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INTEGRATED STUDY MASTER'S THESIS

Pleuros Mezotelioma. Klinikinis Atvejis

Pleural Mesothelioma. Clinical Case Report

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ABBREVIATIONS

- ADC – Apparent diffusion coefficient
- AKI – Acute kidney injury
- ALP – Alkaline phosphatase
- ALU – Alu repetitive elements
- APTT – Activated partial thromboplastin time
- AST – Aspartate aminotransferase
- AUC – Area Under the Curve
- AUCROC – Area Under the Receiver Operating Characteristic Curve
- BAP1 – BRCA1-associated protein 1
- BNP – B-type natriuretic peptide
- Bpm – Beats per minute
- BP – Blood pressure
- BSA – Body surface area
- CEA – Carcinoembryonic antigen
- Cis/Pem – Cisplatin and Pemetrexed
- CK7 – Cytokeratin 7
- CRP – C-reactive protein
- CSF – Cerebrospinal fluid
- ctDNA – Circulating tumor DNA
- CT – Computed tomography
- DC – Dendritic cell
- DFS – Disease-free survival
- DVT – Deep vein thrombosis
- DWI – Diffusion-weighted imaging
- EBUS-TBNA – Endobronchial ultrasound-guided fine needle aspiration
- ECOG – Eastern Cooperative Oncology Group
- EGD – Esophagogastroduodenoscopy
- EPD – Extended pleurectomy/decortication

- EPP – Extrapleural pneumonectomy
- eGFR – Estimated glomerular filtration rate
- FBLN3 – Fibulin-3
- FDA – U.S. Food and Drug Administration
- GI – gastrointestinal
- HBG – Hemoglobin
- HFNC – high-flow nasal oxygen therapy
- HMGB1 – High-mobility group box 1
- HR – Heart rate
- HRO – Hazard ratio
- HAS2 – Hyaluronan synthase-2
- ICIs – Immune checkpoint inhibitors
- ICU – Intensive care unit
- INR – International Normalized Ratio
- IPC – Indwelling pleural catheters
- LC – Local control
- LDCT – Low-dose CT
- LMR – Lymphocyte-to-monocyte ratio
- LMWH – Low molecular weight heparin
- lncRNAs – Long non-coding RNAs
- LP – Lumbar puncture
- MAP – Mean arterial pressure
- MCR – Macroscopic complete resection
- MD – Mean difference
- MDK – Midkine
- miRNAs – MicroRNAs
- mmHg – millimetre of mercury
- MPM – Malignant pleural mesothelioma
- MRI – Magnetic resonance imaging
- MT – Medical thoracoscopy
- NEL – Non-expansile lung
- NEU – Neutrophils
- NIV – Noninvasive ventilation
- NLR – Neutrophil-to-lymphocyte ratio

- NPS – Number of pleural sites
- OPN – Osteopontin
- OR – Odds ratio
- ORRs – Objective response rates
- OS – Overall survival
- P/D – Pleurectomy/decortication
- pDCs - Plasmacytoid dendritic cells
- PCT – Procalcitonin
- PE – Pulmonary embolism
- PET-CT – Positron emission tomography
- PF – Pleural fluid
- PFS – Progression-free survival
- PM – Pleural mesothelioma
- PNI – Prognostic Nutritional Index
- PTM – Procedure-tract metastases
- QoL – Quality of life
- RCT – Randomized controlled trial
- RE – Relative effect
- ROS – Reactive oxygen species
- RV/LV ratio – Right ventricular–to–left ventricular diameter ratio
- SESN1 – Sestrin-1
- SMRP – Soluble mesothelin-related peptides
- SpO_2 – Oxygen saturation
- SSC – Surviving sepsis campaign
- SUV – Standardized uptake value
- TP – Talc pleurodesis
- TiME – Tumor immune microenvironment
- TTF1 – Thyroid transcription factor-1
- TTFields – Tumor-treating fields
- TV – Tumor volume
- UFH – Unfractionated heparin
- US – Ultrasound
- US-PPNB – Ultrasound-guided percutaneous pleural needle biopsy
- UTI – Urinary tract infection

- VMKL – Vilniaus miesto klinikinė ligoninė
- VTE – Venous thromboembolism
- VULSK – Vilniaus universiteto ligoninė Santaros klinikos
- WBC – White blood cell
- WT1 – Wilms' tumor 1 protein

SUMMARY

Malignant pleural mesothelioma is a rare, yet notably aggressive malignancy of the pleural lining and is primarily linked to asbestos exposure. Despite advancements in diagnostics and treatment, managing this disease remains challenging, particularly in advanced stages. This thesis presents a retrospective clinical case analysis of a malignant pleural mesothelioma patient, which integrates a literature review and a comparison of treatment decisions against established guidelines.

The patient's clinical presentation, diagnostic process, treatment course, and disease progression are examined in detail. The literature review covers epidemiology and risk factors, pathophysiology and molecular biology, diagnostic methods and biomarkers, treatment methods and effectiveness, prognostic factors and survival analysis. Treatment decisions were evaluated against the European Society for Medical Oncology (ESMO) 2021/2022 guidelines, and the patient's intensive care management was assessed based on the Surviving Sepsis Campaign guidelines of 2021. The case was further compared to another patient to highlight differences in disease trajectory and response to therapy.

SANTRAUKA

Piktybinė pleuros mezotelioma yra reta, tačiau itin agresyvi piktybinė krūtinplėvės liga, kuri dažniausiai siejama su asbesto poveikiu. Nepaisant diagnostikos ir gydymo pažangos, šios ligos valdymas išlieka sudėtingas, ypač pažengusiose stadijose. Šiame magistro darbe pateikiama retrospektyvi klinikinio piktybinės pleuros mezoteliomos atvejo analizė, kuri apima literatūros apžvalgą ir gydymo sprendimų palyginimą su nustatytomis gairėmis. Išsamiai analizuojama paciento klinikina, diagnostikos procesas, gydymo eiga ir ligos progresavimas. Literatūros apžvalgoje aptariama epidemiologija ir rizikos veiksniai, patofiziologija ir molekulinė biologija, diagnostikos metodai ir biomarkeriai, gydymo metodai ir jų veiksmingumas, prognostiniai veiksniai ir išgyvenamumo analizė. Gydymo sprendimai buvo vertinami pagal Europos medicininės onkologijos draugijos (ESMO) 2021/2022 metų gaires, o gydymas intensyviojoje terapijoje - pagal 2021 metų „*Surviving Sepsis Campaign*“

rekomendacijas. Atvejis taip pat buvo palygintas su kitu pacientu, siekiant išryškinti ligos eigos ir atsako į gydymą skirtumus.

KEYWORDS
Malignant pleural mesothelioma, systemic mesothelioma therapy, sepsis management, mesothelioma clinical guidelines

1. INTRODUCTION

Pleural mesothelioma, a rare and aggressive malignancy affecting the pleura, most commonly associated with asbestos exposure. The disease presents numerous challenges due to its long latency period, diagnostic complexity, and often poor prognosis. Despite advances in medical research, managing pleural mesothelioma remains difficult, with many cases diagnosed at advanced stages, limiting treatment options and affecting patient survival.

This clinical case study provides a comprehensive review of a patient diagnosed with pleural mesothelioma, offering insights into various aspects of the disease, including diagnosis, treatment, and patient outcomes. By analyzing this real-world clinical scenario, this thesis aims to contribute to a better understanding of how pleural mesothelioma manifests and is managed in practice, ultimately supporting improved clinical approaches.

Aim:

The aim of this thesis is to evaluate the clinical presentation, diagnostic process, treatment options, and outcomes of a patient with pleural mesothelioma, drawing broader conclusions for clinical practice.

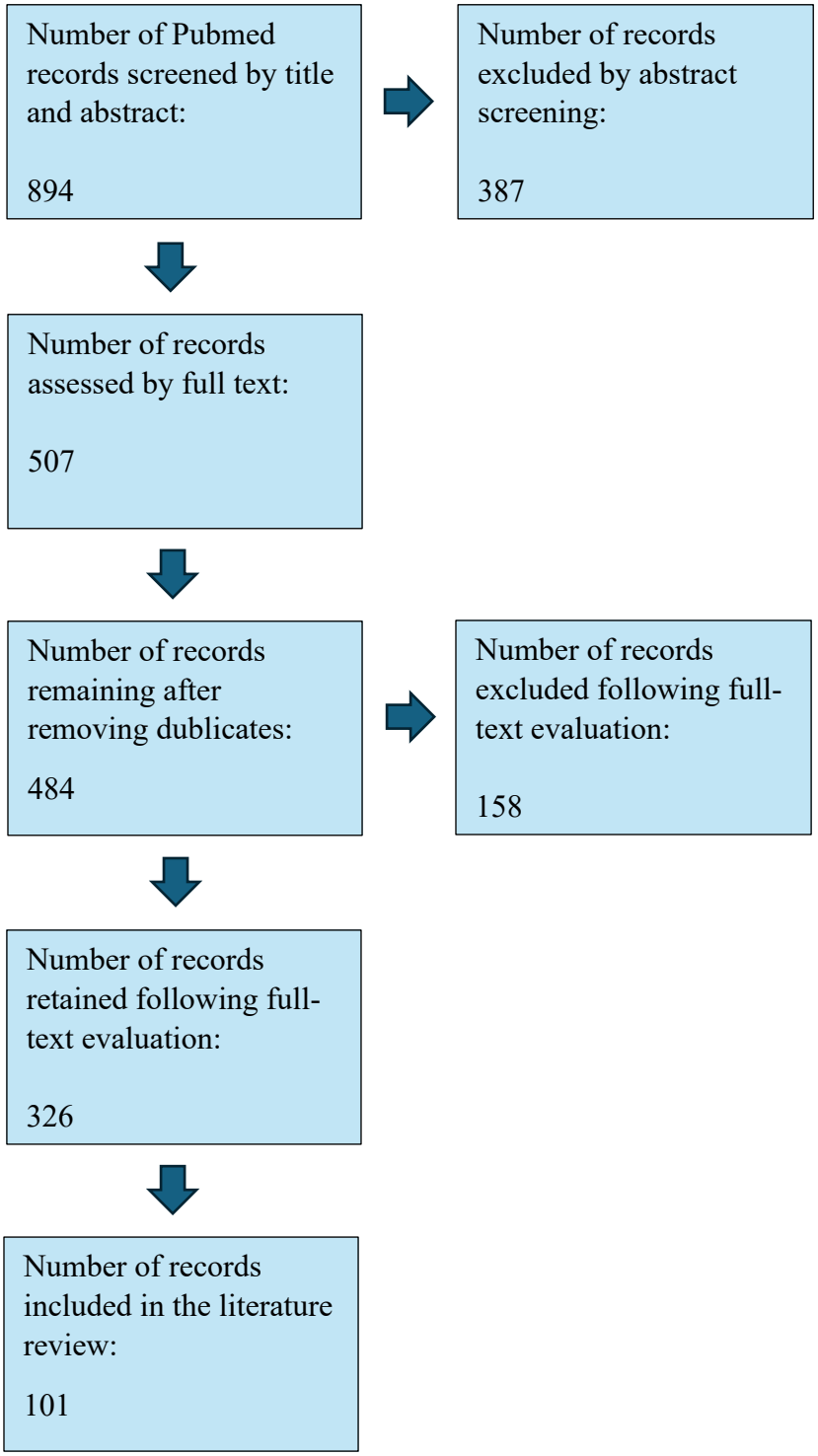
Objectives:

1. To review the literature on the epidemiology, pathophysiology, diagnosis, treatment and prognosis of pleural mesothelioma.
2. To present the clinical course of the patient, including diagnostic and therapeutic decisions.
3. To assess the clinical course and outcomes of the presented case in relation to current guideline-based management strategies for pleural mesothelioma.

2. LITERATURE REVIEW

2.1 Literature review methodology

The literature review was conducted on 23 September 2024.



2.2 Search terms

Epidemiology and Risk Factors:

"Pleural mesothelioma"[Title/Abstract] AND ("epidemiology"[Title/Abstract] OR "risk factors"[Title/Abstract]) AND ("last 10 years"[PDat])

Pathophysiology and Molecular Biology:

"Pleural mesothelioma" AND ("pathophysiology" OR "molecular biology") AND ("last 10 years"[PDat])

Diagnostic Methods and Biomarkers:

("Pleural mesothelioma"[Title/Abstract]) AND (("diagnostic methods"[Title/Abstract] OR "imaging"[Title/Abstract] OR "biomarkers"[Title/Abstract] OR "cytology"[Title/Abstract] OR "biopsy"[Title/Abstract] OR "thoracoscopy"[Title/Abstract]) AND ("last 10 years"[PDat])) NOT ("therapy"[Title/Abstract] OR "treatment"[Title/Abstract] OR "therapeutic"[Title/Abstract] OR "chemotherapy"[Title/Abstract] OR "radiotherapy"[Title/Abstract])

Treatment Methods and Effectiveness:

"Pleural mesothelioma"[Title/Abstract] AND ("standard treatment"[Title/Abstract] OR "chemotherapy"[Title/Abstract] OR "radiotherapy"[Title/Abstract] OR "immunotherapy"[Title/Abstract] OR "surgery"[Title/Abstract]) AND ("outcomes"[Title/Abstract] OR "effectiveness"[Title/Abstract] OR "comparative"[Title/Abstract]) AND ("last 10 years"[PDat])

Prognostic Factors and Survival Analysis:

"Pleural mesothelioma"[Title/Abstract] AND ("prognostic factors"[Title/Abstract] OR "survival analysis"[Title/Abstract]) AND ("last 10 years"[PDat])

2.3 Exclusion criteria

- **Irrelevant populations**: Studies focusing on other types of mesothelioma (e.g., peritoneal mesothelioma) without specific mention or focus on pleural mesothelioma.
- **Publication type**: Editorials, commentaries, letters to the editor, or opinion pieces that do not present primary research data nor systematically synthesize existing data.
- **Case reports**: Individual case reports or case series with small sample sizes, unless they describe unique treatment approaches or rare subtypes that offer significant new insights.
- **Non-English language**: Studies published in languages other than English, unless an English abstract is available that provides sufficient detail for assessment.
- **Outdated studies**: Studies published more than 10 years ago, unless they are seminal works that provide foundational information, which is essential to understand the context of current research.

- **Studies with poor methodological quality**: Studies lacking proper control groups, with unclear or poorly defined methods, or without statistical analysis that limits the validity of their findings.
- **Incomplete Data**: Studies that do not provide complete data on outcomes or have significant gaps in information that cannot be resolved from the abstract.
- **Phase 1 trials and Animal studies:** Studies that focus on preliminary safety, dosage, or mechanisms, lacking relevant clinical data.
- **Papers with narrow molecular focus not broadly applicable to pleural mesothelioma:** Studies exclusively examining molecular mechanisms without broader clinical relevance to pleural mesothelioma.

The bibliography tool Zotero has been used to cite and list the literature sources in the Vancouver citation style.

2.4 Literature review results

2.4.1 Epidemiology and risk factors

Although first described in 1947, Malignant pleural mesotheliomas (MPM) association with asbestos exposure was established by 1960. Initially thought to be uncommon, the disease was later recognized as a direct consequence of occupational asbestos exposure, particularly to blue asbestos (crocidolite), which was widely used in industrial settings (1, 2). Asbestos became widely used in industry starting in the 1880s, with its application growing rapidly in the 1920s and continuing throughout the 20th century, particularly around World War II. This extensive use contributed to a rise in MPM cases by the 1960s, driven by prolonged exposure and a delayed understanding of its health risks (3).

One of the defining features of MPM is its prolonged latency period, often spanning up to 40 years from asbestos exposure to the first symptoms. In fact, in 99% of cases, the latency exceeds 15 years (4). The risk of developing pleural mesothelioma (PM) remains elevated even four decades after asbestos exposure, with individuals exposed 40 years ago facing a significantly higher risk than those whose last exposure was just five years ago (5). The long latency period of MPM is reflected in mortality patterns. Studies analyzing data from the 1960s to the early 2000s found that MPM-related deaths in men peaked approximately 37.5 years after the highest levels of asbestos exposure, which shows the long delay between exposure and disease onset (3).

Estimating the global burden of MPM remains challenging due to inconsistencies in reporting. However, in 2020, approximately 30870 new cases of malignant mesothelioma were recorded worldwide, representing 0.2% of all newly diagnosed malignant tumors. That same year, the

disease was responsible for an estimated 26278 deaths (6). Global data from 2017 estimates that global mesothelioma deaths could reach up to 38400 annually (1). Gender disparities in PM incidence are striking, with men being affected about five times more often than women, a pattern primarily driven by male-dominated occupational asbestos exposure. However, women are not exempt from risk, as significant cases have been reported due to environmental and para-occupational exposure (7). MPM predominantly affects older males at a median age of around 70 years, with a large proportion of deaths occurring in high-income countries (1). In the United States, the incidence of PM in men aged 75 and older has increased annually by 2.2% since 1973, with peak incidence among birth cohorts from 1926 to 1932, which reflects the rise in asbestos exposure during that time (8). Meanwhile, the incidence in men under 75 has declined after peaking between 1978 and 1982, which is assumed to be due to the reduced asbestos exposure following World War II. These patterns indicate the effectiveness of asbestos regulations implemented in many industrialized countries during the late 20th century. However, due to the long latency period of the disease, the full impact of these regulations may not be fully realized for several more decades (4).
MPM incidence shows considerable regional variation. Countries with a long history of asbestos use, such as the United Kingdom, Australia, and New Zealand, report some of the highest rates. In the UK, for instance, the annual incidence is 3.6 cases per 100000 men and 0.7 cases per 100000 women. In contrast, nations like Japan, Slovenia, and several Central European countries have some of the lowest recorded incidence rates (2). In countries with a long history of asbestos use, mesothelioma cases typically peak around 40 years after exposure. In Italy, for example, predictive models estimate that MPM-related deaths reached their highest point in 2021, with approximately 1122 cases. A gradual decline in mortality is expected, with projections indicating around 344 deaths per year by 2039, roughly 30% of the peak level (9). In Norway, the incidence of PM in men decreased from 1.7 to 1.1 per 100000 between 2000 and 2019, which indicates either a decrease in exposure or improved effects from regulations (10).
Over the past 60 years, Western Australia has recorded 2796 cases of mesothelioma, with a median diagnosis age of 70 years and a median latency period of 47 years. The vast majority (93.7%) were PM, with the epithelioid subtype being the most common (61.9%). Among women, non-occupational asbestos exposure was more frequent (52.6%) compared to men (9.5%), with a notable portion of cases (8.1%) linked to home renovations (11).
Non-occupational asbestos exposure plays a significant role in MPM incidence. In Italy, between 1993 and 2008, 15845 mesothelioma cases were recorded, with documented asbestos

exposure in 12065 cases (76.1%). Among these, 4.4% were linked to familial exposure (household contact with an occupationally exposed individual), 4.3% to environmental exposure (living near asbestos-contaminated sites), and 1.6% to asbestos-related hobbies or leisure activities. Clusters of environmental mesothelioma were identified in areas surrounding asbestos-cement plants, shipyards, and soil-contaminated regions (12). The incidence of MPM in individuals without asbestos exposure is extremely low, at less than 1 per million. Other risk factors, including exposure to synthetic substances such as ceramics and nanoparticles, as well as ionizing radiation and infections with Simian Virus 40 (SV-40), are also associated with mesothelioma (4). Genetic susceptibility plays a role as well, with DNA variants that may interact with asbestos exposure to elevate MPM risk such as the rs9939609 polymorphism (13, 14). However, no evidence links cigarette smoke, glass fibers, or mineral glass wool to MPM (4).

2.4.2 Pathophysiology and Molecular Biology

MPM develops through the malignant transformation of mesothelial cells lining the pleura, with asbestos exposure identified as the primary cause in 70–90% of cases. Despite the well-documented link between asbestos and MPM, quantitative data remains limited, as many studies rely on self-reported exposure. The exact mechanisms through which asbestos induces MPM are not fully understood, though several pathways have been proposed. These include the generation of reactive oxygen species (ROS), direct cytotoxic effects, kinase-mediated signaling, chronic inflammation, and the dysregulation of cytokines and growth factors. Some MPM tumors exhibit widespread loss of heterozygosity, possibly indicating spindle damage caused by asbestos fibers. Asbestos fibers are known to generate ROS, leading to both genetic and epigenetic alterations in mesothelial cells through direct and immune-mediated inflammation. While ROS-induced DNA methylation does not always result in gene expression changes, an exception is DKK1, an antagonist of the Wnt/β-catenin pathway, where methylation alters gene expression. Although MPM has a relatively low somatic mutation rate compared to other cancers, asbestos fibers exert mutagenic effects by impairing DNA repair mechanisms. Mutagenesis appears to be a pivotal step in disease progression, with pleural thickening emerging as a consequence of chronic inflammation and ROS activity (15).

Compared to other cancers, somatic mutations in MPM are relatively infrequent. Whole-exome sequencing of 74 MPM tumors revealed fewer than two nonsynonymous mutations per megabase, with alterations predominantly affecting key pathways such as TP53/DNA repair

and PI3K/AKT signaling. In the Bueno cohort (16), an average of 24 protein-altering mutations per tumor was identified, with a notable enrichment of C>T transitions.

One of the most frequently mutated genes in MPM is BAP1 (BRCA1-Associated Protein 1), essential for maintaining DNA integrity and controlling cell cycle progression. Mutations in BAP1 are found in up to 60% of cases, and its loss disrupts the IP3R3 channel, ultimately promoting apoptosis.

Other commonly altered tumor suppressor genes include CDKN2A, CDKN2B, NF2, and TP53. TP53 mutations are particularly prevalent in non-epithelioid MPM and have been linked to worse survival outcomes. Additionally, mutations in LATS2, a crucial regulator of the Hippo signaling pathway, are frequently observed in MPM, which further contributes to tumor progression (15).

