN A SINGLE CENTER

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Abstract

Introduction: Mesothelioma is a devastating, insidious disease with a long latency period. Its peak incidence occurs in the 5th and 6th decades of life, up to 40 years after asbestos exposure which is strongly related to the disease. The optimal treatment is the object of an intense discussion.

Aims: The established outcomes were disease-free survival (DFS) and 1-year survival analyzed in the context of neoadjuvant chemotherapy with subsequent surgery, surgical intervention without any systemic treatment, an upfront surgery and adjuvant chemotherapy and surgical intervention with both neo- and adjuvant therapy to establish the most advantageous treatment in terms of oncological results.

Materials and Methods: We analyzed our center's surgical experience with radical surgery for mesothelioma, evaluating the disease-free time and 1-year survival in relation to the treatment scheme. A search of the department's surgical database for mesothelioma cases between January 2016 and December 2020 revealed 16 cases, which were included in the final analysis. The established outcomes were disease-free survival and 1-year survival.

Results: The 3 patients treated with surgery without any systemic treatment had a median follow-up period (MFUP) of 7 months (3-12), 67% of recurrence, DFS of 6 months (0-12), and 1-year survival of 33%. The 6 patients treated with neoadjuvant chemotherapy, surgical resection, and adjuvant therapy, had an MFUP of 45 months (8-82), 67% of recurrence, DFS of 32 months (2-82), and 1-year survival of 83%. The 1 patient, treated with neoadjuvant chemotherapy and subsequently, surgery had a follow-up of 29 months with DFS of 20 months and he was alive at the time of submission of this article. The 6 patients treated with an up-front surgery and adjuvant chemotherapy had an MFUP of 20 months (8-33), 67% of recurrence, DFS of 15 months (6-33), and 1-year survival of 67%.

Conclusion: Despite the limitations of the study, the multimodal approach with both neoadjuvant and adjuvant chemotherapy demonstrated the longest MFUP, DFS, and 1-year survival. The worst results were observed in patients treated only with radical surgery, while the sequence of systemic treatment did not influence the rate of recurrence.

Keywords: mesothelioma, pleural tumor, induction chemotherapy, neo-adjuvant chemotherapy, pleurectomy, decortication, pleuropneumectomy

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a destructive, insidious disease with an extensive latency period. Its peak incidence occurs between the 5th and 6th decades of life, up to 40 years after asbestos (erionite fibers) exposure which is strongly related to the disease. It can occur not only in the

mesothelial layer of the pleura but has been also described in the peritoneum and tunica vaginalis.¹

According to the updated 2023 National Cancer Database (NCDB) an average of 2417 new cases are diagnosed every year in the USA with the absolute number of patients newly diagnosed with mesothelioma slightly increasing. Males older than 60 years old (mean age 70 years old, median 73

years old) continue to be the most frequently diagnosed cases.

As its association with asbestos exposure was not recognized till 1960 when it was primarily described in South African asbestos mine workers, the disease incidence increased between 1970 and 1990. This tendency shifted but due to the long latency period the change in incidence was unnoted for years. Currently, its prevalence stabilized or even decreased in developed countries, becoming an issue in developing countries².

The pathogenesis of MPM is based on depositing the inhaled asbestos fibers in the lower third of the lungs and initiating the oncogenic process after being phagocytosed by the mesothelial cells.¹ Additional factors related to the development of mesothelioma are exposure to radiation, initially described following radiotherapy for Hodgkin Lymphoma, and polyomavirus - Simian Virus SV-40, a DNA tumor virus capable of infecting and transforming human mesothelial cells in vitro. Although nicotine itself has not been linked to the development of mesothelioma, asbestos exposure, and concomitant smoking enhances the risk of developing the MPM. Although less aggressive, MPM can also occur in carriers of germline BAP1 heterozygous mutations regardless of asbestos exposure.