The tumor suppressor genes CDKN2A, NF2, and BAP1 are frequently inactivated in MPM. Among them, the INK4 locus on chromosome 9p21.3, which encodes p16INK4A and p14ARF, is the most commonly affected, often inactivated through homozygous deletion. Similarly, NF2, located on chromosome 22q12, encodes Merlin, another crucial regulator of the Hippo signaling pathway. Beyond genetic alterations, epigenetic modifications also play a role in MPM carcinogenesis. DNA methylation abnormalities and microRNA dysregulation can silence tumor suppressor genes and disrupt Wnt signaling, further driving tumor progression. In response to these findings, histone deacetylase inhibitors are currently being investigated as potential therapeutic agents to counteract these epigenetic changes (17).

Germline mutations are found in approximately 7–12% of MPM cases, predominantly affecting genes involved in DNA repair and chromatin remodeling. Compared to sporadic cases, patients with these inherited mutations tend to exhibit fewer chromosomal alterations and a less aggressive disease course. There is also evidence that suggests that individuals with germline mutations may respond more favorably to platinum-based chemotherapy and PARP inhibitors, offering potential therapeutic advantages (15).

Aneuploidy patterns in MPM vary by histological subtype. Epithelioid tumors frequently exhibit losses in 3p21 and 17p12–pter, while sarcomatoid tumors are more commonly associated with deletions in 7q31–qter and 15q. Beyond chromosomal alterations, epigenetic dysregulation, particularly DNA hypermethylation, also contributes to disease progression. Higher levels of methylation in tumor suppressor genes have been associated with advanced disease stages and reduced survival rates.

In a study analyzing 50 MPM samples, an average of 6.3% of genes were found to be hypermethylated, compared to 8.8% in lung adenocarcinomas. Notably, specific genes such as

TMEM30B, KAZALD1, and MAPK13 exhibit unique methylation patterns, making them promising candidates for diagnostic biomarkers (15, 18).

MicroRNAs (miRNAs) are key regulators of post-transcriptional gene expression in MPM. Among them, miR-126 functions as a tumor suppressor but is downregulated in MPM. Notably, in vitro studies have shown that introducing exogenous miR-126 can inhibit tumor growth. Similarly, miR-16-5p and miR-193a-3p also act as tumor suppressors in MPM. In contrast, miRNAs such as miR-518f-3p, miR-597-5p, and miR-1260a, which are frequently overexpressed in lung adenocarcinoma, do not exhibit the same upregulation in MPM. These distinct miRNA expression patterns may serve as valuable diagnostic biomarkers, helping to differentiate PM from lung adenocarcinoma (19).

Multiple studies have classified MPM tumors based on gene expression profiles. De Reynies et al. (20) identified two major subtypes, C1 and C2, which correspond to histological features and prognosis. The C1 subtype exhibits a more epithelial-like profile, whereas C2 is characterized by mesenchymal traits.

Further refinements in 2016, based on the transcriptomic analysis of 211 MPM samples, led to the identification of four molecular subtypes: epithelioid, biphasic-E, biphasic-S, and sarcomatoid, forming a spectrum along the epithelial-mesenchymal transition (EMT) gradient. Beyond these main categories, additional rare variants have been recognized, including pleomorphic, deciduoid, small cell, vacuolated, and clear cell subtypes (15).

The epithelial subtype accounts for the majority of MPM cases (86.76%) and is most commonly found in the right chest (57.35%). Diagnosis is supported by immunohistochemical markers, with Calretinin, CK5/6, Wilms' tumor 1 protein (WT1), and D2-40 frequently expressed in MPM tumor cells. In contrast, markers such as TTF-1, Napsin A, and CEA, which are used to distinguish lung adenocarcinoma, are typically negative in MPM, aiding in differential diagnosis (21).

The tumor immune microenvironment (TiME) plays a pivotal role in MPM progression and response to immunotherapy. Research has identified two distinct TiME profiles: TiME-I ("good-TiME") and TiME-II ("bad-TiME"). TiME-I is characterized by partially exhausted CD8+ T cells (PD-1+CTLA-4+) that produce IFN-γ and activate signaling pathways such as ERK, p38, and STAT4. It also includes HLA-DR+ cancer cells and plasmacytoid dendritic cells (pDCs) expressing CD40 and CD86, indicating a more immune-active tumor environment. In contrast, TiME-II is dominated by regulatory T cells (Tregs), CXCR4+CD38– naive CD8+ T cells, and tumor-associated macrophages (TAMs) with high PD-L1 expression. Elevated levels of immunosuppressive cytokines, such as IL-10, further

contribute to immune evasion in TiME-II tumors. A key distinction between these profiles is the extent of neoantigen presentation and MHC expression, which is more pronounced in TiME-I tumors, indicating a more engaged immune response. A 137-gene molecular signature differentiates TiME-I from TiME-II, with TiME-I tumors demonstrating better overall survival (OS) and a greater response to immune checkpoint inhibitors (ICIs), such as PD-1 and CTLA-4 blockade. In contrast, TiME-II tumors exhibit greater resistance to these therapies. Notably, the TiME signature has outperformed traditional immune markers, including PD-L1 expression, in predicting responses to checkpoint inhibitors, making it a promising tool for guiding immunotherapy strategies in MPM (22).

Solitary fibrous tumors (SFTs), previously known as "fibrous mesothelioma," must be distinguished from MPM, as they are believed to originate from fibroblastic cells. These tumors are typically slow-growing and benign, though recurrence is observed in 18.2% of cases, and mortality has been reported at 10.2%. The most significant prognostic factor is complete surgical resection, though tumor size (>10 cm), high mitotic index, necrosis, and hypercellularity have been linked to worse outcomes. Histologically, SFTs consist of spindle-shaped fibroblast-like cells arranged in a "patternless" architecture, with hemangiopericytoma-like blood vessels. Immunohistochemically, they can be distinguished from desmoplastic mesothelioma by their strong expression of CD34, CD99, BCL-2, and STAT6. Common molecular alterations include NAB2-STAT6 fusion variants, activation of the Akt/mTOR pathway, and overexpression of lysine-specific demethylase 1 (17).

2.4.3 Diagnostic Methods and Biomarkers

The definitive method for diagnosing MPM is histological examination of tissue samples, as it provides clear evidence of tissue invasion. This makes it superior to cytology, which may not always distinguish MPM from other pleural malignancies or benign conditions.

Thoracoscopic biopsies are essential for confirming the diagnosis, as they yield sufficient material for histopathological and immunohistochemical analysis. To improve diagnostic accuracy, obtaining multiple biopsies from abnormal pleural areas is recommended. However, certain regions, such as the lung apices or the diaphragm, should be avoided due to the risk of vascular injury. Thoracoscopy is also contraindicated in patients with extensive pleural adhesions, previous pleurodesis, or severe clinical conditions. In such cases, CT-guided biopsy or video-assisted thoracoscopic surgery (VATS) may serve as safer alternatives (23). A comparison of immunohistochemical staining between formalin-fixed pleural biopsies and pleural effusion cytology cell blocks showed high concordance for key markers in epithelioid mesothelioma, with agreement rates ranging from 72% to 100% for calretinin, CK5,

podoplanin, WT1, and EMA. However, in biphasic and sarcomatoid mesothelioma, agreement rates were lower, particularly for calretinin, CK5, and WT1 (24).

PF cytology has traditionally been considered an important tool for diagnosing pleural malignancies, with earlier studies reporting a diagnostic yield of approximately 60%. However, more recent findings suggest this figure may have been overestimated. To improve diagnostic accuracy, it is recommended to submit at least 50–75 mL of PF for cytological analysis. Additionally, repeating the procedure may increase the diagnostic yield by up to 26%, though this is based on limited data. The effectiveness of PF cytology varies widely depending on tumor type. In MPM, diagnosis through this method is particularly difficult, with a diagnostic yield of only 6.1% (25). Despite its low diagnostic yield, thoracentesis remains recommended in some guidelines as an initial step for evaluating symptomatic pleural effusions. As a minimally invasive procedure, it can assist in identifying the epithelioid subtype and also provides temporary relief from dyspnea (26). The diagnostic challenge becomes even greater with certain MPM subtypes. The sarcomatoid variant, for instance, often does not shed tumor cells into PF, significantly lowering the likelihood of a positive cytological diagnosis. Additionally, the presence of reactive epithelioid mesothelial cells in PF should not be automatically considered benign. Features such as mesothelial proliferation or papillary structures may suggest malignancy but can also be found in benign conditions, making it difficult to establish a definitive diagnosis based on cytology alone (25). When cytology is inconclusive, immunocytochemistry can aid in distinguishing malignant mesothelial proliferation from benign conditions. Loss of BAP1, a BRCA-1-associated protein, is highly specific for malignancy, with studies reporting a 100% specificity rate. Additionally, p16 deletions are detected in up to 80% of MPM cases, particularly in the sarcomatoid subtype, which further supports the cytological differentiation of malignancies. Despite these diagnostic tools, the gold standard for confirming malignancy in PM remains the demonstration of tissue invasion through histological examination. Differentiating MPM from secondary pleural tumors also presents challenges. Current guidelines recommend using at least two positive mesothelial markers, such as calretinin, cytokeratin 5/6, WT1, or D2-40, alongside two negative markers for lung adenocarcinoma (TTF-1, CEA, or Ber-EP4) to effectively distinguish MPM from lung adenocarcinoma, which may present with similar features (25).

A study on the genomic-based diagnosis of PM emphasizes the value of integrating morphological and genomic approaches for more accurate detection. The study proposes a three-step diagnostic process for MPM: identifying atypical cells, confirming their

mesothelial origin through immunohistochemistry markers, and distinguishing malignant mesothelioma from benign mesothelial proliferations (BMP). Among key genomic techniques, the loss of BAP1 and CDKN2A/p16, detected by fluorescence in situ hybridization (FISH), demonstrated 100% specificity in differentiating MPM from BMP. This combined strategy significantly improves diagnostic accuracy, particularly in small biopsy or cytology specimens, where traditional methods alone may be insufficient (27).

One of the most extensively studied biomarkers in MPM is mesothelin, which is currently the only FDA-approved blood test for monitoring disease recurrence after surgery and assessing therapy response. Mesothelin, a cell surface glycoprotein, is most primarily expressed in the epithelioid subtype of PM and is also found in ovarian and pancreatic adenocarcinomas. The Mesomark test, an ELISA-based assay, detects soluble mesothelin-related peptides (SMRP) in blood and PF and has received FDA approval for clinical use. However, its sensitivity varies widely across studies, ranging from 19% to 68%, while its specificity falls between 88% and 100%, with influencing factors including age, chronic renal failure, and obesity. High baseline SMRP levels have been linked to poorer survival and higher tumor burden, but its diagnostic value is limited in early-stage disease and the sarcomatoid subtype (28). Mesothelin has been found to promote tumor cell survival and proliferation via the NF-kB pathway and can increase interleukin-6 levels, which may play a role in its association with tumor progression (29). However, current non-tissue-based biomarkers such as mesothelin and also Fibulin-3 (FBLN3) are not yet recommended by most guidelines for routine clinical use due to their limited sensitivity and specificity, e.g. by the American Society of Clinical Oncology (26).

The diagnostic accuracy of mesothelin varies depending on the control groups used in studies. The highest Area Under the Receiver Operating Characteristic Curve (AUCROC) values (0.93–0.94) are observed when comparing MPM patients to those with benign pleural effusions. However, in early-stage MPM (Stage I), its diagnostic performance declines, with an AUCROC of 0.74, indicating reduced effectiveness in early detection.

Another biomarker, osteopontin (OPN), has been found at higher levels in MPM patients compared to controls. However, its ability to distinguish MPM from benign pleural effusions is poor. While OPN performs better when comparing asbestos-exposed individuals to MPM patients, its lack of specificity limits its broader diagnostic utility (30). OPN is an extracellular matrix protein involved in immune modulation and cell migration. Studies have shown that OPN levels are elevated in MPM, particularly among asbestos-exposed individuals. Its diagnostic performance in distinguishing asbestos-exposed individuals from MPM patients has of been reported by Pass et al. in 2005 (31) with a sensitivity of 77.6% and a specificity of

85.5%. However, its diagnostic utility remains controversial, as inconsistent validation across studies has led to mixed conclusions regarding its reliability (28, 29).

Fibulin-3, a glycoprotein involved in tissue remodeling, has been investigated as a diagnostic biomarker for PM. Early studies reported high sensitivity and specificity, with one study showing 96.7% sensitivity and 95.5% specificity in differentiating PM patients from asbestos-exposed controls. However, subsequent studies have failed to consistently reproduce these results, leading to ongoing debate about FBLN3's diagnostic accuracy. In terms of prognosis, lower levels of fibulin-3 in pleural effusions have been associated with prolonged survival (29).

High-mobility group box 1 (HMGB1) has emerged as a promising biomarker for MPM, particularly in its hyperacetylated form. This protein is released by necrotic mesothelial cells following asbestos exposure and plays a key role in inflammation and carcinogenesis. Hyperacetylated HMGB1 has demonstrated high diagnostic accuracy, with 100% sensitivity and 100% specificity at a cutoff value of 2.0 ng/mL, effectively distinguishing MPM patients from asbestos-exposed individuals without the disease. While further research is required to establish its routine clinical use, its potential as both a diagnostic and prognostic marker remains an area of active investigation (28).

Circulating tumor DNA (ctDNA) is an emerging focus in MPM diagnostics, offering potential as a non-invasive biomarker. Derived from tumor cells undergoing apoptosis or necrosis, ctDNA can be detected in the bloodstream and analyzed for diagnostic purposes. Studies have shown that the DNA integrity index, which assesses the ratio of ALU fragment sizes in pleural fluid, is significantly higher in MPM patients compared to those with benign pleural effusions. Additionally, combining ctDNA measurements with mesothelin levels has demonstrated diagnostic potential, with an Area Under the Curve (AUC) of 0.82, which shows the potential of ctDNA to improve diagnostic accuracy (32).

Alongside genetic and protein markers, long non-coding RNAs (lncRNAs) are being investigated as potential biomarkers for MPM. A study by Matboli et al. (33), identified an RNA-based biomarker panel that includes DRAM1, ARSA, miR-2053, and lncRNA RP1-86D1.3, demonstrating 100% sensitivity, 85% specificity, and an overall diagnostic accuracy of 94%. The potential of lncRNAs to differentiate mesothelioma from pleural conditions of benign etiology and other malignancies remains an area of ongoing research (34).

Medical thoracoscopy (MT) is a minimally invasive procedure used for evaluating pleural effusions and obtaining biopsies when pleural fluid analysis is inconclusive. Unlike surgical thoracoscopy, MT is typically performed by pulmonologists under moderate sedation,

allowing for targeted pleural biopsies while the patient remains spontaneously breathing. Ultrasound guidance is commonly used during MT, and findings such as nodules, masses, and pleural thickening are frequently observed in MPM patients. Additionally, MT can be utilized for managing recurrent pleural effusions, either through pleurodesis or by inserting a pleural catheter during the same procedure (23).

A recent study evaluating the diagnostic accuracy of ultrasound-guided percutaneous pleural needle biopsy (US-PPNB) for MPM reported a sensitivity of 83.39% and a specificity of 100%. The adequacy of biopsy samples was significantly influenced by pleural lesion thickness, with thicker lesions yielding higher success rates. While US-PPNB was effective in most cases, three patients required thoracoscopy due to inadequate biopsy specimens. Additionally, a positive correlation was observed between diagnostic accuracy and FDG-PET avidity values of pleural lesions, which further supports the role of imaging in guiding biopsy procedures (35). Other studies have reported a diagnostic accuracy of 75.5% for US-PPNB, identifying a pleural thickness threshold of 4.15 mm as a key factor influencing biopsy success rates. Additionally, the use of larger biopsy needles, such as 16-G, has been associated with improved diagnostic accuracy (36). When videothoracoscopy is not feasible, particularly in cases of "dry" pleural presentations, endobronchial ultrasound-guided fine needle aspiration (EBUS-TBNA) has been shown to be a valuable alternative, successfully obtaining adequate samples for diagnosing MPM (37).

Diagnostic imaging is fundamental to the evaluation and staging of MPM. Chest radiography is often the first-line imaging modality due to its accessibility, though its findings are generally nonspecific. The most common radiographic feature is unilateral pleural effusion, observed in 30%–80% of patients. CT scans, especially thin-section volumetric imaging, play a central role in MPM diagnosis. CT can identify pleural thickening in 90%–92% of cases, as well as pleural effusions and plaques. Additionally, CT is crucial for staging and determining tumor invasion into adjacent structures (38). Several CT features have been found to be more common in MPM patients, including mediastinal pleural thickening, diaphragmatic pleural thickening, and circumferential pleural thickening, all of which are significantly associated with a diagnosis of MPM (39).

Diffusion-weighted imaging (DWI) has demonstrated potential in distinguishing PM from other pleural diseases. A study analyzing apparent diffusion coefficient (ADC) values across various pleural conditions found that ADC values were significantly lower in MPM compared to benign conditions such as empyema and pleural effusion. Additionally, DWI patterns in

MPM cases exhibited strong continuous diffusion, in contrast to benign diseases, which showed weaker or no diffusion (40).

CT screening, particularly low-dose CT (LDCT), is recommended for asbestos-exposed individuals due to their increased risk of lung cancer and MPM. Studies have shown that LDCT is more sensitive than chest X-rays in detecting early-stage tumors, and screening programs in high-risk populations have successfully reduced lung cancer mortality. However, the effectiveness of LDCT in detecting MPM remains uncertain, as some baseline studies have reported no cases of PM identified (41).

Magnetic resonance imaging (MRI) and positron emission tomography (PET-CT) provide mutually supportive diagnostic information in MPM evaluation. MRI offers high contrast resolution, making it particularly useful for assessing chest wall and diaphragmatic invasion. PET-CT, on the other hand, combines metabolic and anatomical imaging, aiding in the differentiation between malignant and benign pleural disease. It is especially valuable for staging and treatment planning, with an standardized uptake value (SUV) cutoff of 2.0–2.2 effectively distinguishing between benign and malignant processes with high sensitivity and specificity (38).

Ultrasonography (US) is another important imaging modality, particularly in detecting pleural effusions and guiding image-assisted procedures such as thoracocentesis, needle biopsy, and drainage placement. Studies suggest that US can differentiate between benign and malignant pleural effusions based on findings like pleural thickening and diaphragmatic involvement, offering comparable diagnostic value to CT in certain contexts (38).

A necropsy-based study by Barbieri et al. demonstrates the value of post-mortem examinations in confirming diagnoses when clinical or histologic diagnostics were inconclusive by performing autopsy on 171 PM cases. Autopsy confirmed MPM in 169 cases (98.8%), including 7 cases (4.1%) where histological assessment had initially produced false-negative results. Cytology alone was positive in 18 cases (10.5%) and negative in 14 cases (8.2%), while radiologic imaging detected 16 positive cases (9.4%) but failed to identify 11 cases (6.4%). Pleural plaques and asbestosis were frequently observed in these patients (42).

2.4.4 Treatment Methods and Effectiveness

MPM poses substantial therapeutic challenges due to its aggressive nature and poor prognosis. Standard treatment approaches, including surgery, chemotherapy, and radiotherapy, have demonstrated limited effectiveness, with median survival generally ranging between 1 and 2 years (43,44). Outcomes are heavily influenced by histological subtype, with epithelioid

MPM associated with generally better survival compared to biphasic and sarcomatoid variants (44).

For many years, chemotherapy was the standard treatment for unresectable MPM, with platinum-pemetrexed-based regimens serving as the primary approach. However, treatment strategies have evolved, and ICIs are now a key component of first-line therapy for unresectable disease (45,46). Surgery with radical intent is reserved for highly selected patients, typically within a multimodal treatment approach at specialized centers. Its survival benefit compared to systemic therapy remains a subject of ongoing debate (47). Radiotherapy is used either as part of a multimodality approach as adjuvant therapy after surgery to reduce local recurrence or as a palliative measure (48, 49).

The section of the literature review examines different perspectives on the current treatment landscape for MPM, covering both established therapies and emerging innovations that may influence future disease management.

2.4.4.1 Symptom control

PM commonly presents with dyspnea and chest pain. The leading cause of dyspnea in MPM is pleural effusion, which occurs in approximately 91% of patients, with 71% experiencing related symptoms.

Two primary interventions for pleural effusion management are indwelling pleural catheters (IPC) and talc pleurodesis (TP). Both methods are similarly effective but differ in side effect profiles. IPCs are often preferred in outpatient settings as they minimize initial hospitalization and are particularly beneficial in cases of non-expansile lung (NEL). However, they require more frequent healthcare interventions and carry a risk of infection. In contrast, TP is successful in about 75% of malignant effusions but may be less effective in MPM, as larger tumor volumes and NEL, present in one-third of cases, can limit its efficacy. Findings from the OPTIMUM trial indicated no significant difference in quality of life (QoL) between IPC and TP (43).

Pain management is a crucial component of symptom control in PM, as chest pain can result from tumor infiltration, pleural effusion pressure, or procedures such as thoracoscopy. Standard approaches include analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids. In some cases, neuropathic agents may provide additional relief (43). Localized pain can be managed with palliative radiotherapy, while more diffuse pain may be addressed through cervical cordotomy, though evidence supporting this approach remains limited (49).

Beyond respiratory and pain symptoms, patients with PM often develop systemic symptoms, such as anorexia, weight loss, and cachexia. Nutritional support and low-dose steroids can aid in maintaining caloric intake, though steroids should be used cautiously, particularly in patients being considered for immunotherapy (43).

2.4.4.2 Systemic therapy

Systemic therapy, particularly first-line chemotherapy, has been for a long time the cornerstone of MPM treatment and is still being used today. The EMPHACIS study established the combination of cisplatin and pemetrexed (Cis/Pem) as the standard of care, showing a significant improvement in OS compared to cisplatin alone (median OS 12.1 vs. 9.3 months). However, in order to reduce pemetrexed side effects folic acid and vitamin B12 supplementation are essential (50). For patients who cannot tolerate cisplatin, carboplatin/pemetrexed serves as an alternative, providing similar efficacy with better tolerability. Both regimens are generally administered for up to six cycles. However, non-epithelioid MPM tends to show resistance to chemotherapy, resulting in poorer outcomes (51).

The MAPS trial investigated the addition of bevacizumab, an anti-VEGF antibody, to the standard cisplatin-pemetrexed regimen, leading to a 2.8-month improvement in OS (52). However, bevacizumab is not recommended for patients with poor performance status (PS ≥ 2), significant cardiovascular comorbidities, uncontrolled hypertension, age over 75, or an increased risk of bleeding or thrombosis. Careful patient selection is crucial to weigh the potential survival benefit against the risk of adverse effects (26).

The effectiveness of chemotherapy in MPM varies by histological subtype. A real-world study of 189 patients found that those with epithelioid MPM had significantly better outcomes compared to non-epithelioid subtypes. Among patients receiving first-line chemotherapy, the median OS was 26.7 months for epithelioid MPM, compared to 15.0 months for non-epithelioid cases. Similarly, progression-free survival (PFS) was longer in epithelioid tumors (4.8 vs. 3.6 months) (53).

ICIs have significantly transformed cancer treatment, including MPM. TheCheckMate 743 (54) trial valuated a combination of nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) in 605 patients with unresectable MPM, demonstrating a clear OS benefit over standard cisplatin-pemetrexed chemotherapy. The median OS was 18.1 months with nivolumab-ipilimumab compared to 14.1 months with chemotherapy. This advantage was particularly pronounced in non-epithelioid MPM, where OS improved from 8.8 to 18.1 months (HRO 0.48). Consequently, nivolumab and ipilimumab are now considered the

standard of care for fit patients with non-epithelioid MPM. However, cisplatin-pemetrexed remains the preferred option for epithelioid MPM, particularly when a rapid response is needed or when ICIs are contraindicated. Despite their benefits, ICIs have a slower onset of action and are linked to a higher incidence of grade 3–4 treatment-related adverse events (43). Regarding toxicities, the RIOMeso study assessed the safety profile of ipilimumab and nivolumab in PM. Among 119 patients, 24% experienced grade ≥3 adverse events, with colitis being the most frequently reported severe toxicity. Additionally, three treatment-related deaths were documented in patients receiving combination immunotherapy, resulting from fulminant hepatitis, encephalitis, and acute kidney failure. These results emphasize the importance of vigilant follow-up and managing adverse effects in patients receiving combination immunotherapy (55).

Pembrolizumab, another immune checkpoint inhibitor (ICI), was assessed in the KEYNOTE-028 phase I trial, where it demonstrated early promise (56). However, the PROMISE-Meso phase III trial did not demonstrate significant benefits for pembrolizumab in the second-line setting (57).

In the second-line setting, the therapeutic options are less established.

Vinorelbine and gemcitabine are under investigation for second-line treatment of relapsed MPM. The VIM trial, a randomized phase II study, found that vinorelbine significantly improved PFS compared to best supportive care (BSC). However, it did not demonstrate a statistically significant OS benefit. These results support the off-label use of vinorelbine in this context, although its effect on prolonging survival remains uncertain (58).

ICIs have shown promising activity in the second-line treatment of relapsed MPM. The MAPS2 trial reported disease control rates at 12 weeks of 40% with nivolumab monotherapy and 52% with the nivolumab-ipilimumab combination. Although toxicity was higher in the combination group, the overall safety profile remained consistent with previous ICI studies (59).

The RAMES trial showed that combining gemcitabine with ramucirumab, an anti-VEGFR-2 antibody, resulted in improved OS compared to gemcitabine alone. These findings suggest that VEGF pathway inhibition may have a beneficial role in MPM treatment. However, phase III trials have not yet been conducted (60, 61).

In addition to ICIs, other immunotherapy approaches are being explored for MPM. CAR-T cell therapy, which has shown success in hematologic cancers, presents unique challenges in solid tumors like MPM due to immune evasion mechanisms. Targeting mesothelin, which is overexpressed in 80–90% of MPM cases, has shown promising results. Early-phase trials

have demonstrated anti-tumor activity with a manageable safety profile. Additionally, combining CAR-T cell therapy with ICIs is under investigation to further enhance immune responses (61).

Another promising approach is dendritic cell (DC) therapy, which aims to stimulate T-cells by presenting tumor antigens. The ongoing DENIM phase II/III trial (62) is investigating DC therapy as maintenance treatment following chemotherapy, showing potential for sustained disease control (61).

2.4.4.3 Surgery

Surgical interventions for MPM remain controversial, as clear evidence supporting their effectiveness is lacking. The two primary surgical approaches are extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D). EPP on the one hand is an extensive procedure that involves the removal of the lung, pleura, pericardium, and diaphragm. On the other hand, P/D is a lung-sparing procedure that removes the parietal and visceral pleura to eliminate visible tumors. A more extensive variant, extended P/D (EPD), may include diaphragm and pericardium resection if involved. However, partial P/D, often performed for palliative purposes, leaves visible tumors behind and has shown no survival benefit over TP, as demonstrated by the MesoVATS trial (63). EPP was once widely used but saw a decline after the MARS trial in 2011, which demonstrated limited benefits. Nowadays, P/D is the surgical method of choice due to its decreased morbidity and mortality with comparable long-term survival (64). However, most MPM patients are unresectable, and chemotherapy or immunotherapy remains the primary treatment (47). Achieving complete tumor resection with negative microscopic margins (R0 resection) is rarely feasible in MPM due to the disease's complex anatomy. As a result, surgery is typically integrated into a multimodal treatment approach, with radiotherapy often administered postoperatively to improve OS (65). In terms of neoadjuvant chemotherapy, preliminary results from the MARS2 trial suggest that neoadjuvant chemotherapy followed by surgery may lead to higher mortality and reduced QoL compared to chemotherapy alone (43, 66). The systematic review by Cao et al. found that neoadjuvant chemotherapy, followed by EPP and adjuvant radiotherapy, was associated with better survival outcomes and lower perioperative mortality. In contrast, administering adjuvant chemotherapy after EPP led to higher morbidity (50–82.6%) and perioperative mortality of up to 12.5%. These findings show that post-surgical chemotherapy may be more difficult for patients to tolerate, thus limiting its overall benefit (67).

Maximal cytoreductive surgery, aimed at achieving macroscopic complete resection (MCR) with residual tumor <1 cm, is generally performed in early-stage disease. Better outcomes have been observed in patients with epithelioid histology, whereas the sarcomatoid subtype is associated with a worse prognosis. Surgery is rarely beneficial for patients with advanced disease, sarcomatoid histology, or significant lymph node involvement, as these patients typically experience poor outcomes (26).

Recurrence patterns in PM patients treated with multimodal therapy differ based on the surgical approach. Among those who underwent EPP, distant metastases were more frequent, whereas localized recurrences were more common after P/D. Despite these differences, post-recurrence survival did not vary significantly between the two groups. The median survival after recurrence was 14 months for EPP patients and 8 months for those who underwent PD. Patients with epithelioid histology and a longer disease-free interval (≥12 months) had better outcomes in recurrent cases (68).

A lung-sparing approach combined with Hyperthermic IntraThoracic Chemotherapy (HITHOC) has shown promise in early-stage MPM. A retrospective study of 26 patients who underwent open pleurectomy and partial decortication followed by HITHOC reported a median OS of 35.6 months, with stage I patients achieving particularly favorable outcomes. This lung-sparing strategy may serve as a viable alternative to more aggressive surgeries in early-stage patients, though larger studies are necessary to confirm its efficacy (69).

Immunotherapy has emerged as a promising adjuvant to surgical treatment, particularly for surgical candidates with biphasic or sarcomatoid PM. A comparative study reported a median survival of 22.6 months in patients who received surgery combined with immunotherapy, compared to 11.7 months in those treated with chemotherapy alone. The benefit was especially pronounced in biphasic or sarcomatoid subtypes, where the 12-month survival rate was 76.2% for those who received immunotherapy, compared to 13.6% for those who did not (70).

The prognosis following surgery in PM is largely determined by the histological subtype. Data from the Surveillance, Epidemiology, and End Results (SEER) database suggests that epithelioid PM, which accounts for 70% of cases, has the best outcomes, with a median survival of 19 months. In contrast, biphasic PM, representing 15–20% of cases, has a median survival of 12 months, while sarcomatoid PM, comprising 10–15% of cases, has the poorest prognosis, with a median survival of only 4 months. Surgery is most beneficial for epithelioid PM and selected biphasic cases, whereas sarcomatoid PM generally does not benefit from

surgery due to its aggressive nature and poor survival outcomes (44).

2.4.4.4 Radiotherapy

Radiotherapy has a limited role in the treatment of MPM due to the disease's radiation resistance and the risk of significant toxicity. However, it is sometimes used palliatively to manage localized pain.

The SYSTEMS trial found that 35% of patients experienced pain relief following palliative radiotherapy (20 Gy in five fractions), though response rates varied widely (0%–69%) (43,71).

Prophylactic radiotherapy to prevent procedure-tract metastases (PTM) has been largely discontinued following the SMART and PIT trials, which showed no reduction in PTM incidence (72, 73).

Similarly, radical radiotherapy, such as adjuvant radiotherapy after EPP, has been limited due to high toxicity and no proven benefit in locoregional control, as seen in the SAKK 17/04 trial (74). Research from TomoTherapy centers in Japan found that patients who received hemithoracic radiation post-EPP had a lower 2-year survival rate (33%) compared to those who received lung-sparing radiation alone (60%). Additionally, patients in the EPP group experienced higher incidences of severe lung toxicity, which indicated that hemithoracic radiation following EPP may not deliver survival benefits and increases the risk of complications. Nonetheless, newer techniques such as intensity-modulated radiotherapy and proton beam therapy are being explored in the IMPRINT trial (75) to improve targeting precision while minimizing toxicity (43, 74–76).

Recent studies have explored the use of stereotactic body radiation therapy in MPM treatment. A clinical study involving 44 patients with 59 tumors treated with SBRT showed excellent local control (LC) rates, with 1-year LC of 96.3% for pleural tumors and 90.9% for epithelioid tumors. Side effects included mild fatigue, nausea, and pneumonitis, with no grade 3 or higher adverse events reported, indicating that SBRT may be a promising option for oligoprogressive MPM (77).

2.4.4.5 Novel approaches

To improve MPM outcomes, novel therapeutic strategies are being explored, including oncolytic viral therapy, tumor-treating fields (TTFields), and chemotherapy-immunotherapy combinations. Among these, oncolytic viral therapy is one of the most promising experimental approaches. This approach employs genetically engineered viruses that preferentially target and lyse cancer cells while concurrently activating an immune response. The localized growth of MPM and the accessibility of the pleura make it particularly well-

suited for intratumoral viral injections. Early oncolytic therapies used replication-incompetent viruses, which were designed to deliver therapeutic genes without viral replication, thereby minimizing toxicity. However, advances in viral selectivity have enabled the development of replication-competent viruses, which can replicate within tumor cells, induce cell lysis, and spread further, enhancing both tumor destruction and immune activation. Preclinical models have demonstrated the efficacy of these replication-competent viruses, such as those engineered to express the adenovirus death protein, which significantly improves cytolytic activity (78).

Another innovative treatment approach in MPM is the use of the above-mentioned TTFields. The NovoTTF system, approved by the FDA in 2019, utilizes alternating electric fields to disrupt cancer cell division. When combined with chemotherapy, TTFields has shown promising results. The STELLAR trial demonstrated an OS of 18.2 months in patients receiving TTFields alongside chemotherapy, leading to its FDA approval. Ongoing phase III trials aim to validate and refine these results and assess whether TTFields could be more broadly used in the treatment of MPM (61).

2.4.5 Prognostic Factors and Survival Analysis

Numerous prognostic factors have been identified that influence survival outcomes of MPM patients. These factors span patient demographics, tumor biology, laboratory markers, and treatment approaches.

Age and gender have been consistently highlighted as key prognostic factors in MPM. Older patients, particularly those above 65 years of age, tend to have worse outcomes compared to younger patients (79).

In terms of gender differences, several studies demonstrate better survival outcomes for females compared to males. Biological factors, such as estrogen receptor expression, have been suggested to contribute to this gender-based survival advantage (80). Studies have further shown that female patients tend to have longer disease-free survival (DFS) and OS rates compared to male patients (81).

Beyond demographic factors, systemic inflammation and nutritional status also influence survival outcomes in MPM. A key marker in this context is the prognostic nutritional index (PNI), which is calculated using serum albumin levels and total lymphocyte count. PNI captures aspects of both nutritional balance and inflammatory status. Studies have shown that patients with a PNI below 40 tend to have poorer survival outcomes. Specifically, those with PNI $\leq$40 had a median OS of 12 months, while patients with PNI >40 had a median OS of 21

months. In multivariate analysis, a low PNI remained an independent predictor of worse survival (79).

Histological subtype remains one of the most critical determinants of prognosis in MPM. The epithelioid subtype, present in over half of all cases, is associated with significantly better survival outcomes compared to the more aggressive sarcomatoid and biphasic subtypes. This is supported by studies that show median survival for epithelioid patients to be around 412 days, whereas for sarcomatoid patients, it is as low as 125 days (82, 83). Furthermore, in studies focusing on the impact of multimodal therapy, epithelioid histology consistently emerges as a positive prognostic factor in terms of both response to treatment and OS (84).

Functional status, often measured by performance scores, is another key prognostic factor. Patients with better performance status, typically indicated by a Karnofsky or Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, tend to have significantly better survival outcomes. These findings have been reinforced across multiple studies, where better functional status was linked to improved response to treatments and extended survival (85, 86).

Peripheral blood-based markers, particularly inflammation-related scores, have been investigated for their prognostic significance in MPM. Among these, the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) have drawn attention as potential indicators of patient outcomes. A higher LMR has been consistently associated with prolonged OS in MPM patients, with studies showing that patients with an LMR above 2.6 had a median survival of 17 months, compared to 9.6 months for those with an LMR below this threshold (87–89). In contrast, the prognostic value of NLR remains uncertain, as findings in the literature have been inconsistent and sometimes conflicting. While some studies suggest that an elevated NLR is linked to poorer outcomes (88, 89), others have reported mixed results (87). Additionally, the C-reactive protein-to-albumin ratio (CAR) has emerged as a reliable marker of poor prognosis in patients with inoperable MPM (90).

Soluble factors in pleural effusions have been recognized as important prognostic indicators in MPM. Elevated levels of interleukin-8 (IL-8) and interleukin-2 receptor alpha (IL-2Ra, CD25) have been linked to poorer survival outcomes, whereas lipocalin-2 and interleukin-4 (IL-4) are associated with a better prognosis. Profiling these soluble factors provides valuable insights into disease progression and may enhance the ability to predict survival outcomes in patients with MPM (91).

Laboratory markers, particularly elevated levels of aspartate aminotransferase (AST) and higher monocyte counts, have been shown to independently predict worse survival in MPM

patients. Elevated AST levels have been linked to anemia and higher levels of other enzymes like alkaline phosphatase (ALP), while increased monocyte counts are associated with lower LMRs, both of which are indicative of poorer prognosis (92). Other laboratory factors, such as low hemoglobin (HGB) levels and elevated Ca125, have also been shown to negatively impact prognosis (93).

Recent research has underscored the prognostic significance of various molecular biomarkers in MPM. Midkine (MDK), hyaluronan synthase-2 (HAS2), and sestrin-1 (SESN1) have been strongly associated with improved survival outcomes. Specifically, low expression of MDK and fibulin-3, combined with high expression of HAS2 and SESN1, correlates with longer survival, particularly in epithelioid MPM patients (94).

Similarly, the combination of calretinin, MALAT1, and GAS5 has shown promise as a predictive tool for tumor recurrence and PFS in MPM patients undergoing cytoreductive surgery. Studies have demonstrated that this biomarker combination exhibits high sensitivity and specificity in identifying patients at higher risk of recurrence, presenting a potential way for optimizing multimodal treatment strategies in MPM (95).

The tumor immune microenvironment (TME) and immune checkpoint markers, including PD-1, PD-L1, and TIM-3, are emerging as important factors influencing prognosis as well. High expression of CD4 and TIM-3 in lymphoid aggregates has been correlated with better survival, while CD45RO expression in the stroma predicts poor response to chemotherapy (96). Other studies have shown that CD10 expression is significantly associated with more aggressive histological types, such as biphasic and sarcomatoid mesothelioma, and is correlated with higher mitotic activity. CD10-positive patients tend to have significantly shorter survival (97).

Tumor burden reduction has also been shown to significantly improve survival outcomes, with patients who responded to frontline therapy demonstrating a median OS of 20.6 months (98).

Studies have emphasized the prognostic significance of histopathological features such as nuclear grade and necrosis in MPM. Lower nuclear grades and the absence of necrosis are linked to significantly better survival, with survival outcomes stratified into distinct prognostic groups based on these factors (99). Other studies point to mitotic count, nuclear atypia, and necrosis as key predictors of survival in epithelioid mesothelioma (100).

Quantitative measures such as tumor volume (TV) and the number of pleural sites (NPS) have also been identified as superior prognostic indicators when compared to traditional TNM staging. Patients with larger tumor volumes (>483 cm^3) and involvement of multiple pleural

sites tend to have significantly worse survival outcomes. Since TV and NPS independently correlate with survival, the study suggests that combining TV and NPS may improve prognostic classification compared to using TNM staging alone (101).

3. METHODS

This thesis employs a retrospective case study approach to analyze the clinical progression of a patient diagnosed with malignant pleural mesothelioma. The primary data source consisted of anonymized clinical records spanning a four-year period. These records included documentation of the patient's diagnostic evaluations, therapeutic interventions, laboratory and imaging findings, and follow-up outcomes. The data were anonymized prior to being shared and complied with applicable data protection standards. I was not involved in the original collection of the data but received the complete dataset for retrospective analysis.
The retrospective case study method was chosen for its relevance to rare diseases like MPM, where prospective data collection is often limited. This approach allows for an in-depth examination of diagnostic and therapeutic processes and patient-specific outcomes, and in doing so, provides insights that may inform clinical practice.
The analysis was conducted in a sequential and systematic manner. First, the clinical data were organized chronologically to establish a clear timeline of events, including diagnostic milestones, therapeutic interventions, and disease progression markers. Each time-stamped entry was carefully reviewed to ensure consistency and accuracy across different sources, such as imaging reports, treatment protocols, and clinical follow-up notes. This chronological organization facilitated the identification of critical turning points in the patient's disease trajectory.
The patient's diagnostic and therapeutic course was then evaluated according to the European Society for Medical Oncology (ESMO) 2021/2022 clinical practice guidelines for malignant pleural mesothelioma. Special emphasis was placed on the staging process, including the use of contrast-enhanced CT and PET-CT imaging, the histopathological confirmation of diagnosis, and the assignment of TNM stage. Treatment decisions — such as the initiation of chemotherapy or immunotherapy — were analyzed with respect to their timing, rationale, and adherence to guideline-based standards of care. Laboratory and imaging findings were integrated into the interpretation of therapeutic response and disease progression.
In addition, the patient's stay in the intensive care unit (ICU) was evaluated in accordance with the 2021 Surviving Sepsis Campaign (SSC) guidelines, focusing on the timeliness and

appropriateness of diagnostic and therapeutic measures for sepsis, hemodynamic stabilization, organ support, and antimicrobial therapy.

Following the structured case evaluation, the patient's course was prepared for comparison with a second case of pleural mesothelioma, with the aim of contextualizing individual findings, identifying similarities and divergences, and reflecting on variability in real-world management.

Throughout the analysis, I cross-referenced the patient's clinical data with evidence-based literature to ensure that interpretations were consistent with current best practices and guidelines. While the single-case nature of the study precluded statistical analysis, qualitative methods were used to identify patterns and trends within the data.

4. DETAILED CASE PRESENTATION

The following detailed case presentation is structured in accordance with the high-level timeline outlined in Annexes 1 and 2.

2020-08-03: Initial Presentation

On August 3, 2020, the patient presented to Vilnius City Clinical Hospital with acute shortness of breath and chest pain. The symptoms were initially attributed to somatoform dysfunction without further diagnostic evaluations. However, persistent exertional dyspnea prompted outpatient cardiology evaluation. Echocardiography revealed fluid in the left pleural cavity, leading to a referral to Vilnius University Hospital Santaros Clinics (VUH SC) Emergency Department (ED) for further diagnostics.

2020-08-21: Admission to Hospital

On August 21, 2020, the patient was admitted to VUHSC with worsening dyspnea and a referral diagnosis of "Pleural effusion, not elsewhere classified". Physical examination revealed absent breath sounds in the left lung, oxygen saturation of 96% on room air, and a blood pressure (BP) of 90/50 mmHg. The patient was afebrile, with no peripheral edema. Laboratory results at admission indicated elevated D-dimers (4255 μg/L) and mildly elevated CRP levels (7.44 mg/L). Hematological parameters, including WBC (6.00 × 10^9/L), hemoglobin (151 g/L), and platelets (296 × 10^9/L), were within normal ranges. Coagulation studies (activated partial thromboplastin time (APTT): 38.0 s, International Normalized Ratio (INR): 1.08) and renal function (Creatinine: 94 μmol/L, Estimated glomerular filtration rate (eGFR): 73 mL/min/1.73 m^2) were unremarkable. Imaging studies were initiated to investigate the underlying cause of the patient's symptoms.

A lung ultrasound confirmed a large fluid collection in the left pleural cavity with compression atelectasis of the lower lobe, while no abnormalities were detected in the right pleural cavity.