Median survival ranges from 9 to 12 months from the time of the diagnosis and is multifactorial depending on the histology, stage, performance status, sex, age, white blood cell count, and platelet count¹. What adds to its poor prognosis and lethality is a common late diagnosis mostly due to the very unspecific symptoms that are shared with most thoracic diseases like dyspnea, chest pain, cough, and pleural effusion. There have been also described several paraneoplastic symptoms associated with mesothelioma, like hypercalcemia, hypoglycemia, autoimmune hemolytic anemia, hypercoagulable states, and disseminated intravascular coagulation, but being non-specific they do not facilitate the diagnosis.¹

As an adequate diagnosis of mesothelioma is dependent on the quantity of tissue obtained, the thoracic liquid cytology or needle biopsy is usually not sufficient to identify the disease. The diagnostic gold standard is video thorascopic biopsy with the diagnostic yield being as high as 98% and giving the possibility of simultaneous pleurodesis¹. The most common and the one with the best prognosis is the epithelioid type of MPM occurring in almost 50% of the cases.² The remaining include mixed (biphasic) and sarcomatoid morphology being the least favorable in terms of life expectancy.¹

The currently used staging system for MPM is based on the TNM (tumor, nodes, metastasis) classification developed by the International Mesothelioma Interest Group (IMIG) in 1994. The National Comprehensive Cancer Network (NCCN) and the American Joint Committee on Cancer (AJCC) both recommend using the TNM staging system developed by the IMIG. Due to the limitations discovered during the following years, the International Association for the Study of Lung Cancer (IASLC) developed a series of recommendations included in the 8th version of TNM.

OBJECTIVES

Our objective was to compare the outcomes of neoadjuvant chemotherapy with subsequent surgery, surgical intervention without any systemic treatment, an upfront surgery and adjuvant chemotherapy and surgical intervention with both neo- and adjuvant therapy to establish the factors that influence 1-year survival and a disease-free period.

Additionally, we analyzed the impact of staging and stratification for T and N on 1-year survival and a disease-free period. Since all patients had epithelioid mesothelioma and all but one were submitted to PD (pleurectomy/decortication) with resection and reconstruction of the diaphragm and pericardium, the histology subtype and the type of surgery could not have been analyzed. The established outcomes were

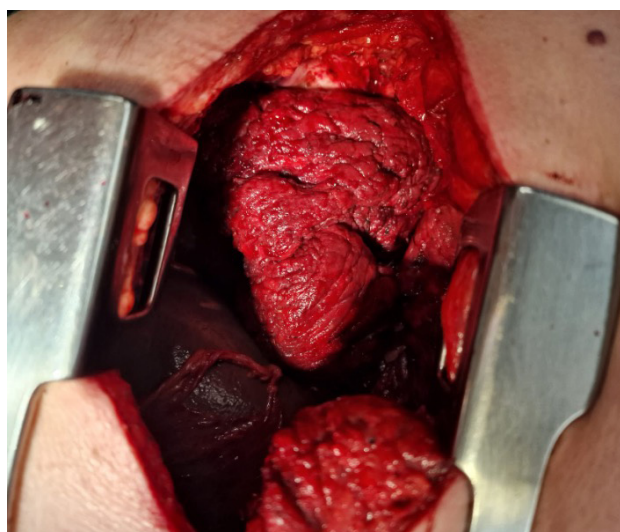


Figure 1

Lung tissue without visceral pleura.



Figure 2

PD en bloc resection.

Table 1 Patients Characteristics

n=16	
Gender	
Women	3 (19%)
Men	13 (81%)
Exposition	
Tobacco	3 (19%)
Asbestos	2 (13%)
Asbestos + tabacco	5 (31%)
Fiber cement	1 (6%)
Unknown	5 (31%)
Age at the time of surgery	61 years old (range 33-72)
Surgery	
Pleuropneumectomy	1 (6%)
Pleurectomy -decortication	15 (94%)
TNM	
pT1 N0 M0	2
pT2 N0 M0	4
pT2/3 N0 M0	1
pT2/3 N2 M0	1
pT3 N0 M0	7
pT4 N2 M0	1
Pathologic results	
Epithelioid invasive mesothelioma	16 (100%)
Mean length of hospital stay	27.3 days (range 9-115 days)

Table 2 Group treatment results

n=16	
The mean follow-up	27 months (range 3 to 82 months)
Recurrence	67%
Disease free survival	27 months (range 3 to 82 months)
1-year survival	20 months (range 0 to 82 months)

disease-free survival (DFS) and 1-year survival, which were analyzed in correlation with neo-adjuvant chemotherapy or upfront surgery and adjuvant chemotherapy to determine the most advantageous treatment in terms of oncological results.

MATERIAL AND METHODS

Our analysis is a retrospective study conducted at a single center, based on the 8-year experience within our department. We searched our database for cases of Mesothelioma between January 2016 and December 2020, resulting in a total of 16

cases included in the final analysis. The inclusion criteria were a confirmed diagnosis of Mesothelioma, surgical excision performed between January 2016 and December 2022, and access to follow-up data.