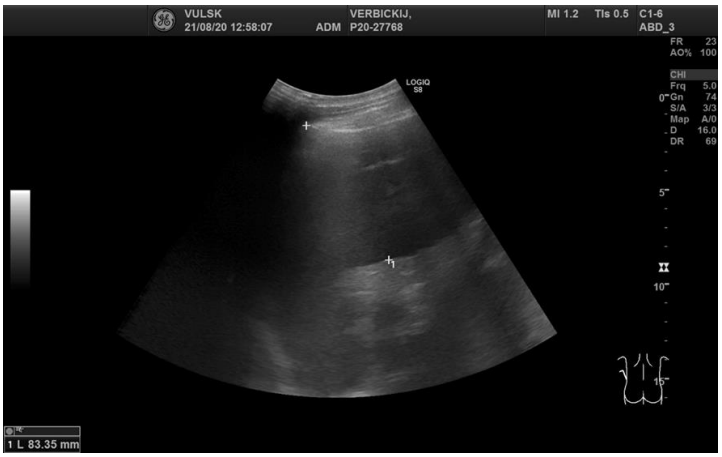


Fig. 1. Lung US: large amount of fluid in left pleural cavity

A chest X-ray on the same day demonstrated a pleural effusion in the left thoracic cavity, with a fluid level at the IV rib and compression of the left lung. Slight mediastinal displacement to the right was observed.

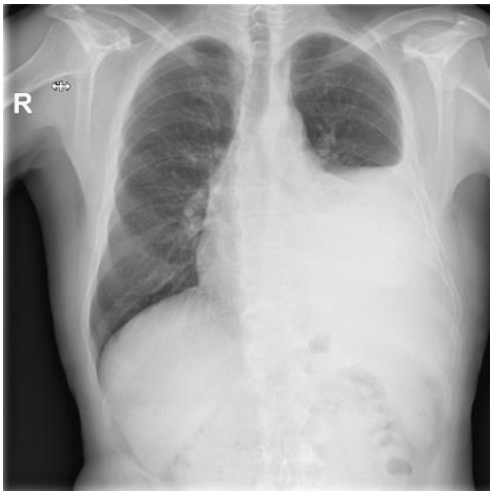


Fig. 2. Posteroanterior chest X-ray: pleural effusion in left thoracic cavity

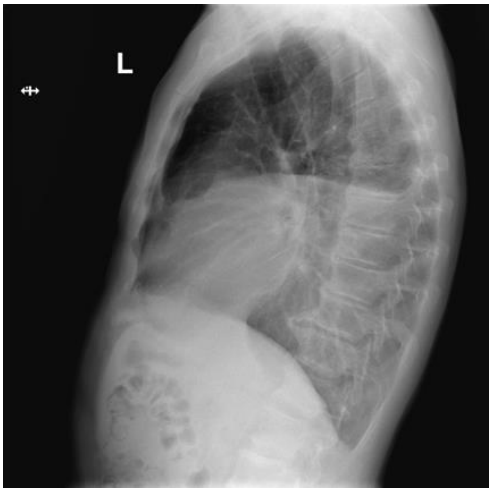


Fig. 3. Lateral chest X-ray: pleural effusion in left thoracic cavity

2020-08-21: Chest CT Angiography

On August 21, 2020, a chest CT angiography was performed to further evaluate the patient's dyspnea and suspected thromboembolic disease. The imaging confirmed pulmonary

embolism (PE), with thrombi located in the right pulmonary artery bifurcation and extending into the lobar arteries. Additional findings included a left-sided pneumothorax, a significant pleural effusion in the left thoracic cavity, and basal segment atelectasis in the left lung. The diaphragm appeared normal, with no evidence of lymphadenopathy.
These findings established the diagnosis of PE, accompanied by hydropneumothorax and secondary atelectasis, and guided the decision to initiate anticoagulation therapy.

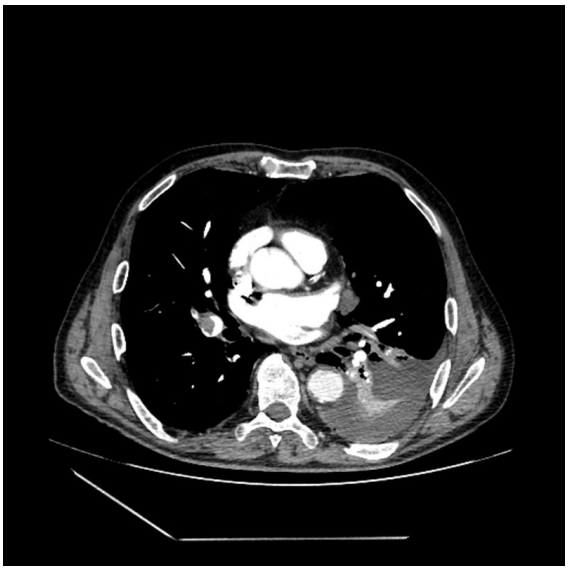


Fig. 4. Chest CT angiography: pulmonary embolism, left-sided pleural effusion and left-sided atelectasis

Further investigations were conducted to rule out potential sources of emboli and evaluate cardiac function. On August 27, a cardiac ultrasound revealed no dilation of the right heart chambers and normal tricuspid valve function. BNP levels (43.4 ng/L) excluded acute cardiac stress or failure.
A lower limb venous ultrasound on August 31 showed no evidence of thrombi in the deep veins, excluding deep vein thrombosis (DVT) as the source of the emboli. Chronic venous insufficiency and a post-phlebectomy state were noted but were deemed clinically insignificant in this context.

2020-08-25: Pleural Drainage Procedure

On August 25, 2020, the patient underwent pleural drainage to address persistent effusion in the left pleural cavity. The procedure was performed under local anesthesia, with 40 mL of 1% Lidocaine administered under sterile conditions. A 24Fr chest drain was inserted through a 2 cm incision in the VI intercostal space, and approximately 800 mL of serous fluid was aspirated.

Cytological examination of the drained fluid revealed reactive mesothelial changes, with no evidence of malignancy or atypical cells. The leukocyte differential showed a predominance of lymphocytes (72%), with smaller proportions of eosinophils (13%) and neutrophils (12%). Histological analysis confirmed the benign nature of the findings, with negative staining for Ber-EP4 and positive desmin expression in 90% of mesothelial cells. Additionally, Thyroid transcription factor-1 (TTF1) negativity was noted.

Subsequent imaging and follow-up assessments documented the patient's recovery. A chest X-ray performed on August 26 confirmed a post-drainage state, with decreased aeration in the left basal lung and traces of fluid above the diaphragm.

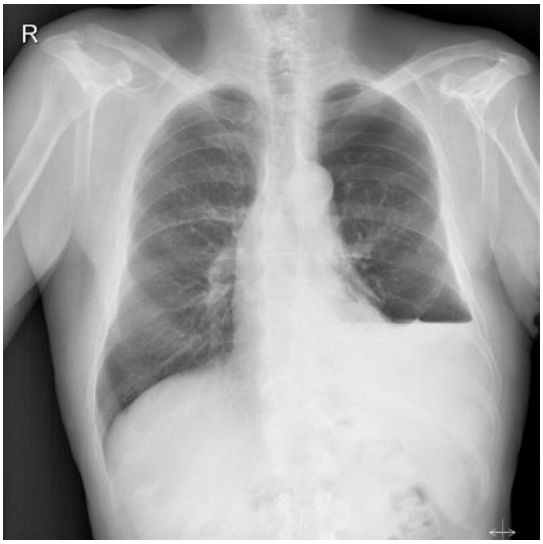


Fig. 5. Posteroanterior chest X-ray: post-drainage state with decreased pleural effusion on left thoracic cavity

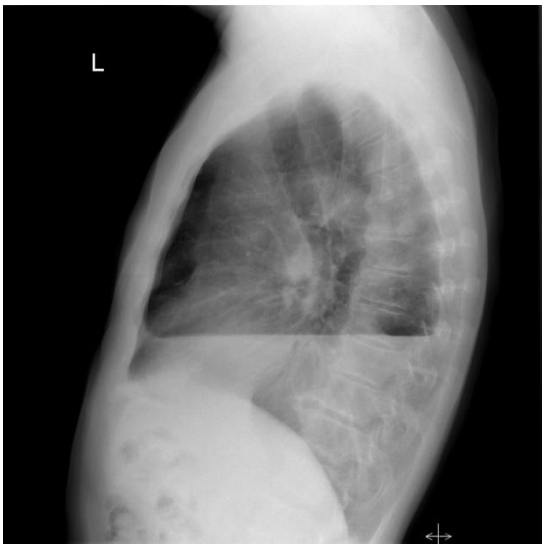


Fig. 6. Lateral chest X-ray: post-drainage state with decreased pleural effusion on left thoracic cavity

On September 9, a lung and pleural ultrasound showed a small encapsulated fluid accumulation with fibrin septa persisting in the left pleural cavity, while no fluid was detected in the right cavity. The pleural drain was removed on the same day without complications. These findings indicated resolution of the acute hydropneumothorax, with minimal residual fluid requiring further follow-up. A chest X-ray on September 10 revealed no air or free fluid in the pleural cavities, no focal or infiltrative changes, although possible adhesions with residual fluid were observed in the left cavity.

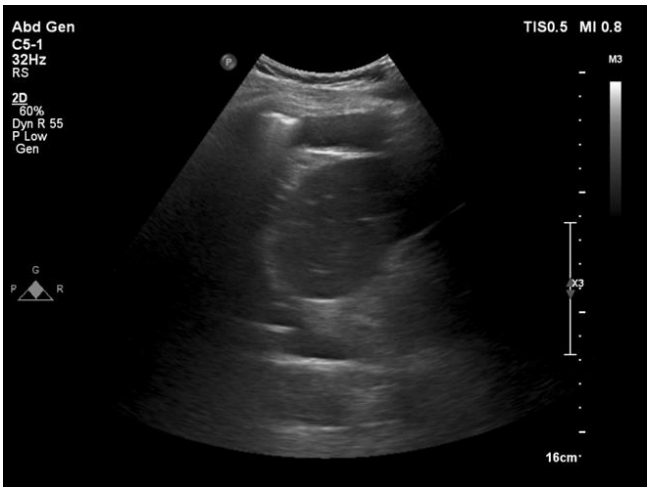


Fig. 7. Lung US: small encapsulated fluid accumulation in left pleural cavity

2020-09-11: Discharge

By September 11, 2020, the patient demonstrated significant clinical improvement following hospitalization and pleural drainage. At the time of discharge, the patient's clinical status was stable, with an oxygen saturation of 98% on room air and a respiratory rate of 14 breaths per minute. BP was measured at 120/80 mmHg, and the heart rate (HR) was 88 bpm with a regular rhythm. Auscultation revealed vesicular breath sounds bilaterally, without any crackles. The patient reported no dyspnea, and no peripheral edema was observed.
Discharge recommendations included continuation of anticoagulation therapy with Rivaroxaban at a dose of 20 mg once daily. Instructions for wound care following the pleural drain removal were provided, with sutures to be removed within 7 to 10 days. Preventive measures included annual influenza vaccination and strategies to avoid respiratory infections. Follow-up plans involved a pulmonology consultation and a scheduled control chest CT on December 30, 2020, to monitor the resolution of the pleural effusion and the patient's overall pulmonary status.

2020-10-08: Chest CT Angiography

On October 8, 2020, a chest CT angiography was performed to investigate persistently elevated D-dimer levels and evaluate the resolution of the previously diagnosed PE. The imaging confirmed the absence of thrombi in the pulmonary trunk, lobar, or segmental arteries, and the RV/LV ratio had decreased.
However, the scan revealed the presence of a pathological mass in the left pleural cavity, which had grown significantly compared to prior imaging studies. According to the available sources, this finding had not been documented in earlier reports and is only known from retrospective medical history. The presence of this pleural mass raised the suspicion of a

malignant or infiltrative process and prompted further diagnostic evaluations. It was decided to evaluate the dynamics of the changes, to repeat the CT on December.

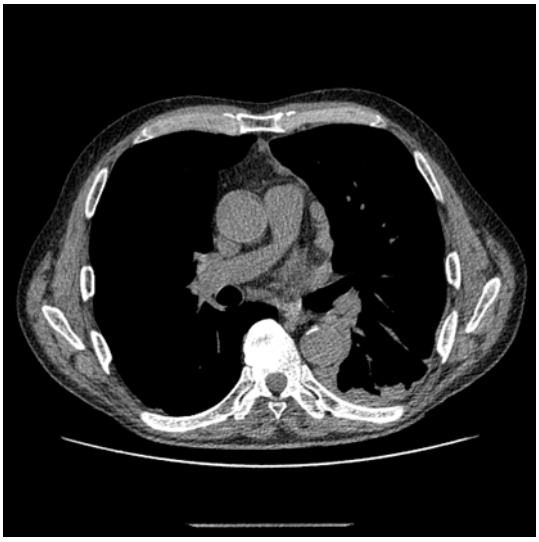


Fig. 8. Chest CT angiography: suspicion of masses in left pleura

2020-12-30 Chest CTA

Chest CTA revealed multiple contrasted masses on the left pleura differentiated between mesothelioma and infiltration of other cause. Biopsy of the pleura is planned.

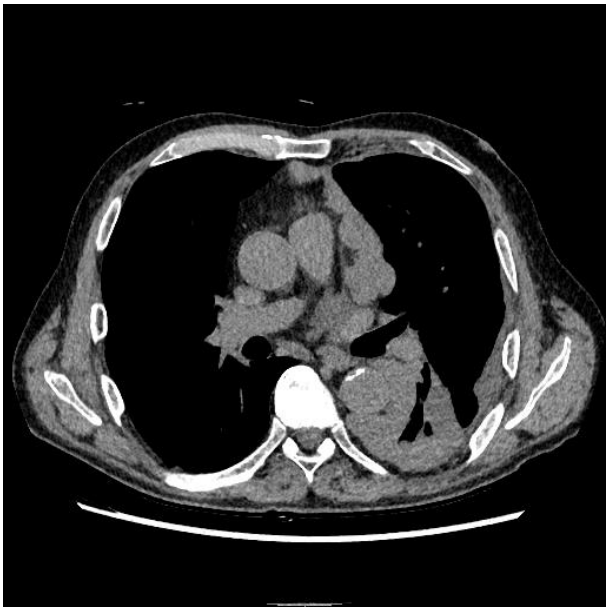


Fig. 9. Chest CT angiography: multiple contrasted masses on the left pleura

2021-01-13: VATS Pleural Biopsy

On January 13, 2021, the patient underwent a planned VATS pleural biopsy (Video-Assisted Thoracoscopic Surgery) to investigate the pathological masses in the left pleural cavity. The procedure was performed without complications, and postoperative recovery was uneventful. A chest X-ray performed after the biopsy revealed uneven and thickened left pleura, accompanied by mediastinal displacement and deformation. Additionally, non-aerated zones were observed in the lower left lung, findings consistent with compressive hypoventilation or infiltrates. No free air or fluid was detected in the pleural cavities.

Postoperative care included the administration of Cefuroxime 1.5 g twice daily, Fraxiparine 0.3 ml subcutaneously, and Ketanov 30 mg as needed. The surgical wounds were described as calm and healing primarily, with no signs of infection or delayed recovery. The patient's clinical status at discharge was satisfactory with stable hemodynamics.

The patient was instructed to follow up with the treating physician to obtain the histology results and remove the sutures on January 20, 2021. Recommendations included analgesic use as needed, continuation of Rivaroxaban 20 mg once daily, and initiation of Ciprofloxacin 500 mg twice daily for five days, along with Ambroxol 30 mg three times daily.

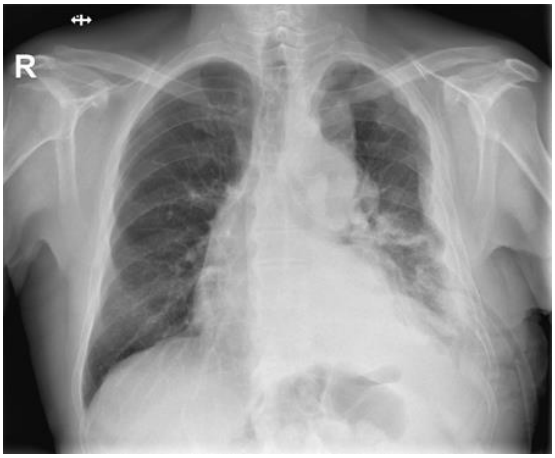


Fig. 10. Posteroanterior chest X-ray: left pleural thickening, mediastinal shift, and left lower lobe hypoventilation

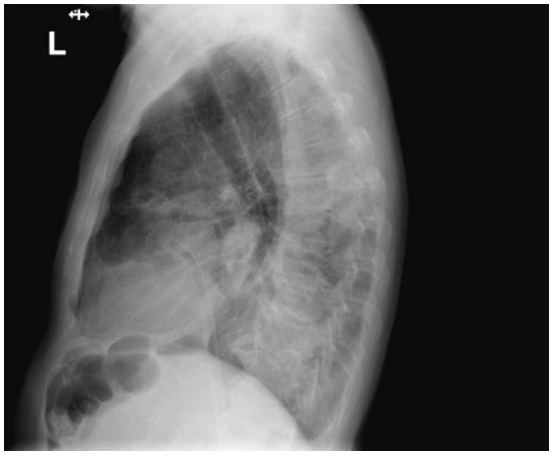


Fig. 11. Lateral chest X-ray: left pleural thickening, mediastinal shift, and left lower lobe hypoventilation

2021-01-19: Histological Diagnosis and Tumor Board

On January 19, 2021, the histological examination of tissue obtained during the VATS pleural biopsy confirmed the diagnosis of epithelioid mesothelioma of the pleura. The pathological findings revealed pleural spread of the tumor, with immunohistochemical analysis showing positivity for calretinin, BAP1, Cytokeratin 7 (CK7), WT1, and partial positivity for D2-40,

while TTF1 was negative. Macroscopically, the tumor tissue was described as brown, fragile, and fragmented, reconstructed to a size of 2.2 × 1.8 × 0.6 cm, with an additional pleural fragment measuring 1.7 × 0.5 × 0.2 cm.

At the outpatient visit, the patient reported symptoms of shortness of breath during intense physical activity, mild chest pain, loss of appetite, and cough. Functional status was assessed as ECOG 1, indicating slight restrictions in strenuous activities but full ambulatory capacity. The patient's case was scheduled for discussion at a multidisciplinary tumor board on January 20, 2021, to establish the most appropriate treatment strategy. Systemic anticancer treatment with Cisplatin and Pemetrexed was recommended.

2021-02-05: First Chemotherapy Session

On February 5, 2021, the patient initiated systemic anticancer therapy with Cisplatin and Pemetrexed at the Pulmonary and Pleural Tumors Chemotherapy Day Unit. Premedication was administered prior to the session, and the chemotherapy course was completed without complications.

The patient's functional status was assessed as ECOG 1. Physical measurements included a height of 167 cm, weight of 59 kg, and a Body Surface Area (BSA) 1.65 m². Physical examination revealed a respiratory rate of 15 breaths per minute, vesicular breath sounds slightly diminished in the lower part of the left lung, and no cyanosis or use of accessory muscles in breathing. The patient's heart rhythm was regular, with a pulse rate of 100 bpm and BP of 124/83 mmHg. No abnormalities were noted in the abdomen or peripheral edema, and the patient was afebrile, with a recorded temperature of 36.1°C.

The chemotherapy regimen consisted of Cisplatin 123 mg (75 mg/m²) and Pemetrexed 825 mg (500 mg/m²), both administered intravenously every three weeks. Post-chemotherapy care included a premedication protocol comprising Folic Acid 1000 mg daily, Vitamin B12 500 IU intramuscularly every three weeks, and Dexamethasone 4 mg on the day of chemotherapy, as well as one day before and one day after. For nausea management, the patient was prescribed Ondansetron 8 mg twice daily as needed, and for fever exceeding 38°C, Amoxicillin-Clavulanate 875/125 mg three times daily was recommended.

The patient was advised to continue treatment for chronic conditions under the supervision of their family physician. The next chemotherapy session was scheduled for February 26, 2021.

2021-02/06 Treatment continuation and Follow-up Chest CT

Chemotherapic treatment was given every 3 weeks with good tolerance and every 2 courses of treatment chest CT was done to evaluate if the disease is not progressing. CT showed stable disease.

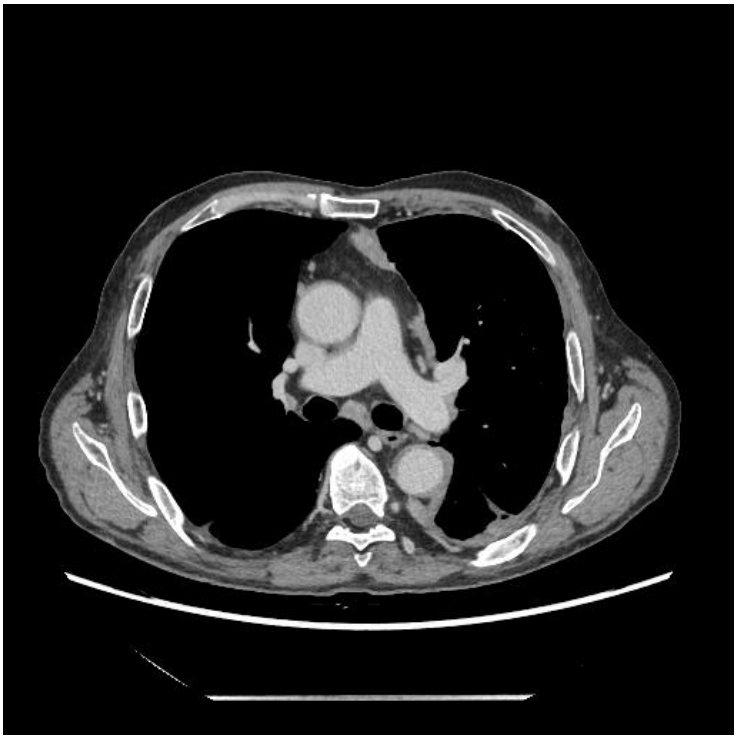


Fig. 12. Chest CT: stable disease without progression

2021-09-02: Follow-Up Chest CT

On September 2, 2021, a follow-up chest CT scan was performed to evaluate the patient's disease status after completing six cycles of Cisplatin and Pemetrexed chemotherapy on May 31, 2021.

The patient’s functional status was assessed as ECOG 1. Physical measurements included a height of 167 cm, weight of 63 kg, and a BMI of 21.5 kg/m². The respiratory rate was 15 breaths per minute, with an SpO_2 of 98% on room air. Lung auscultation revealed vesicular breath sounds, slightly diminished in the lower left lobe, with crepitations heard in the same region. There was no use of accessory muscles for breathing, no cyanosis, and no peripheral edema. The patient was afebrile.

The imaging results indicated a mixed response to the treatment. The paramediastinal masses showed a reduction, with the largest lesion decreasing from 11 mm to 9 mm, and an anterior mediastinal nodule associated with the pericardium reduced from 25 mm to 11 mm. Conversely, there was an increase in interlobar pleural nodules, which grew from 7 mm to 15 mm, and paracostal nodules increased from 3 mm to 6 mm. Additionally, a new subsolid nodule measuring 13 mm appeared in the right lung's S2 segment. The left lung exhibited compression with reduced aeration in the lower lobe. Subcarinal lymph nodes measured up to

10 mm, paratracheal nodes were not enlarged (~9 mm) and axillary nodes remained structured, larger ones contain fatty cores.

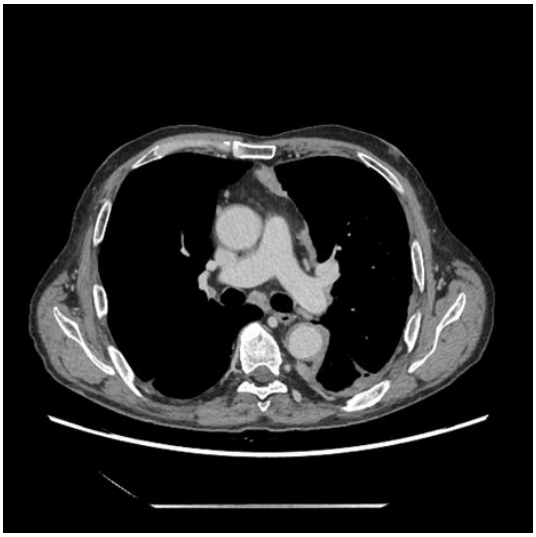


Fig. 13. Chest CT: after 4 cycles of Cis/Pem – stable disease

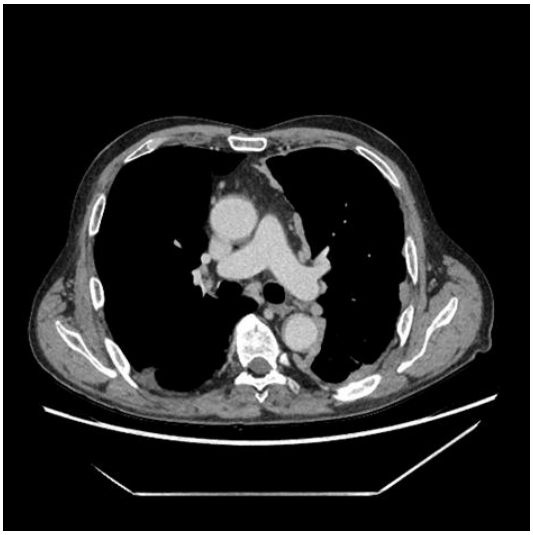


Fig. 14. Chest CT: follow-up CT after completed chemotherapy - mixed response - mediastinal lesions regressed, pleural nodules progressed, new subsolid nodule in S2; left lower lobe compressed, lymph nodes stable

2021-09-06: Multidisciplinary Team Conclusions

On September 6, 2021, the multidisciplinary tumor board reviewed the patient's case, taking into account the recent CT findings. The team concluded that the disease was progressing, despite reductions in certain masses. Given the lack of more effective treatment options and the limited efficacy of Gemcitabine in advanced epithelioid pleural mesothelioma, they recommended initiating Gemcitabine monotherapy. The patient was informed about the limited clinical evidence supporting this treatment but agreed to proceed.

2021-09-21: First Gemcitabine Chemotherapy Cycle

On September 21, 2021, the patient began Gemcitabine monotherapy at the Pulmonary and Pleural Tumors Chemotherapy Day Unit.

The patient’s clinical assessment revealed a functional status of ECOG 1. The patient’s physical measurements included a height of 167 cm, weight of 63 kg, and a BSA of 1.7 m^2. Vesicular breath sounds were slightly diminished in the lower left lung, a respiratory rate of 15 breaths per minute, and no signs of cyanosis or peripheral edema. HR was 86 bpm, and BP was 127/79 mmHg. The patient was afebrile, with a temperature of 36.1°C.

The chemotherapy regimen included Gemcitabine 2125 mg (1250 mg/m²), administered intravenously on days 1, 8, and 15 of a 4-week cycle. Premedication was provided with Dexamethasone 16 mg intravenously and Ondansetron 8 mg orally on the day of treatment. The first dose was administered without complications.

Recommendations included maintaining a protective regimen to avoid strenuous physical activity, viral infections, and direct sunlight exposure. The patient was also advised to monitor for chemotherapy-related side effects, including nausea, managed with Ondansetron 8 mg as needed, and fever exceeding 38°C, treated with Amoxicillin-Clavulanate 875/125 mg three times daily. The second dose of chemotherapy was scheduled for September 28, 2021, with regular monitoring and palliative care management under the supervision of the family physician.

2021-11-19: Chest CT

On November 19, 2021, the patient underwent a contrast-enhanced chest CT scan to evaluate the response to two cycles of Gemcitabine monotherapy.

The patient's clinical condition was assessed as ECOG 1. The patient's physical measurements included a height of 167 cm, weight of 63 kg, and a BSA of 1.7 m². Physical examination revealed a respiratory rate of 15 breaths per minute, slightly diminished vesicular breath sounds in the lower left lung, and no signs of cyanosis or peripheral edema. The HR was 76 bpm, BP measured 128/72 mmHg, and the patient was afebrile with a temperature of 35.8°C.

Compared to the previous scan on September 2, 2021, the imaging revealed significant progression of the disease. The paramediastinal masses in the left pleura had increased in size to 20 mm from 10 mm, and masses in the interlobar fissure of the left lung had grown to 15 mm from 10 mm. Additional growth was observed in lesions above the left diaphragm and in the left cardio-diaphragmatic angle. The previously identified subsolid lesion in the right lung's S2 segment was no longer visible. No new lesions were detected, and mediastinal lymph nodes remained stable.

The findings confirmed radiological progression, with an increase in the size of pleural masses and growth in pre-existing lesions. As no standardized treatment options are available for mesothelioma after repeated progression, Docetaxel therapy was identified as the next course of action. The patient was informed of this recommendation and instructed to maintain a protective regimen, avoiding strenuous physical activity, fatigue, colds, viral infections, and direct sunlight exposure.

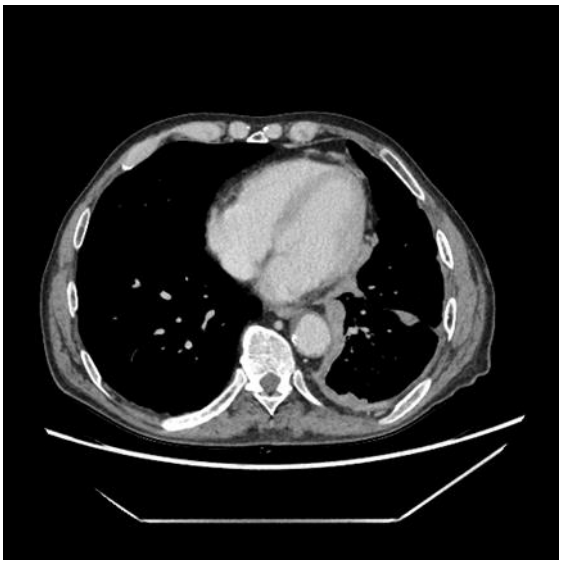


Fig. 15. Contrast-enhanced chest CT: scan from September 2 (2021), after 6 cycles of Cis/Pem

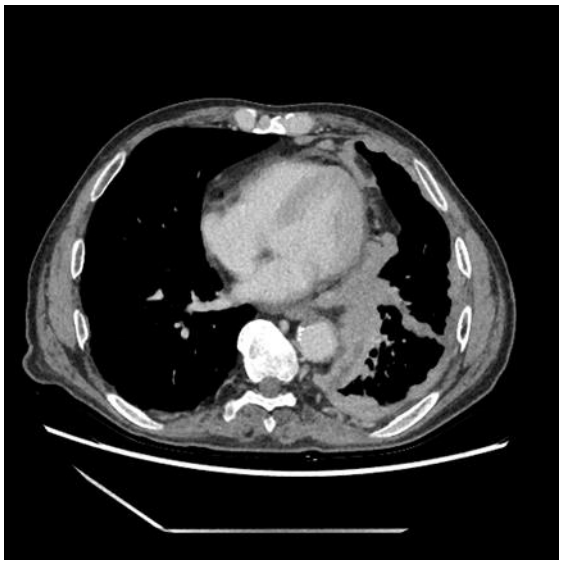


Fig. 16. Contrast-enhanced chest CT: scan from November 19 (2021), after 2 cycles of Gemcytabine – disease progression with enlargement of pleural masses, growth of pre-existing lesions, regression of S2 nodule, no new lesions, stable lymph nodes

2021-12-03: First Docetaxel Cycle

On December 3, 2021, the patient was scheduled to begin Docetaxel chemotherapy at the Pulmonary and Pleural Tumors Chemotherapy Day Unit.

The patient's functional status was assessed as ECOG 1. Physical measurements showed a height of 167 cm, weight of 63 kg, and a BSA of 1.7 m². The respiratory rate was 15 breaths per minute, with vesicular breath sounds slightly diminished in the lower left lobe, and no signs of cyanosis or accessory muscle use. The heart rhythm was regular, with a pulse of 82 bpm and a BP of 121/88 mmHg. No peripheral edema was noted. The patient was afebrile, with a body temperature of 36.2°C.

According to the available documentation, premedication was prescribed, including Dexamethasone 16 mg daily and Ondansetron 8 mg, and the planned chemotherapy dose was 128 mg of Docetaxel, to be administered intravenously in 500 ml of 0.9% NaCl solution.

Due to the absence of the specific medical record for this date, the details of the first Docetaxel administration are not available. However, subsequent visits confirm that the therapy was successfully initiated and continued without reported complications in the following cycles.

2022-01-19: Chest CT

Chest CT after 2. course of Docetaxel was done. It revealed positive dynamics, a significant decrease of left pleura masses and lesions.

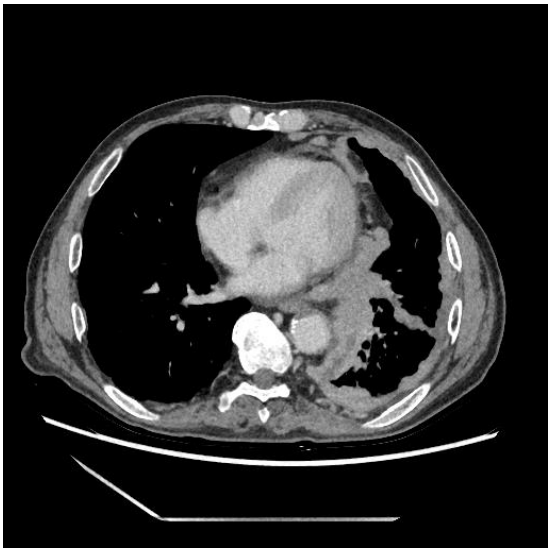


Fig. 17. Chest CT: scan from November 19 (2021), before the start of Docetaxel

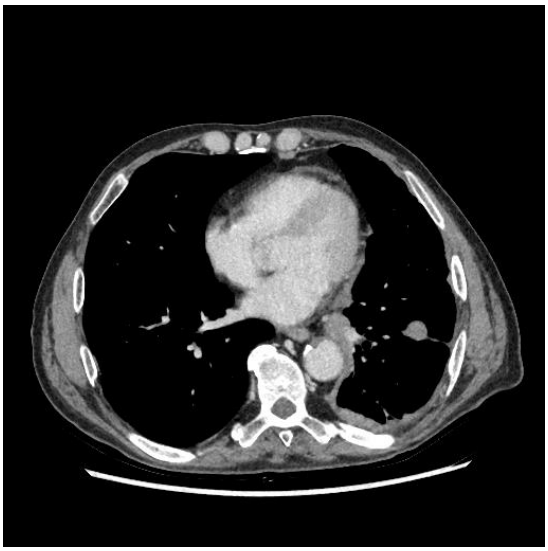


Fig. 18. Chest CT: Scan from January 19 (2022), after 2 courses of Docetaxel, decrease of left pleura masses and lesions

2022-03-16: Chest CT and Transition to Nivolumab Therapy

On March 16, 2022, the patient underwent a contrast-enhanced chest CT scan to assess the response to Docetaxel therapy.

The patient's clinical condition was assessed as ECOG 1. Physical measurements included a height of 167 cm, weight of 65.5 kg, and a BSA of 1.7 m². The respiratory rate was 15 breaths per minute, with vesicular breath sounds slightly diminished in the lower left lobe, and no signs of cyanosis or accessory muscle use. The heart rhythm was regular, with a pulse of 91 bpm and a BP of 132/83 mmHg. No peripheral edema was noted. The patient was afebrile, with a body temperature of 36.2°C. Blood tests from March 7, 2022, revealed no clinically significant abnormalities.

Compared to the primary CT from November 19, 2021, and the nadir CT from January 19, 2022, the imaging revealed a 21% increase in the size of target lesions, confirming disease progression. The left pleural masses paravertebrally, spreading to the diaphragmatic surface, measured 76 mm, up from 68 mm at the nadir, but down from 86 mm at the initial measurement. Interlobar thickening in the left lobe increased to 32 mm, compared to 23 mm at the nadir and 24 mm initially. Aortopulmonary window lymph nodes enlarged to 35 mm, up

from 27 mm at the nadir and 28 mm initially. The total dimensions of the target lesions reached 143 mm, up from 118 mm at the nadir and 138 mm initially.
Non-target lesions showed an increase in tumor masses in the left pleura, with signs of basal liquefaction. Ground-glass opacity in the right lung was reduced, and no fluid was detected in the pleural cavities. A low-density lesion in liver segment 7 remained unchanged at approximately 9 mm, and no evidence of bone destruction was observed.

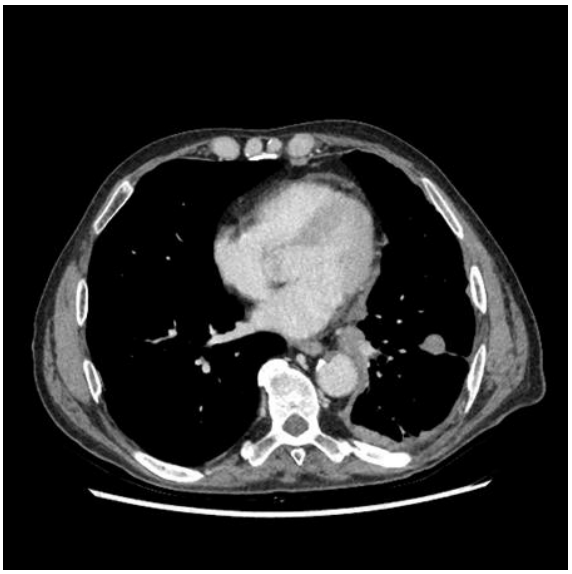


Fig. 19. Chest CT: scan from January 19 (2022), after 2 courses of Docetaxel

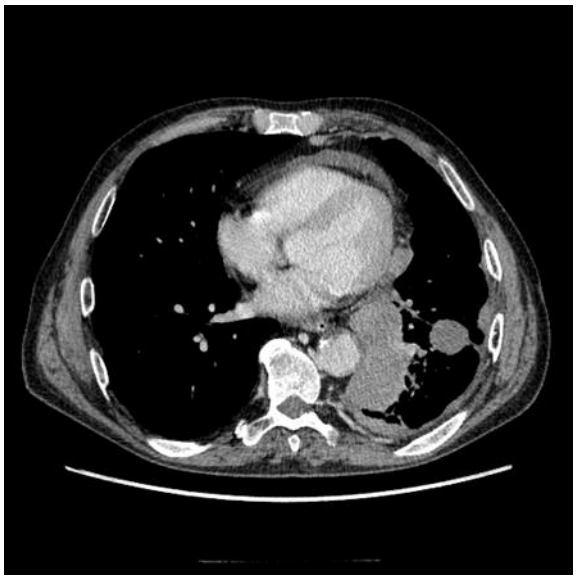


Fig. 20. Contrast enhanced-Chest CT: scan from March 16 (2022), disease progression with 21 % increase in target lesions, pleural and node growth, basal liquefaction left

Based on these findings, Docetaxel therapy was discontinued. During a multidisciplinary team discussion, it was decided to initiate Nivolumab therapy. The plan involved administering 240 mg of Nivolumab intravenously every two weeks, with an evaluation of treatment effectiveness after two months (four cycles). The patient was informed about the treatment plan, potential side effects of immunotherapy, and agreed to proceed. The first dose of Nivolumab was administered without complications.
The patient was advised to maintain a gentle regimen, avoiding heavy physical exertion, fatigue, colds, viral infections, and direct sunlight exposure. For nausea, the patient was prescribed Ondansetron 8 mg, to be taken up to four tablets per day as needed. In case of fever exceeding 38°C, the patient was instructed to take Amoxicillin with Clavulanic Acid 875/125 mg three times daily and to consult their physician.

Follow-up care was planned under the supervision of the family physician, focusing on palliative care and the management of comorbid conditions. The patient was scheduled to return for continued treatment on April 1, 2022.

2022-03/2023-01 Treatment continuation and Follow-up Chest CT

Immunotherapy was given every 2 weeks without any significant adverse effects and every 2 months chest CT was done to evaluate if the disease is not progressing. CT showed partial response of the disease.

2023-01-24: Nivolumab Treatment Ongoing

On January 24, 2023, the patient received the 21st cycle of Nivolumab therapy at the Pulmonary and Pleural Tumors Chemotherapy Day Unit. This treatment reached at this point a total of 20 completed cycles. Imaging had shown a partial response, and no significant adverse effects typical of immunotherapy had been reported to date.

The patient's functional status had been assessed as ECOG 1. Physical measurements had included a height of 167 cm, a weight of 65 kg, and a regular heart rhythm with a pulse rate of 63 bpm. BP had been measured at 129/74 mmHg, and the patient had been afebrile, with a body temperature of 36.1°C. Blood tests performed on January 19, 2023, had shown no clinically significant abnormalities apart from elevated TSH, which had been managed by an endocrinologist.

A contrast-enhanced chest CT scan performed on the same day had revealed that the target lesions remained stable, with no change in size compared to the nadir CT from September 22, 2022. The left pleural masses paravertebrally measured 39 mm, and interlobar thickening on the left at the eighth rib level remained at 12 mm, resulting in a total target lesion dimension of 51 mm, unchanged since the nadir. Non-target lesions had shown significant reductions in the size of tumor masses in the left pleura, while persistent centrilobular emphysema, subsegmental atelectasis, and minimal fluid in the left pleural cavity (slightly increased compared to the previous CT) had been observed. Additionally, trace fluid in the right pleural cavity had been detected. A stable subpleural nodule in the left KS4 region (14x7 mm) and several small nodules in KS9 and KS10 (up to 4 mm) had also been noted. Findings had included "tree-in-bud" nodules in the right lung's KS6 region, likely indicative of infectious bronchiolitis, which supports the conclusion that the non-target lesions were associated with a previous infection. The CT findings had been interpreted as stable disease with no evidence of progression.

The 21st cycle of Nivolumab (240 mg) was administered intravenously without complications. The patient was advised to maintain a gentle regimen, avoiding heavy physical

exertion, fatigue, colds, viral infections, and direct sunlight exposure. For nausea, the patient was prescribed Ondansetron 8 mg, to be taken up to four times per day, and for fever exceeding 38°C, they were instructed to take Amoxicillin and Clavulanic Acid 875/125 mg three times daily. Additionally, for elevated liver enzymes, the patient was advised to take Livosil 140 mg, three times daily.

Follow-up care included supervision by the family physician for palliative care and the management of comorbidities, as well as ongoing endocrinological monitoring for elevated TSH. The next treatment session was scheduled for February 7, 2023.

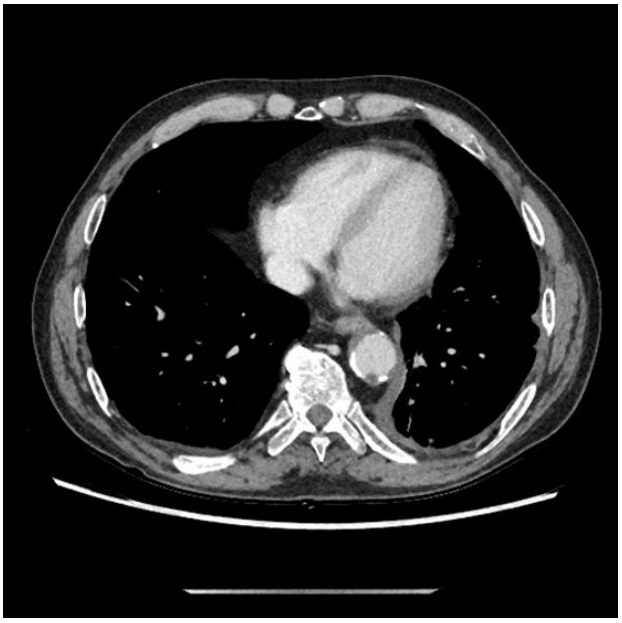


Fig. 21. Contrast-enhanced chest CT: Stable disease without progression of target lesions

2023-02-07 Patient doesn’t come for treatment, because of bad condition.