The characteristics of the patients can be found in Table I.

A search of the department's surgical database between Jan/2016 and Dec/2022 revealed 16 cases of epithelioid invasive mesothelioma. We analyzed the neo-adjuvant chemotherapy or upfront surgery, and adjuvant chemotherapy in correlation with 1-year survival, as well as disease-free survival.

Despite the relatively small size of our patient cohort, which did not allow us to conduct a statistical analysis we analyzed the data using descriptive analysis techniques.

RESULTS

The median follow-up period (MFUP) was 27 months (ranging from 3 to 82 months), calculated from the surgery date until the date of last contact or death from any cause. The group had 68% of recurrence, DFS of 20 months (0-82), and 1-year survival of 69%. The results of the cohort can be found in Table II.

The 15 patients were submitted to pleurectomy and decortication with resection of the pericardium together with resection of the diaphragm and its reconstruction. One patient was submitted to pleuropneumectomy.

The 3 patients treated with surgery without any systemic treatment, had a MFUP of 7 months (3-12), 67% of recurrence, DFS of 6 months (0-12), and 1-year survival of 33%.

The 6 patients treated with neoadjuvant chemotherapy, surgical resection, and adjuvant therapy, had an MFUP of 45 months (8-82), 67% of recurrence, DFS of 32 months (2-82), and 1-year survival of 83%.

The 1 patient was treated with neoadjuvant chemotherapy and subsequently, surgery had a follow-up of 29 months with DFS of 20 months and was alive at the time of submission of this article.

The 6 patients treated with an up-front surgery and adjuvant chemotherapy had an MFUP of 20 months (8-33), 67% of recurrence, DFS of 15 months (6-33), and 1-year survival of 67%. Table III lists the treatment results.

The impact of staging and stratification for T and N on 1-year survival, a disease-free period, and a recurrence rate are presented in Table IV.

DISCUSSION

For the early-stage disease, radiotherapy and surgery can be potentially curative but this is the case for the minority of patients, most of whom present either with advanced disease or are too frail to endure the surgical aggression. The optimal treatment is the object of an intense discussion.

Current guidelines elaborated by the ESMO Guidelines Committee and published in the Annals of Oncology in 2021 define the standard of modern care in mesothelioma patients and the role of surgery in its diagnosis, treatment,

Table 3 **Treatment results**

	Group A n=3	Group B n=6	Group C n=1	Group D n=12	n=16
	Surgery	Neoadj + surgery + adjuvant	Neoadjuvant + surgery	Surgery + adjuvant	
Median follow-up time	7 months (range 3-12 months)	45 months (range 8-82 months)	29 months	20 months (range 8-33 months)	27 months (range 3 to 82 months)
Recurrence	67%	67%	100%	67%	67%
Disease free survival	6 months (range 0-12)	32 months (range 2-82)	20 months	15 months (range 6-33 months)	20 months (range 0 to 82 months)
1-year survival	33%	83%	alive	67%	69%

Table 4 **The impact of staging and stratification for T and N**

Stage	n	1-Year Survival	Median Disease Free Survival
I	2	100%	10.5 months
II	5	80%	28.4 months
IIIA	8	62.5%	18.6 months
IIIB	1	0%	6 months
1-year survival	33%	83%	alive

and palliation.

Surgery is an essential instrument in the diagnostic process as video-thoroscopic (VATS) biopsy is recommended to obtain sufficient material, to define the histology, to stage optimally, and to allow pleural fluid evacuation. A transthoracic biopsy or medical thoracoscopy is often used as a first step to investigate pleural effusion but one can risk seeding the malignant cells along the needle tract. According to the recent consensus ideally three separate locations of the pleura should be sampled.

The role of surgery in palliation englobes principally control of pleural effusion. Although currently, talc poudrage pleurodesis remains the procedure of choice, the randomized, controlled trial (MesoVATS) did not find differences in overall survival at 1 year between VATS partial pleurectomy (VATSPP) with talc pleurodesis. Partial pleurectomy or indwelling pleural catheters (IPCs) can be alternative solutions for patients with entrapped lungs who would experience no benefit from chemical pleurodesis.

In selected patients recommended treatment consists of macroscopic complete resection (MCR) as part of the multimodality treatment. Cytoreductive surgery with the intent to remove all the macroscopically visible disease was historically accomplished by the en bloc resection of the lung, parietal pleura, pericardium, and diaphragm as an Extrapleural Pneumonectomy (EPP) procedure.