2023-03-18: ICU Admission

On March 18, 2023, the patient was admitted to the ICU with a primary diagnosis of advanced epithelioid pleural mesothelioma and secondary diagnoses including acute respiratory failure, sepsis, bilateral pneumonia, delirium, and urinary tract infection (UTI). The patient also had a history of gout, hypothyroidism, and metabolic encephalopathy.

In the weeks prior to admission, the patient’s general health had significantly declined. This was reflected by the missed scheduled treatment visit on February 28, 2023, attributed to severe weakness and poor overall condition.

The patient presented to the emergency department with complaints of fever and low BP, as well as a history of vomiting black-colored content reported by the spouse. An

esophagogastroduodenoscopy (EGD) performed on March 17, 2023, revealed a hernia, erosive gastropathy, and erythematous duodenopathy. Upon arrival, the patient's vital signs indicated severe hemodynamic instability, with a BP of 63/36 mmHg, a HR of 99 bpm, and elevated inflammatory markers, including a CRP of 210 mg/L and procalcitonin of 7.13 µg/L. Chest X-ray findings showed bilateral nonhomogeneous infiltrates in the peripheral regions and signs of stasis. Laboratory results also showed leukocytosis (WBC 13.70 × 10^9/L), dominated by neutrophils (NEU 72.5%), and mild anemia (HGB 105 g/L).

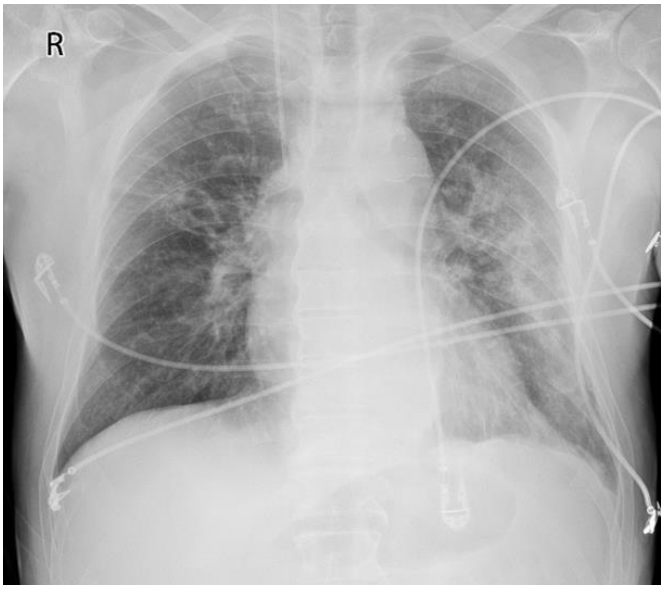


Fig. 22. Posteroanterior chest X-ray: bilateral peripheral nonhomogeneous infiltrates with signs of stasis

Immediate ICU management of the sepsis/ septic shock included antibiotic therapy with Tazocin (4.5 g four times a day for 7 days), oxygen therapy at 5 L/min via nasal cannula and IV fluids. Arterial blood gas analysis revealed mild metabolic acidosis, with a pH of 7.442, a bicarbonate level of 18.9 mmol/L, and a lactate of 0.92 mmol/L. Coagulation studies showed elevated APTT (53.7 s) and fibrinogen levels (5.17 g/L). Urinalysis revealed 300 erythrocytes/µL and 25 leukocytes/µL, which indicates an UTI. During the ICU stay, an epicystostomy was performed, with turbid urine noted in the drainage system (2023-03-18). Over the course of ICU treatment, the patient's condition stabilized. By March 23, 2023, the CRP had decreased to 119.5 mg/L, the procalcitonin dropped to 1.96 µg/L (2023-03-21) and the WBC count decreased to 6.65 × 10^9/L (2023-03-21). Microbiological cultures, including blood and urine, showed no bacterial or fungal growth (2023-03-20). Additionally, the symptoms of delirium resolved by this time.

On March 24, 2023, the patient was transferred to the Intensive Pulmonology Unit for continued management of acute respiratory failure and bilateral pneumonia. At the time of transfer, oxygen therapy was reduced to 2 L/min, maintaining an SpO_2 of 97%. Vital signs included a BP of 86/60 mmHg and a HR of 78 bpm. Auscultation revealed fine wet crackles bilaterally, and functional status was assessed as ECOG 3. Peripheral edema absent. The patient's condition was considered moderate in severity, with a functional suprapubic catheter draining clear urine.

As part of the broader treatment regimen during the ICU stay, the patient received prophylaxis for deep vein thrombosis and stress ulcers, L-thyroxine, enteral feeding, and antipsychotic medication.

2023-04-19: Neurologist Consultation and Lumbar Puncture

On April 19, 2023, the patient was evaluated by a neurologist due to worsening lethargy and drowsiness, with CRP levels remaining elevated at approximately 100 mg/L. This represented a notable deterioration compared to previous assessments. On April 6, 2023, the patient had been partially disoriented and lethargic but still able to engage in partial contact, demonstrating awareness of the year, month, and general location context despite mumbled speech and motor deficits to varying degrees with reduced reflexes. Also on April 6, 2023, a brain CT showed no evidence of acute focal lesions, pathological density changes, metastasis, edema, or hemorrhage. Mixed-origin delirium was suspected, and a lumbar puncture (LP) was deferred due to decreasing inflammatory markers, absence of fever, headache, or photophobia. On April 17, 2023, further evaluation noted persistent delirium symptoms despite psychiatric treatment, with recurrent fever episodes (with a diagnosis of UTI) and disorientation. No new focal symptoms were observed. Despite antibiotic therapy and replacement of the epicystostomy, the inflammatory markers had improved only partially, leading to a recommendation for a lumbar puncture to exclude secondary neuroinfection or other causes.

By April 19, the patient's condition had further declined. They were described as more lethargic and dowsy, responding only to voice and simple commands. Given the absence of contraindications, including normal platelet levels and an APTT of 43 seconds, a lumbar puncture (LP) was performed.

Cerebrospinal fluid analysis revealed a cell count of 13 cells/μL (100 % mononuclear cells), a protein concentration of 0.72 g/L, and a glucose level of 1.9 mmol/L, consistent with reactive changes due to systemic inflammation. No sufficient evidence of neuroinfection or carcinomatosis was found.

Further recommendations included extending CSF biochemistry to include albumin, IgM, and IgG, with viral panel testing suggested if IgM levels were significantly elevated. Manual review of CSF cells was advised to identify atypical features. To exclude deep brain venous thrombosis or sinus thrombosis, a head CT angiography with venography or an MRI was recommended, and it was suggested to correlate CSF glucose levels with serum glucose to enhance diagnostic accuracy.

2023-04-19: Head CT and CT Angiography

On April 19, 2023, a head CT and CT angiography were performed to further investigate the patient's neurological symptoms. The imaging was conducted with both native and IV contrast in angiographic mode.

The results showed no acute focal density changes or hemorrhagic signs. The midline structures were not displaced, and the ventricular system appeared of medium width with well-differentiated subarachnoid spaces. Angiographic findings indicated that the major intracranial arteries were patent, with no evidence of hemodynamically significant stenoses in the extracranial arteries. However, the right internal carotid artery (C1 segment) was narrowed by approximately 40% over a 14 mm length due to mixed atherosclerotic plaques. The venous sinuses showed adequate filling.

The conclusion noted that there were no acute brain changes, hemorrhages, or perfusion defects, but the 40% stenosis of the right internal carotid artery was identified as a significant finding.

2023-04-24: Hospital Discharge

On April 24, 2023, the patient was discharged after an extended hospitalization for the management of sepsis, septic shock, bilateral pneumonia, UTI and delirium. Despite recurring episodes of fever and persistently elevated inflammatory markers, the source of infection could not be identified, even after extensive diagnostic efforts, including a chest X-ray, abdominal ultrasound, LP, and brain CT.

At discharge, the patient’s condition was described as moderate to severe, with encephalopathy, characterized by drowsiness and partial responsiveness to commands. Vital signs included a HR of 80 bpm, BP of 119/70 mmHg, respiratory rate of 14 breaths per minute, and an oxygen saturation of 96% on room air. Respiratory examination revealed bilateral vesicular breath sounds with occasional fine crackles. The epicystostomy was functional, draining clear yellow urine without signs of infection, and there was no evidence of peripheral edema.

Given the patient's poor overall health and an ECOG score of 4, further cancer-specific treatment was deemed contraindicated. The patient's condition was attributed to systemic exhaustion and the progression of the oncological disease. The focus shifted to palliative care and symptom management, with the patient's family informed of the poor prognosis. They agreed with the care plan, which prioritized comfort and Qol.

The patient was discharged with a care plan that included continued L-thyroxine therapy, alternating doses of 75 mg and 50 mg daily, and Fraxiparine 0.3 ml subcutaneously for deep vein thrombosis prophylaxis. Allopurinol 150 mg was prescribed for nighttime use, with NSAIDs to be used as needed for joint pain or gout flare-ups. Regular care of the epicystostomy, last replaced on April 13, 2023, was emphasized. The care plan also encouraged patient mobilization and activation, while psychiatric recommendations were to be followed if delirium symptoms recurred.

The patient was transferred to a palliative care facility in stable condition.

5. CASE EVALUATION

5.1 Evaluation of the case according to the ESMO-MPM guidelines

This section assesses the diagnostic and therapeutic approach of the presented case in alignment with the most current (2021/2022) European Guidelines for MPM: "Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" (102). Key aspects include diagnosis, staging accuracy and treatment selection. By comparing clinical decisions to these guidelines, this evaluation highlights areas of adherence, deviations, and potential improvements in patient management.

Although this case originated in 2020, the 2021/2022 ESMO guidelines were used for evaluation, as they reflect the most up-to-date, evidence-based standards for diagnosing and managing MPM. In certain instances, the 2015 ESMO guidelines (103) were also referenced for comparison.

5.1.1 Diagnosis

The patient first presented on August 3, 2020, with acute shortness of breath and chest pain. These symptoms, consistent with MPM as described in the 2022 guidelines, were initially attributed to somatoform dysfunction without further diagnostic evaluation. While this conclusion, in absence of overt signs of cardiorespiratory compromise or specific red flags, was based on clinical reasoning at the time, the lack of follow-up investigations delayed the identification of pleural abnormalities. According to the ESMO guidelines, symptoms such as dyspnea and chest pain, combined with findings like pleural effusion, should prompt a

structured diagnostic work-up. The ESMO 2022 guidelines recommend a structured diagnostic work-up when patients present with symptoms such as dyspnea, chest pain, and weight loss, which can develop gradually over several months. The guidelines note that "unilateral effusions are typical" on physical examination, which reinforces the need for further evaluation upon suspicion.

When MPM is suspected due to radiological findings or a history of significant asbestos exposure, pleural fluid cytology may be performed to detect malignant cells. However, since the guidelines acknowledge that cytology "may yield false negatives", immunohistochemical confirmation is necessary to establish the diagnosis.

The key issue here is that, based on the available data, no occupational history was documented. This represents a missed opportunity to identify the most prominent risk factor for PM: Asbestos exposure, which would have definitely raised clinical suspicion. Recognition of this risk factor could have prompted a more targeted diagnostic approach, as previously discussed. This shows the importance of thorough anamnesis the diagnostic process.

On August 21, 2020, the patient was admitted to the hospital due to his worsening respiratory condition. Here, the diagnostic approach appropriately focused on the patient's worsening dyspnea and the identification of a significant pleural effusion. Initial imaging, including a chest X-ray and lung ultrasound, confirmed the effusion and compression atelectasis of the left lower lobe. These steps align with the ESMO 2022 guidelines, which recommend chest X-ray, alongside with occupational history and general blood tests, as a first-line tool for identifying pleural abnormalities. Although chest X-ray can be used as an initial imaging tool, it is insufficient for diagnosing PM, as it lacks the sensitivity and specificity needed for staging or malignancy detection. The ESMO 2022 guidelines explicitly state that "plain chest radiography lacks sufficient sensitivity and specificity for diagnosis and staging".

The contrast-enhanced CT scan performed on August 21 provided a detailed assessment of pleural abnormalities, aligning with the ESMO 2022 guidelines, which recommend CT imaging as an essential component of the MPM diagnostic work-up. The guidelines specify that "diagnostic procedures should encompass […] contrast-enhanced CT of the thorax and upper abdomen [II, A]". However, the imaging findings did not indicate pleural thickening or pleural plaques, which are key criteria in the guidelines for recommending pathological confirmation. As stated in the guidelines, "in all patients who have a unilateral pleural thickening, with or without fluid and/or pleural plaques, efforts should be made to obtain a

pathological specimen [II, A]". Therefore, the decision not to pursue thoracoscopy or biopsy at this stage was in line with the available evidence.

On August 25, 2020, the patient underwent pleural drainage to relieve symptoms caused by the effusion. Cytological analysis of the aspirated fluid showed reactive mesothelial changes without malignancy, and immunohistochemistry further supported a benign etiology. This approach aligns with the ESMO 2022 guidelines, which state that "cytology can be used to detect malignant cells (but may yield false negatives), and immunohistochemical confirmation should be undertaken". Given the absence of malignancy, further pathological evaluation may still be warranted if unilateral pleural thickening is present, as the guidelines recommend that "in all patients who have a unilateral pleural thickening […] efforts should be made to obtain a pathological specimen [II, A]". When additional tissue sampling is necessary, thoracoscopy is the preferred method ("Thoracoscopy is preferred [III, B]"). At this stage, no overt radiological or clinical indicators of mesothelioma were present, and the diagnostic process remained in line with the guidelines without obtaining a biopsy.

Follow-up imaging confirmed the resolution of the effusion, and the patient was discharged on September 11, 2020, without further advanced diagnostic measures. The clinical trajectory changed on October 8, 2020, when a chest CT angiography performed to investigate persistently elevated D-dimer levels revealed a pathological mass in the left pleural cavity. Definitive diagnostic efforts were finally undertaken on January 13, 2021, when the patient underwent a video-assisted thoracoscopic surgery (VATS) pleural biopsy. At the same time, a chest X-ray revealed uneven and thickened pleura on the left side. The identification of pleural thickening at this point is significant, as it fulfilled one of the key criteria in the ESMO guidelines for obtaining a pathological specimen. The ESMO 2022 guidelines recommend obtaining a pathological specimen in all cases of unilateral pleural thickening, regardless of the presence of pleural fluid or plaques, stating that "in all patients who have a unilateral pleural thickening, with or without fluid and/or pleural plaques, efforts should be made to obtain a pathological specimen [II, A]". The selection of VATS for tissue sampling aligns with the ESMO guidelines, which identify thoracoscopy as the preferred method for obtaining diagnostic specimens. The guidelines specify that "thoracoscopy is recommended to obtain adequate histology, to stage optimally and to allow pleural fluid evacuation (with or without pleurodesis). This can be carried out by pleuroscopy or by video-assisted thoracic surgery (VATS)". Though, the available information does not specify how many biopsy sites were sampled. The guidelines emphasize the importance of deep biopsies from multiple sites to

enhance diagnostic accuracy, stating that “MPM can be difficult to identify and therefore deep biopsies from ideally three sites are recommended”.

However, the biopsy confirmed epithelioid mesothelioma based on histological and immunohistochemical analysis, with positive “mesothelioma-associated” markers of calretinin, WT1, D2-40, and BAP1, adhering to the guidelines. However, there is no documentation indicating that “(adeno)carcinoma-associated markers”, such as CEA, Ber-EP4, or MOC-31, were used as part of the immunohistochemical analysis. The ESMO 2022 guidelines explicitly recommend using a combination of at least two mesothelioma-associated markers and two carcinoma-associated markers to improve diagnostic accuracy, stating that “for epithelioid mesotheliomas, diagnosis can usually be made by using a combination of two ‘mesothelioma-associated’ markers [e.g., calretinin, Wilms’ tumour-1 (WT-1), cytokeratin 5/6] and two ‘(adeno)carcinoma-associated’ markers [e.g., CEA, Ber-EP4, MOC-31], supplemented by other markers dependent on possibility of known, suspected or occult malignancies”. However, while some of these markers were mentioned in the 2015 ESMO guidelines, they were not firmly recommended as in the 2022 update.

5.1.2 Staging

According to the ESMO 2022 guidelines, staging of MPM requires a structured approach that integrates both clinical and pathological assessments, based on the 8th revision of the UICC TNM staging system. This includes evaluation of the tumor extent (T descriptor), lymph node involvement (N descriptor), and distant metastases (M descriptor). The ESMO 2022 guidelines recommend contrast-enhanced CT of the thorax and upper abdomen as the baseline imaging modality for T staging, as it allows for the assessment of tumor infiltration into the diaphragm, chest wall, and lung parenchyma. The guidelines specify that “contrast-enhanced CT of the thorax and upper abdomen is the recommended baseline imaging for diagnosis and staging for all patients”.

For M staging, PET-CT is advised to exclude distant metastases and detect occult disease, while MRI plays a role in addressing specific surgical considerations, particularly evaluating tumor invasion into the diaphragm or chest wall. This aligns with the guidelines, which state that “for M stage, although rarely metastatic at diagnosis, in surgical candidates it is important to exclude metastases by, for example, positron emission tomography (PET)-CT”.

The assessment of mediastinal lymph nodes is crucial for N staging, particularly in surgical candidates with suspicious lymph node findings on imaging. The guidelines emphasize that “for surgical candidates, consideration of mediastinal staging by endobronchial ultrasound (EBUS) or mediastinoscopy should be given to exclude contralateral involvement.

Mediastinoscopy is recommended in case of potential resectable disease and if EBUS is negative […]".

In the index patient's case, a contrast-enhanced CT angiography performed on October 8, 2020, identified a pathological pleural mass in the left thoracic cavity. However, since the primary focus of this imaging was to evaluate for PE, it did not specifically address the staging requirements for mesothelioma. While the CT scan detected the pleural mass, it did not assess tumor infiltration into key adjacent structures such as the diaphragm or chest wall, which could have provided a clearer understanding of available treatment options. The ESMO 2022 guidelines acknowledge the need for improved T staging techniques, noting that "currently different imaging protocols are being explored for better T staging, specifically for lung parenchyma, diaphragm and chest wall infiltration, critical points if considering resection".

Furthermore, no PET-CT was performed to evaluate for distant metastases, leaving M staging incomplete and limiting the ability to fully determine tumor resectability. The guidelines emphasize the importance of PET-CT in staging, stating that it is "recommended for identifying distant metastases [...] It remains valuable for excluding occult disease and assessing maximum standard uptake values for prognosis", further specifying that "for patients considered for MCR, additional staging including PET-CT should be carried out [III, B]".

Clinical N staging remained incomplete, as there is no documentation of mediastinal lymph node evaluation, whether through EBUS, mediastinoscopy, or any other modality. This assessment is crucial for differentiating localized (N1) disease from advanced (N2) spread, as this classification plays a key role in treatment planning for surgical candidates. The ESMO 2022 guidelines emphasize that "for surgical candidates, consideration of mediastinal staging by endobronchial ultrasound (EBUS) or mediastinoscopy should be given to exclude contralateral involvement".

Pathological diagnosis was conducted through VATS biopsy on January 13, 2021, confirming the diagnosis of epithelioid mesothelioma. However, neither pathological T nor N staging was conducted. While the biopsy confirmed pleural involvement, it did not provide sufficient information to assess the extent of tumor invasion into adjacent structures, such as the diaphragm, chest wall, or lung parenchyma, which are critical elements of the T descriptor. Similarly, pathological N staging was not conducted, as indicated by the absence of lymph node sampling during the VATS procedure. While the VATS biopsy provided essential

diagnostic confirmation, the guidelines indicate that smaller specimens obtained through diagnostic procedures are not fitting for pathological staging.

Pathological staging in MPM is dependent on the availability of a macroscopically complete resection (MCR) specimen, as smaller biopsy samples are classified under clinical staging. The ESMO 2022 guidelines specify that “pathological staging should be limited to MCR specimens with smaller specimens being clinically staged [V, B]”.

Pre-treatment staging investigations are essential in determining whether a patient is a candidate for active treatment or should receive supportive care, as emphasized in the ESMO 2022 guidelines, which state that “pre-treatment staging investigations are crucial for deciding on active treatment versus supportive care”. This assessment includes factors such as age, performance status (PS), and overall physiological condition to evaluate eligibility for systemic therapy, radiotherapy, or surgery, in accordance with the guidelines' recommendation that “factors such as the patient’s age, performance status (PS), and overall physiological condition should be assessed” (ESMO 2022).

In the index patient’s case, ECOG performance status was always documented, usually as ECOG 1, reflecting slight functional limitations but overall suitability for active therapy. The staging process in this case, though not exhaustive, may still align with the ESMO guidelines, which noted proportionate staging efforts fitting to the intended treatment plan. Surgery was not an option due to the advanced growth of the tumor. When surgery or multimodality therapy is not being considered, a less extensive staging approach can be appropriate, with a focus on gathering the necessary information to conduct systemic therapy or supportive care. The guidelines state that “more extensive staging is recommended for those considered suitable for surgical resection with multimodality therapy”.

As outlined in Table 1 of the ESMO Guidelines 2022, basic staging, consisting of a contrast-enhanced CT of the thorax and upper abdomen, is appropriate for all patients and fulfills the minimum requirements for those receiving systemic therapy or supportive care. More extensive staging, such as FDG-PET or mediastinal staging via EBUS/EUS, is recommended for patients suitable for multimodality therapy. In cases of borderline resectability, even more detailed investigations are required, including combinations of FDG-PET, MRI, laparoscopy, contralateral VATS, or mediastinoscopy.

In this case, basic staging with a CT of the thorax and upper abdomen was performed, but no further investigations such as FDG-PET, EBUS, or MRI were documented. This approach reflects the decision to focus on systemic therapy, as recommended by the tumor board, rather than pursuing surgery or multimodality treatment.

5.1.3 Treatment

The surgical management aligns with the ESMO 2022 guidelines, as no surgery was performed. The patient was neither treated in a specialized mesothelioma center, as such facilities are not available in Lithuania, nor explicitly selected for surgical intervention. The guidelines state that “macroscopic complete resection (MCR), aiming to remove all visible and palpable tumors, may be appropriate for selected patients in specialized centers as part of a multimodality treatment”. Since the patient was neither treated in a specialized mesothelioma center nor explicitly evaluated as a surgical candidate within such a setting, the lack of cytoreductive surgery was appropriate.

Furthermore, the MARS trial demonstrated that surgical intervention, particularly EPP, did not provide a survival benefit and was associated with higher mortality compared to non-surgical treatment. The guidelines summarize this evidence, stating that “the MARS trial compared EPP with non-surgical treatment, identifying poorer survival outcomes for EPP”. However, this trial does not fully address the question of whether surgery in general is inferior to systemic therapy, as extended pleurectomy/decortication (EPD) was not included in the comparison. The ESMO 2022 guidelines explicitly state that “EPD is a lung-preserving procedure and is preferred over EPP”, due to its lower perioperative mortality and, while achieving comparable survival outcomes. Since EPD is now the by the ESMO-guidelines recommended surgical approach, conclusions drawn from the MARS trial, which only compared EPP to systemic therapy, may not be directly applicable to cases where EPD is an option. A search of PubMed and Web of Science did not reveal any randomized controlled trials (RCT) directly comparing extended pleurectomy/decortication (EPD) with non-surgical therapy alone in MPM patients.

5.1.3.1 First-line systemic treatment

The first-line systemic treatment administered to the patient aligns with the ESMO 2022 guidelines, as cisplatin-pemetrexed followed by gemcitabine was chosen, which is an accepted regimen for MPM patients with a performance status (PS) of 0–2. Even though the ESMO 2015 guidelines were applicable at the time. The ESMO 2022 guidelines specify three main first-line options for patients unsuitable for multimodality treatment and a PS of 0-2:

- Nivolumab–ipilimumab (up to 2 years equivalent dosing) for PS 0–1 [I, A; MCBS 3]
- Cisplatin–pemetrexed or carboplatin–pemetrexed (up to 6 cycles) followed by maintenance gemcitabine [II, C]
- Cisplatin–pemetrexed–bevacizumab (up to 6 cycles) followed by maintenance bevacizumab [I, A]

Since the patient had a PS of 1, all three options were guideline-compliant, but cisplatin-pemetrexed followed by gemcitabine was selected, making the treatment appropriate according to the recommendations.

The six cycles of cisplatin–pemetrexed were administered as per the recommended limit, as the guidelines state: "Cisplatin–pemetrexed or carboplatin–pemetrexed should be given for up to 6 cycles in patients showing no progression, provided that toxicity remains manageable". Progression was detected after six cycles, leading to the next-line treatment, which was also in accordance with guideline recommendations.

Following first-line chemotherapy, gemcitabine was used, which is included in the guidelines as a maintenance therapy option. However, maintenance therapy should only be given if the disease remains stable after first-line chemotherapy. Since the patient had documented progression before switching to gemcitabine, this was not true maintenance therapy but rather a second-line treatment attempt. The guidelines do not recommend continuing ineffective therapy, stating: "Systemic treatment should not be continued in case of disease progression". Since the patient had progression after two cycles of gemcitabine, discontinuation was appropriate and in line with the guidelines.

The option of first-line nivolumab-ipilimumab was not chosen, despite being a category I, A recommendation for PS 0-1 patients. The CheckMate 743 trial showed that nivolumab-ipilimumab improves OS compared to chemotherapy, especially in non-epithelioid subtypes, although PFS and objective response rates (ORRs) were similar to chemotherapy (Baas P et al., Lancet. 2021). Since the OS benefit was less pronounced in epithelioid histology, choosing chemotherapy over immunotherapy in this case was justifiable but not the only possible approach. However, the decision not to use immunotherapy in the first-line setting was mainly determined by the fact that, at the time of this decision, the ESMO 2022 guidelines had not yet been released. The ESMO 2015 guidelines, which were in effect at the time, did not yet list immunotherapy as a first-line option but instead recommended chemotherapy as the standard first-line treatment. The 2015 guidelines defined first-line treatment as cisplatin combined with either pemetrexed or raltitrexed, noting that “combination doublet chemotherapy of cisplatin, with either pemetrexed or raltitrexed, has shown a longer survival compared with cisplatin alone in randomised phase III trials (ESMO 2015).

Carboplatin was already recognized as an acceptable alternative to cisplatin, particularly for elderly patients or those with contraindications to cisplatin. The ESMO guidelines support this approach, stating that “carboplatin is an acceptable alternative to cisplatin and may be better

tolerated in the elderly population" (ESMO 2015). Thus, the treatment choice was fully in line with the guidelines at that time.

Additionally, the bevacizumab-containing regimen was not used, even though the MAPS trial (52) demonstrated a 2.7-month OS advantage when bevacizumab was added to cisplatin-pemetrexed, increasing median OS from 16.1 to 18.8 months. However, at the time of the decision, bevacizumab had not yet been recognized as an effective standard-of-care addition to first-line therapy, as earlier trials had failed to demonstrate an improvement over standard treatment.

"Trials of anti-angiogenic agents such as bevacizumab or sunitinib have so far failed to demonstrate improvement over standard treatment" (ESMO 2015).

Given this, the decision not to use bevacizumab in first-line therapy was in line with the available evidence at the time.

5.1.3.2 Second line treatment

The second-line treatment decision for this patient was as well initially based on the ESMO 2015 guidelines, as the ESMO 2022 guidelines had not yet been released. The 2015 guidelines explicitly state that "there is currently no second-line standard of care". However, they acknowledge that "post-study chemotherapy has been shown to be associated with significantly longer survival, with an adjusted hazard ratio of 0.56". Among chemotherapy options, "single-agent vinorelbine has shown useful activity in phase II trials, demonstrating a trend towards longer survival as was seen in the first-line study (MSO1)". Since immunotherapy had not yet been established as a standard option, chemotherapy was chosen for second-line treatment.

Under the ESMO 2022 guidelines, multiple systemic therapy options exist for second-line treatment in PS 0-1 and PS 0-2 patients. The recommended chemotherapy regimens include "Vinorelbine [II, B] OR Gemcitabine [II, B] OR Pemetrexed [III, C]" as monotherapy. Additionally, platinum-based rechallenge is listed as an option with "Cisplatin–pemetrexed [II, B; MCBS 3] OR Carboplatin–pemetrexed [II, B]". The guidelines also include "Gemcitabine and ramucirumab [III, C]" as a possible second-line option.

The patient received gemcitabine monotherapy, which is listed in the guidelines as a valid second-line option.

For immunotherapy, the ESMO 2022 guidelines favor ICIs over chemotherapy, listing "Nivolumab [I, A] OR Pembrolizumab [II, C] OR Nivolumab–ipilimumab [II, C]" as second-line treatment options in immunotherapy-naive patients. The guidelines state that "single-agent nivolumab is superior to BSC [best supportive care] in pretreated immunotherapy-naive

patients and is a treatment option [I, A]". Similarly, "single-agent pembrolizumab in immunotherapy-naive patients as second-line therapy has similar outcomes to single-agent chemotherapy and is a treatment option [II, C]". The guidelines also acknowledge that "combination nivolumab-ipilimumab can be considered in immunotherapy-naive patients as a second- or third-line treatment option [II, C]". The preference for ICIs over chemotherapy in second-line treatment in the guidelines is mainly supported by evidence from the MAPS2 and CONFIRM, which have already been explained in earlier. These in combination with other trials evaluating different ICIs established nivolumab as the highest-rated second-line option [I, A], with chemotherapy remaining a lower-rated alternative [II, B].

This patient, however, received chemotherapy with gemcitabine rather than immunotherapy in the second line setting, meaning that the strongest ESMO 2022 second-line recommended option was not administered.

However, at the time of treatment selection, the ESMO 2015 guidelines were still in effect, and immunotherapy was not yet an established second-line option. The 2015 guidelines explicitly state that "there is currently no second-line standard of care". Chemotherapy was regarded as an available option, as stated earlier. Immunotherapy, on the other hand, was still under investigation, as the guidelines mention that "immunotherapy targeting CTLA4 with tremelimumab is under evaluation in a large global phase III trial [NCT01843374]" and that "recent data suggest that PDL1, a putative biomarker for PD1/PDL1 therapy, is significantly expressed in mesotheliomas, particularly the sarcomatoid subtype".

The ESMO 2022 guidelines recognize the limited efficacy of cytotoxic chemotherapy in second-line treatment, stating that "single-agent gemcitabine or vinorelbine [II, B] has limited second-line activity, as suggested by ORRs or OS, with encouraging activity for gemcitabine-ramucirumab combination [III, C]". This is supported by the RAMES trial (60), a Phase II randomized, double-blind, placebo-controlled study, which demonstrated a significant survival benefit for gemcitabine-ramucirumab over gemcitabine monotherapy in second-line MPM. The trial was published in September 2021, meaning before the initiation of this patient’s second-line treatment. Additionally, the limited efficacy of gemcitabine and also vinorelbine monotherapy in second-line settings has been established in other studies (104). However, despite emerging evidence favoring gemcitabine-ramucirumab, the ESMO 2022 guidelines still rank gemcitabine monotherapy [II, B] higher than its combination with ramucirumab [III, C]. This reason for that is most likely because the RAMES trial, while demonstrating a survival benefit, was only a Phase II study, and no Phase III trial had yet validated these findings, resulting in a more cautious guideline recommendation.

Thus, while the use of gemcitabine monotherapy in this patient can be questioned in light of newer data, it remained within guideline recommendations and was a clinically justifiable choice.

5.1.3.3 Third line and fourth line systemic treatment

The ESMO 2022 guidelines state that there is "no evidence basis for routine third-line therapy in MPM" and recommend that "clinical trial participation should be considered [V, C]". At the time third-line treatment with docetaxel was initiated in December 2021, the ESMO 2022 guidelines had not yet been published, meaning there were no formal recommendations for third-line therapy at that time. The ESMO 2015 guidelines did not establish a clear standard of care for third-line treatment, making the decision to administer docetaxel a discretionary choice rather than a guideline-supported approach.

By contrast, when nivolumab was initiated in March 2022 as fourth-line therapy, the ESMO 2022 guidelines had been released, recommending "Nivolumab [I, A] OR Nivolumab–ipilimumab [II, C]" as the only guideline-endorsed third-line treatment options for PS 0-1 patients, while advising best supportive care for PS ≥2. Given that nivolumab was selected in accordance with the updated guidelines, its use at this stage aligned with the strongest available recommendation for third-line treatment.

Thus, while docetaxel was not a guideline-endorsed third-line option, its use in December 2021 was not a clear deviation from standard care, as no formal third-line recommendations existed at the time. However, the subsequent switch to nivolumab in March 2022 fully aligned with the newly available guidelines, which reinforces its appropriateness as the preferred third-line therapy at that time.

5.1.3.4 Why no utilization of radiotherapy

No radiotherapy (RT) was administered, which was the correct approach based on the ESMO 2022 guidelines. The guidelines indicate that radiotherapy (RT) can be considered for pain relief in patients with MPM, such as in cases involving chest wall invasion or other thoracic structures. However, high-quality evidence supporting RT for pain management is limited (49). Since there is no mention of severe tumor-related pain requiring RT in this patient, the use of palliative radiotherapy was not necessary.

Additionally, the guidelines state that the role of prophylactic RT to “reduce the risk of subcutaneous metastasis” following pleural procedures has been debated for decades, and large, multicenter randomized trials have shown no benefit of routine prophylactic RT. Given these findings, prophylactic RT following pleural interventions is no longer recommended, further supporting the decision not to administer RT in this case.

High-dose RT, particularly in perioperative settings, remains controversial due to toxicity concerns, as studies indicate that "delivering perioperative RT is challenging due to the complex volumes of irradiation related to growth patterns" of the tumor, with significant toxicity risks, including "radiation pneumonitis in up to 46% of cases". The guidelines specify that RT in these contexts should be delivered in specialized centers. However, since this patient did not undergo EPP or extended pleurectomy/decortication (EPD), there was no indication for high-dose RT in a multimodal setting.

Furthermore, newer RT modalities such as proton therapy and stereotactic ablative radiotherapy (SABR) remain investigational. Current studies indicate that data on the use of SABR for oligorecurrent MPM after multimodality treatment are limited, and proton therapy, despite its potential to spare normal tissues, lacks sufficient clinical data, with most evidence coming from small, single-center studies". Given the lack of strong supporting evidence for these approaches in routine clinical use, the decision not to pursue RT was consistent with current recommendations.

5.1.1.5 Treatment choices in the light of genomic alterations

The ESMO 2022 guidelines highlight that "mutations occur most frequently in BAP1 (25%-60% of cases), CDKN2A/B (40%-45%), and NF2 (20%-50%)". In this case patient has a MPM with BAP1-mutation.

This BAP1 loss is associated with chemosensitivity, as the guidelines state that "preclinical evidence and some series suggest that sensitivity to chemotherapeutic agents may be BAP1 driven and this has been observed also in MPM patients". Despite this, no genomic alterations in MPM have led to approved targeted therapies, and standard treatment relies on chemotherapy and ICIs.

The guidelines also state that "clinical trials are ongoing, but the absence of selection of patients based on genotyping may hamper the identification of any signal of clinical efficacy". Since clinical trials on ICIs in MPM did not stratify patients by genomic alterations, the guidelines recommend treatment cannot be based on molecular subgroups.

The ESMO 2015 guidelines did not recommend ICIs, which explains why first-, second-, and third-line treatment consisted exclusively of chemotherapy. By March 2022, the ESMO 2022 guidelines recommended nivolumab [I, A] and nivolumab-ipilimumab [II, C] as third-line options for PS 0-1 patients. However, because BAP1-mutated tumors are more chemosensitive, the guidelines' preference for ICIs over chemotherapy does not necessarily reflect the optimal treatment choice for this patient. The CheckMate 743 trial (54)

demonstrated that ICIs provided the greatest benefit in non-epithelioid MPM, while epithelioid cases showed a less pronounced advantage over chemotherapy.
Despite this, the patient's fourth-line nivolumab treatment led to prolonged disease stability, supporting its effectiveness despite histological and molecular factors that could have favored chemotherapy.

5.2 Evaluation of the case according to the Surviving Sepsis Campaign guidelines

This section examines the management of sepsis in the presented case, beginning with the patient's ICU admission on March 18, 2023, in accordance with the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (2021) (105). Key aspects include initial resuscitation, antimicrobial therapy, hemodynamic management, oxygen and ventilation, stress ulcer prophylaxis, venous thromboembolism (VTE) prophylaxis, glucose control, bicarbonate therapy and nutrition.

5.2.1 Initial rescucitation

The SSC recommends: "For patients with sepsis-induced hypoperfusion or septic shock we suggest that at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hours of resuscitation". Since the patient weighed 76 kg, the minimum recommended volume was 2.3 liters of crystalloid fluid. The administration of intravenous fluids was documented, but there is no explicit mention of whether the full 30 mL/kg volume was given within the first three hours. The lack of documentation on the exact total volume administered makes it unclear whether this threshold was met.
The SSC further advises that fluid resuscitation should be guided by dynamic measures, such as passive leg raising, stroke volume variation, or pulse pressure variation, rather than relying solely on static parameters like BP and HR: "For adults with sepsis or septic shock, we suggest using dynamic measures to guide fluid resuscitation over physical examination or static parameters alone". There is no documentation that dynamic fluid responsiveness testing was performed, which means fluid resuscitation may have been based only on static variables such as BP and HR. This does not fully comply with the SSC recommendation, as static measurements alone are considered less reliable.
The SSC also recommends guiding resuscitation based on lactate clearance when lactate is elevated, stating: "For adults with sepsis or septic shock, we suggest guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate". However, the patient's initial lactate was 0.92 mmol/L, which is within the normal range. Since lactate was not elevated, this strategy was not applicable.

There is also no documentation that capillary refill time was used as an adjunct to perfusion assessment, despite the SSC suggesting its role: "For adults with septic shock, we suggest using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion". While its absence in the documentation does not necessarily mean it was not assessed, explicitly noting it would have enhanced the completeness of the perfusion evaluation in retrospect.

5.2.2 Antimicrobial therapy

Upon ICU admission, the patient was diagnosed with sepsis, bilateral pneumonia, and a UTI. In consequence, broad-spectrum antibiotic therapy with Piperacillin/Tazobactam was started, which was later switched to Meropenem. Additionally, Fluconazole was administered for antifungal coverage. The SSC emphasizes the need for continuous reevaluation in suspected sepsis without a confirmed infection: "For adults with suspected sepsis or septic shock but unconfirmed infection, we recommend continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected".

Microbiological testing was repeatedly performed to identify a source of infection, including serial blood and urine cultures. Despite negative blood cultures on March 23, April 1, and April 22 and a sterile urine culture on April 18, broad-spectrum antibiotics were not de-escalated. Additionally, an intravascular catheter culture on March 29 grew Staphylococcus capitis, a common skin contaminant, but there was no clear documentation of catheter removal. Yet, it is standard clinical practice to remove a potentially infected catheter. Given this, it is reasonable to assume that it was managed accordingly, even if direct confirmation is missing from the records.

On April 12, a urine culture from the urinary tract catheter grew Enterococcus faecium (susceptible to multiple antibiotics) and Candida tropicalis (resistant to fluconazole) without positive findings in blood cultures. The SSC suggests avoiding empiric antifungal therapy unless a patient is at high risk for invasive fungal infection: "For adults with sepsis or septic shock at low risk of fungal infection, we suggest against empiric use of antifungal therapy." The SSC cites a meta-analysis and the EMPIRICUS trial, both of which found no mortality benefit from empiric antifungal therapy in critically ill patients: "In an updated meta-analysis of empiric antifungal therapy versus no antifungal therapy in adult critically ill patients, no difference in short-term mortality was observed. In the largest and most recent RCT-EMPIRICUS-there was also no difference in outcome between patients receiving empiric antifungal therapy (micafungin) and patients receiving placebo" (106).

Fluconazole was administered for 18 days during the patient's stay in the pulmonology department and was most likely discontinued after Candida tropicalis was found to be resistant on April 12. Urinalysis revealed 300 erythrocytes/µL and 25 leukocytes/µL upon ICU admission, which indicates a UTI. During the ICU stay, an epicystostomy was performed, with turbid urine noted in the drainage system on the same day. Given these findings, the presence of symptomatic candiduria cannot be ruled out, particularly in critically ill patients.

While the SSC recommends against routine empiric antifungal therapy in sepsis without high-risk factors for invasive candidiasis, the combination of suspected UTI, epicystostomy, turbid urine, and the isolation of C. tropicalis suggests that antifungal therapy may have been justified. At the time fluconazole was administered, its resistance status was not yet known, so the decision to initiate therapy was not necessarily inappropriate based on available information. However, the eventual resistance finding on April 12 meant that fluconazole was unlikely to have been effective, and discontinuation at that point was appropriate.

Molecular testing on April 11 found no viral respiratory pathogens, effectively ruling out viral pneumonia as a complicating factor.

The guideline encourages to stop unnecessary antimicrobials or narrowing therapy based on clinical improvement, even if cultures remain negative: "Thoughtful de-escalation of antimicrobials based on adequate clinical improvement is appropriate even if cultures are negative. Early discontinuation of all antimicrobial therapy if infection is ruled out is advisable".

The guideline also states: "For adults with sepsis or septic shock, we suggest daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation".

A meta-analysis cited by the SSC found that de-escalation was associated with improved short-term mortality and shorter hospital stays, which suggests that timely de-escalation improves outcomes (107).

However, the continued use of broad-spectrum antibiotics was clinically justified in this case given the patient's ongoing sepsis and persistently elevated inflammatory markers. CRP fluctuated significantly, with an initial peak at 186.2 mg/L on March 21, a decrease to 119.5 mg/L on March 23, followed by a rise to 174.7 mg/L on March 27. A further drop to 80.6 mg/L on April 3 was followed by another peak at 205.8 mg/L on April 11, remaining above 100 mg/L until April 23. This fluctuation, despite antimicrobial therapy, suggests ongoing inflammatory activity rather than a steady resolution of infection. White blood cell (WBC)

count also showed variability, initially elevated at 13.7 × 10^9/L on March 18 before dropping to 6.65 × 10^9/L by March 21. However, it fluctuated around this range rather than steadily normalizing, with levels of 8.80 × 10^9/L on March 27 and 7.57 × 10^9/L on April 10.
Based on that “adequate clinical improvement” as the SSC suggests as a basis for antimicrobial de-escalation could not be seen in a broader scale, as based on the provided data, the evaluation of clinical progress relies solely on laboratory measures and vital signs, without additional clinical context that suggests overall improvement.
Given the patient's advanced MPM, these trends complicate the assessment of treatment response and raise questions about whether the inflammation was driven by persistent infection, an unresolved non-infectious inflammatory process, or other factors such as malignancy-related systemic inflammation.