In 2011 a multicentre randomized controlled trial in 12 UK hospitals called Mesothelioma and Radical Surgery (MARS)

feasibility study concluded that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients.

Subsequently, the interest was turned into less aggressive surgery: pleurectomy-decortication (PD) consisting of removing all the visible disease but preserving the lung itself (pictures 1,2). In 2014 a systematic review and meta-analysis of 1145 patients published in Lung Cancer compared PD with EPP. Perioperative mortality (2.9% versus 6.8%, p-value: 0.02) and morbidity (27.9% versus 62.0%, p-value: 0.001) were significantly lower in the PD group with comparable overall survival (OS) between the two groups. The meta-analysis from 2015 published in the Annals of Thoracic Surgery describing an analysis of 2903 patients, reached similar conclusions. Short-term deaths in the EPP group versus the PD group were significantly higher (4.5% vs 1.7%; p-value: 0.05). Although the authors did not notice any difference in 2-year mortality, the PD group had a 2.5-fold lower short-term mortality (perioperatively and within 30 days) than EPP.

Last year brought the conclusion of the long-awaited MARS 2 trial, the first multicentre randomized trial of 328 patients comparing PD versus no PD for patients with MPM. The data were presented during the Presidential Plenary at the 2023 World Conference on Lung Cancer. The hypothesis of the trial was the statement that surgery along with chemotherapy is superior to chemotherapy alone in terms of OS. Secondary outcomes were health-related quality of life, progression-free survival, measures of safety (adverse events), and resource use

to 2 years. The researchers concluded that PD combined with chemotherapy was associated with worse survival outcomes, a higher incidence of serious adverse events, and diminished quality of life compared to platinum and pemetrexed chemotherapy alone. However, the study did not include stratification based on tumor histology, T, N, or overall stage, and it relied solely on a chest CT scan without mediastinal staging using PET-CT scans or MRI. This raised significant concerns regarding the quality of the study. Moreover, no induction chemotherapy regimens or surgical and radiotherapy (RT) techniques were standardized. As multiple aspects of the study and its execution were questioned, we remain without a definite clarification on the role of surgery in mesothelioma patients.

In our patient sample, we observed that whether or not the patient was submitted to surgical intervention has not surely influenced the prognosis as only patients submitted to the systemic treatment experienced significantly improved MFUP, DFS, and 1-year survival. These results also align with the MARS 2 conclusions in defining surgery as a factor of less influence in the multimodality treatment.

Meanwhile, data presented recently by a group from Pennsylvania, USA, supported the importance of multimodality treatment². In this 2023 review of the National Cancer Database (NCDB), the group that had undergone surgery had a median survival of 19.8 months [95 CI: 19.2–20.3] compared to 7.9 months [95% CI: 7.8–8.1] in those who had not undergone surgery. ($p < 0.001$). Those who underwent chemotherapy had a median survival of 14 months [95% CI: 13.8–14.3] compared to 6.01 months [95% CI: 5.8–6.2] among those who did not ($p < 0.001$). Patients submitted to both chemotherapy and surgery achieved a median survival of 21.7 months. Conclusions drawn from that study stated that patients who had received chemotherapy and surgery had superior median survival to both chemotherapy or surgery alone further corroborating the importance of multi-modality in treating MPM.

In the 2023 NCDB review comparing stages among those who had received surgery, patients with Stage II ($p=0.2$) and Stage III ($p=0.1$) had comparable 2- and 5-year percentage survivals to Stage I. However, those who were Stage IV had a worse percentage of survival compared to all other stages ($p < 0.001$)². In our patient sample, we observed a gradual failing of 1-year survival and DFS and an increase of relapse rate without comparable results between stages I, II, and III.

The findings of our review should be approached with caution due to the retrospective nature of the study, and the limitations of our small cohort which makes it challenging to draw robust conclusions.

Our results, despite these limitations, suggest that the multimodal approach with both neoadjuvant and adjuvant chemotherapy demonstrates the longest MFUP, DFS and 1-year survival. The worst results were observed in patients treated only with radical surgery.

As we continue to analyze larger patient cohorts, we hope to validate these findings and demonstrate the value of

multimodal treatment.

CONCLUSIONS

Despite the limitations of the study, the multimodal approach with both neoadjuvant and adjuvant chemotherapy demonstrated the longest MFUP, DFS, and 1-year survival. The worst results were observed in patients treated only with radical surgery, while the sequence of systemic treatment did not influence the rate of recurrence.

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