5.2.3 Biomarkers to start antibiotics

The initiation of antimicrobial therapy in this patient adhered to the 2021 SSC guidelines, as it was based on clinical presentation rather than guided by biomarkers. The SSC does not recommend using procalcitonin in combination with clinical evaluation to determine when to start antimicrobials, as studies have not demonstrated a clear benefit: "For adults with suspected sepsis or septic shock, we suggest against using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone". This recommendation is based on data from RCTs, which have not demonstrated a mortality benefit or reduction in ICU or hospital length of stay when procalitonin (PCT) is used to guide the timing of antibiotic initiation (108–110).
At the time of ICU admission, antibiotics were started due to fever, hypotension (BP 70/50 mmHg), elevated inflammatory markers (CRP 210 mg/L, procalcitonin 7.13 µg/L), leukocytosis (WBC 13.70 × 10^9/L), and suspected pneumonia. While there is no explicit documentation on which factors guided the decision to initiate antibiotics, it is reasonable to assume that the overall clinical picture, meaning a combination of hemodynamic instability, elevated inflammatory markers, and suspected infection were the reason. The significantly elevated procalcitonin level may also have influenced the decision, despite SSC guidelines advising against its use as a primary determinant for initiating antimicrobial therapy.
Despite the rationale for starting antibiotics, a key issue in this case is the lack of documented temperature measurements beyond the emergency department report, with no recorded exact temperature. While fever was reported in the emergency department, no exact values were documented thereafter. Continuous temperature monitoring is crucial for managing sepsis, as it helps guide clinical decisions, assess disease progression, and evaluate treatment response.

Without regular temperature recordings, an essential parameter for sepsis management is missing, which limits the ability to monitor the patient's condition effectively and adjust therapy as needed, such as evaluating the effectiveness of antimicrobial therapy.

5.2.4 Hemodynamic management

5.2.4.1 Mean arterial pressure

The 2021 SSC guidelines recommend targeting a mean arterial pressure (MAP) of 65 mmHg in patients requiring vasopressors, stating: "For adults with septic shock on vasopressors, we recommend an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets".

At the time of ICU admission on March 18 (BP 70/50 mmHg, MAP 56.7 mmHg), the patient was hypotensive despite assumed initial fluid resuscitation in the emergency department, suggesting that vasopressors may have been required. However, there is no documentation confirming their administration.

By March 24, at the time of transfer to the Pulmonology Unit (BP 86/60 mmHg, MAP 68.7 mmHg), approximately six days later, the MAP was above the recommended threshold, indicating improved hemodynamic stability. Whether this improvement resulted from vasopressor therapy, continued fluid administration, or spontaneous recovery remains unclear due to the lack of explicit documentation.

The SSC guidelines also note that aiming for higher MAP values (80–85 mmHg) does not improve survival and can increase the risk of atrial fibrillation. This supports the recommendation of 65 mmHg as an optimal target. A meta-analysis of two RCTs cited in the guidelines confirms this, reporting that "higher MAP targets did not improve survival in septic shock" (111).

5.2.4.2 Fluid Management

The SSC recommends crystalloids as the first-line resuscitation fluid in sepsis and septic shock due to their availability, cost-effectiveness, and comparable efficacy to colloids: "For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation".

The SSC also suggests using balanced crystalloids instead of normal saline, due to evidence suggesting a reduction in mortality and acute kidney injury (AKI) when chloride-restrictive fluids are used. "For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation".

The documentation confirms that the patient received intravenous fluids, but the type of crystalloid solution is not specified. There is no information confirming whether balanced

crystalloids were used instead of normal saline, making it unclear if this guideline was followed.

The SSC does not provide a specific recommendation on restrictive vs. liberal fluid strategies in the first 24 hours of resuscitation due to insufficient evidence: "There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after initial resuscitation".

However, the guidelines emphasize that fluid resuscitation should be given only if patients present with signs of hypoperfusion. The patient was admitted with hypotension (BP 63/36 mmHg, later 70/50 mmHg), which justified IV fluid administration. The documentation confirms that IV fluids were given upon ICU admission, but there is no information on the total volume administered or how fluid status was monitored over time.

The SSC highlights that excessive IV fluid administration may damage vascular integrity and lead to organ dysfunction. While the evidence remains inconclusive, observational studies have suggested a possible association between high-volume fluid resuscitation and increased mortality. As noted in the literature, “recent evidence suggests that IV fluids used to restore organ perfusion may damage vascular integrity and lead to organ dysfunction” (112). There is no clear documentation on whether a restrictive or liberal fluid strategy was used in this case. Since the patient’s BP improved over time (86/60 mmHg on March 24, 119/70 mmHg at discharge on April 24), it is possible that fluid resuscitation was sufficient without the need for ongoing liberal fluid therapy. However, without detailed documentation of total fluid balance and fluid responsiveness assessments, it is unclear whether fluids were appropriately titrated according to guideline-based recommendations.

5.2.4.3 Vasoactive Agents

The patient presented with severe hypotension (BP 63/36 mmHg at admission, later 70/50 mmHg), which is a hallmark of septic shock and typically necessitates early vasopressor therapy if fluids alone do not restore adequate perfusion. The SSC strongly recommends norepinephrine as the first-line vasopressor in septic shock due to its vasoconstrictive properties, lower arrhythmia risk compared to dopamine, and demonstrated survival benefit: "For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors".

Additionally, if the patient required norepinephrine or epinephrine at ≥0.25 mcg/kg/min for at least 4 hours after initiation to maintain target MAP, the SSC guidelines suggest using IV

corticosteroids: "For adults with septic shock and an ongoing requirement for vasopressor therapy we suggest using IV corticosteroids".
An updated meta-analysis found that systemic corticosteroids accelerate the resolution of shock, with a mean difference (MD) of 1.52 days (113). Additionally, the guideline revision includes a meta-analysis showing that corticosteroid use leads to more vasopressor-free days, with an MD of 1.5 days, as reported in Supplemental Digital Content: Appendix 5 of the SSC-guidelines (http://links.lww.com/CCM/G895).
Based on these findings, corticosteroids are recommended to accelerate shock resolution and reduce the duration of vasopressor therapy, although no clear survival benefit has been established.
Despite the clear indication for vasopressor therapy, there is no documentation confirming that norepinephrine, nor corticosteroids were administered. If vasopressors were not used despite persistent hypotension, this would represent a deviation from SSC guidelines. If they were administered but not recorded, adherence to guidelines cannot be confirmed.
On March 24, the patient's BP had improved to 86/60 mmHg, and at discharge on April 24, BP was recorded as 119/70 mmHg, indicating eventual hemodynamic stabilization. However, the lack of documentation on vasopressor use raises concerns about how the patient's hypotension was managed in the early ICU phase. If fluids alone were sufficient to restore MAP ≥65 mmHg, vasopressors may not have been necessary, but this is not clearly recorded.

5.2.4.4 Inotropes

The SSC recommends adding dobutamine to norepinephrine or using epinephrine alone for patients with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume resuscitation and arterial BP: "For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone".
The patient initially presented with hypotension (BP 63/36 mmHg, later recorded as 70/50 mmHg) and required IV fluid resuscitation. However, there is no mention of persistent hypoperfusion or signs of myocardial dysfunction that would have required inotropic support.
The SSC suggests using inotropes when low cardiac output is suspected or measured, particularly in patients with signs of ongoing tissue hypoxia despite resuscitation, stating: "Inotropic therapy can be used in patients with persistent hypoperfusion after adequate fluid resuscitation, and in patients with myocardial dysfunction, based on suspected or measured low CO and elevated cardiac filling pressures".

There is no evidence that cardiac output was specifically assessed or that dobutamine or epinephrine was used, suggesting that inotropic therapy was not decided to be necessary during the ICU stay. Additionally, a heart ultrasound on March 29 showed no echocardiographic signs of infective endocarditis, but there is no documentation of left ventricular function or cardiac output assessment. If no clinical signs of cardiac dysfunction were present, the omission of inotropes was appropriate according to the SSC guidelines.

5.2.5 Oxygen and ventilation

The patient's oxygenation management adhered appropriately to the 2021 SSC guidelines. On ICU admission (March 18), oxygen therapy at 5 L/min via nasal cannula effectively maintained adequate oxygenation (SpO_2 97%). By March 24, oxygen requirements had decreased to 2 L/min with the same oxygen saturation. Ultimately, before transfer to palliative care on April 24, the patient maintained adequate oxygenation on room air (SpO_2 96%).

The SSC makes no specific recommendation regarding conservative oxygen targets (PaO_2 55–70 mmHg, SpO_2 88–92%) due to insufficient evidence: "There is insufficient evidence to make a recommendation on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure".

Additionally, the SSC suggests the use of high-flow nasal oxygen therapy (HFNC) over noninvasive ventilation (NIV) for sepsis-induced hypoxemic respiratory failure: "For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high-flow nasal oxygen over noninvasive ventilation".

In this case, HFNC or NIV was neither used nor indicated, as the patient maintained adequate oxygenation with conventional low-flow nasal cannula oxygen therapy and subsequently without supplemental oxygen.

5.2.6 Stress ulcer prophylaxis

The use of stress ulcer prophylaxis in this patient adhered to the SSC guidelines, by administration of prophylactic omeprazole (20 mg every morning). The SSC suggests using stress ulcer prophylaxis in adults with sepsis or septic shock who exhibit specific risk factors for gastrointestinal (GI) bleeding: "For adults with sepsis or septic shock, and who have risk factors for gastrointestinal bleeding, we suggest using stress ulcer prophylaxis".

According to a systematic review evaluated by the SSC guidelines, risk factors for clinically significant GI bleeding include coagulopathy, shock, and chronic liver disease. The review reported that coagulopathy was associated with a relative effect (RE) of 4.76, shock with an RE of 2.60, and chronic liver disease with an RE of 7.64 (113).

The patient exhibited both coagulopathy (APTT elevated to 53.7 s on March 18) and shock (initial BP 63/36 mmHg), thereby meeting these criteria.

5.2.7 Venous thromboembolism prophylaxis

The use of VTE prophylaxis in this patient adhered to SSC recommendations, by administration of Fraxiparine (Nadroparin) 0.3 ml subcutaneously every evening.

The SSC strongly recommends pharmacologic VTE prophylaxis in sepsis or septic shock, unless contraindicated: "For adults with sepsis or septic shock, we recommend using pharmacologic VTE prophylaxis unless a contraindication to such therapy exists".

The use of Nadroparin aligns with this recommendation, and there is no indication that the patient had contraindications to anticoagulation (such as major bleeding, thrombocytopenia, or coagulopathy severe enough to rule out anticoagulation).

The SSC also recommends LMWH over UFH due to its lower incidence of DVT and greater convenience: "For adults with sepsis or septic shock, we recommend using low molecular weight heparin (LMWH) over unfractionated heparin (UFH) for VTE prophylaxis".

This recommendation is supported by a meta-analysis previously included in the 2016 SSC guidelines, which showed that LMWH significantly reduced DVT rates compared to UFH, without differences in mortality or major bleeding risk. No subsequent RCTs have contradicted these findings. Therefore, the use of nadroparin, an LMWH, in this patient was consistent with SSC recommendations.

In addition, the SSC advises against combining mechanical and pharmacologic VTE prophylaxis, as supported by the PREVENT trial, a large RCT which found no significant differences in mortality, DVT, or PE when mechanical prophylaxis was added to pharmacologic therapy (114). The guidelines state: "For adults with sepsis or septic shock, we suggest against using mechanical VTE prophylaxis in addition to pharmacological prophylaxis, over pharmacologic prophylaxis alone". There is no documentation of mechanical VTE prophylaxis in this case, which is aligns with SSC recommendations.

5.2.8 Glucose control

The patient’s blood glucose levels throughout the ICU stay were consistently within the normal range, with no documented episodes of hyperglycemia exceeding the SSC threshold of ≥180 mg/dL (10 mmol/L) that would require insulin therapy.

This aligns with the SSC recommendation: “For adults with sepsis or septic shock, we recommend initiating insulin therapy at a glucose level of ≥ 180 mg/dL (10 mmol/L)”.

Throughout the ICU stay, documented glucose values ranged between 3.3 and 6.1 mmol/L (59–110 mg/dL), which is well below the insulin therapy threshold: March 18: 4.9 mmol/L, March 18 (second test): 6.1 mmol/L, March 19: 4.9 mmol/L, March 20: 4.1 mmol/L, March 21: 3.3 mmol/L, April 6: 4.4 mmol/L, April 18: 4.28 mmol/L.

These values show that the patient never developed significant hyperglycemia that would have required insulin therapy.

The SSC also warns against excessive insulin administration leading to hypoglycemia. Specifically, they note, recent network meta-analysis, that “target concentrations of <110 mg/dL (6.1 mmol/L) were associated with a four- to nine-fold increase in the risk of hypoglycemia” (115). The patient did not experience severe hypoglycemia (<3.0 mmol/L or <54 mg/dL), nor were glucose levels aggressively lowered with insulin therapy. The lowest recorded value was 3.3 mmol/L (March 21), which is borderline low but does not indicate critical hypoglycemia. Therefore, the patient’s glucose management aligns with SSC guidelines, and no insulin therapy was required.

On April 6, 2023, the patient was evaluated by a neurologist due to disorientation. The consultation report noted: “Decreasing CRP. Notable erythrocyturia and pronounced glucosuria in urine”. (Neurologist Consultation, 06.04.2023).

However, a critical issue in this context is the complete lack of evidence of elevated blood glucose levels throughout the patient’s ICU stay. Blood gas analyses consistently showed normoglycemia, with values ranging from 3.3 to 6.1 mmol/L, never exceeding the renal glucose threshold (~10 mmol/L/180 mg/dL), above which glucosuria would typically be expected. Additionally, urinalyses performed on April 6, April 7, and earlier on March 18 all reported glucose levels of 0 mmol/L, with no documented episode of hyperglycemia that could explain the neurologist’s observation.

Given this fundamental lack of supporting evidence, it remains unclear whether glucosuria was ever actually present or if the finding resulted from an error in documentation or interpretation. Without additional information, this discrepancy cannot be resolved.

5.2.9 Bicarbonate therapy

There is no documentation indicating that the patient received sodium bicarbonate therapy during the ICU stay. Based on the SSC guidelines, the administration of bicarbonate in sepsis-induced lactic acidosis is generally not recommended, except under specific conditions, stating: "For adults with septic shock and hypoperfusion-induced lactic acidemia, we suggest against using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements". And "For adults with septic shock, severe metabolic acidemia (pH ≤ 7.2) and AKI (AKIN score 2 or 3), we suggest using sodium bicarbonate therapy".

In this case, the patient exhibited a normal acid-base status at ICU admission, with a pH of 7.442, HCO_3^- of 18.9 mmol/L, and a lactate of 0.92 mmol/L, which does not meet the criteria for severe metabolic acidemia (pH ≤ 7.2). Additionally, throughout the ICU course, pH values

remained within the acceptable range (lowest documented pH 7.384 on March 18, 2023), and lactate levels did not indicate severe hypoperfusion.

Furthermore, no evidence of severe AKI (stage 2 or 3) was reported, which would have supported bicarbonate use under SSC guidelines. A multicenter RCT found that bicarbonate therapy did not improve 28-day mortality or organ failure in patients with metabolic acidosis, except for the subgroup with AKI stage 2 or 3, where a 17.7% absolute risk reduction in mortality was observed (116). Since this patient did not meet these criteria, the decision not to administer bicarbonate was in line with SSC recommendations.

5.2.10 Nutrition

The patient received early enteral nutrition, aligning with the SSC guidelines, which suggest initiating enteral nutrition within 72 hours in patients with sepsis or septic shock who can be fed enterally. "For adult patients with sepsis or septic shock who can be fed enterally, we suggest early (within 72 hours) initiation of enteral nutrition".

The rationale for early enteral feeding includes maintaining gut integrity, preventing intestinal permeability, dampening the inflammatory response, and modulating metabolic responses to reduce insulin resistance (117,118).

There was no documentation of contraindications to enteral feeding in this patient.

A multicenter trial evaluating mechanically ventilated patients with shock found no significant benefit of early enteral over parenteral nutrition for major clinical outcomes (119). A subsequent meta-analysis incorporating this study rated the quality of evidence as low or very low. However, despite these findings the SSC did not change its recommendation, as no harm was observed with early enteral feeding, and the above listed physiologic benefits may support its use in patients with sepsis and septic shock, regardless of ventilation status.

6. COMPARISON OF CLINICAL CASES

To better understand the presented clinical case, a comparison with a similar case from the literature is conducted. Specifically, reference is made to the case report “Unexplained Pleural Effusion Leads to the Revelation of a Malignant Mesothelioma: A Case Report” published by Rhazari et al. in Cureus in 2022 (120). This allows for an evaluation of similarities and differences in patient characteristics, disease progression, diagnostic workup, and treatment approaches. By contrasting both cases, insights can be gained regarding potential prognostic factors and variations in clinical management. The following section outlines the details of the comparison case before juxtaposing it with the presented patient.

6.1 Comparison case presentation

The case describes a 55-year-old male patient with a significant history of occupational asbestos exposure, having worked in the construction industry for 12 years. His last documented exposure occurred 28 years prior to his diagnosis. The patient initially presented one year before his definitive diagnosis with acute, sharp pain in the left chest. At that time, he reported no additional symptoms such as dyspnea, cough, hemoptysis, or night sweats. His medical history was unremarkable, and he denied any history of smoking, alcohol consumption, or other toxic habits.

On physical examination, decreased breath sounds were noted on the left side, raising suspicion of a pleural effusion. A chest X-ray confirmed the presence of a mild left-sided pleural effusion. A subsequent pleural puncture revealed an amber-colored exudative fluid with a total WBC count of 2,455/μL, consisting of 19% neutrophils, 75% lymphocytes, and 6% monocytes. Microbiological analysis showed no evidence of Mycobacterium tuberculosis, and cytological examination did not reveal any atypical cells. Additionally, a pleural biopsy at that time was negative for malignancy.

Despite the absence of clear evidence of malignancy, the patient underwent a follow-up chest X-ray four weeks later, which showed the development of white pulmonary infiltrates. Consequently, empirical antibiotic therapy was initiated, and the patient was scheduled for regular follow-up. However, he was lost to follow-up and returned to medical attention 11 months later with worsening symptoms, including persistent, sharp left-sided chest pain, progressive dyspnea classified as grade 3 on the Modified Medical Research Council (mMRC) scale, and self-reported weight loss. Upon re-evaluation, the patient exhibited tachypnea, with a respiratory rate of 32 breaths per minute, and persistently decreased breath sounds on the left lung.

A contrast-enhanced chest computed tomography (CT) scan revealed nodular pleural thickening associated with pulmonary, subdiaphragmatic, and supradiaphragmatic lymph node metastases. A CT-guided transparietal biopsy was performed, demonstrating large aggregates of malignant cells characterized by eosinophilic intracytoplasmic inclusions and irregular nuclei. Immunohistochemical analysis confirmed strong positivity for D2-40, calretinin, Wilms' tumor 1 (WT1), cytokeratin 5/6 (CK5/6), and epithelial membrane antigen (EMA), confirming the diagnosis of malignant epithelioid pleural mesothelioma.

Following the diagnosis, the patient was started on first-line systemic chemotherapy consisting of pemetrexed plus carboplatin. After three months of treatment, he reported a remarkable clinical improvement and remained under regular follow-up.

6.2 Comparison of both cases

Both cases describe male patients diagnosed with epithelioid MPM, following an initial presentation with chest pain and pleural effusion. In both cases, pleural fluid cytology was negative for malignancy, delaying definitive diagnosis. However, while the comparison case experienced a significant delay due to loss to follow-up, the index patient underwent earlier histopathological confirmation via VATS, allowing for a timelier initiation of systemic therapy.

A key difference between the two cases is the presence of a documented history of occupational asbestos exposure in the comparison patient, who had worked in construction for 12 years with exposure occurring 28 years prior to diagnosis. In contrast, no asbestos exposure was documented of the index patient, though it remains unclear whether this was due to a lack of exposure or simply because the anamnesis was not specifically obtained.

Both patients received first-line platinum-based chemotherapy (Cisplatin/Pemetrexed). The comparison patient showed early symptomatic improvement and remained under follow-up after three months, whereas the index patient experienced disease progression, requiring multiple lines of therapy. The treatment course of the index patient followed a pattern of disease progression approximately every 6 to 7 months before extended stability was achieved with immunotherapy.

After progression on first-line chemotherapy, the index patient was switched to Gemcitabine monotherapy (second-line) in September 2021. Despite initial control, follow-up imaging in November 2021 showed continued tumor growth, prompting a switch to Docetaxel (third-line) in December 2021. By March 2022, further progression was noted, leading to discontinuation of chemotherapy and the initiation of Nivolumab (fourth-line immunotherapy).

Unlike previous therapies, Nivolumab provided disease stabilization for nearly a full year, from March 2022 to early 2023. By January 2023, after 20 cycles of Nivolumab, the disease remained stable, with a reduction in non-target lesions and overall clinical improvement. However, in March 2023, the index patient was admitted to the ICU for sepsis and pneumonia, rather than direct tumor progression. While nivolumab itself is not known to directly increase infection risk, the overall clinical picture, including prior chemotherapy, prolonged disease course, and impaired pulmonary reserve, likely contributed to increased vulnerability to infection. In April 2023, due to an advanced oncological disease state (ECOG 4), the decision was made to transition to palliative care, and he was transferred to a hospice facility.

In contrast, the comparison patient had a shorter overall disease course but responded well to first-line chemotherapy with pemetrexed/carboplatin, with no reported progression at the three-month follow-up. As of the last documented update, he remained alive and under follow-up. While both cases shared an initial negative pleural fluid cytology and similar treatment strategies, the index patient's disease followed a more aggressive trajectory, requiring multiple lines of therapy before reaching a period of stability with immunotherapy. Despite this, his condition ultimately deteriorated, leading to palliative care, while the comparison patient remains on active follow-up.

This contrast points out the variability in disease progression and treatment response in MPM, even among patients with similar histology. While the comparison patient benefited from an early response to chemotherapy, the index patient required multiple treatment adjustments before achieving temporary disease stability. However, it is uncertain how long the comparison patient will maintain disease stability. The impact of asbestos exposure history remains uncertain in this case, but it reinforces the relevance of a thorough occupational history in all potential mesothelioma patients.

7. CONCLUSIONS

This case study illustrates the diagnostic and therapeutic challenges associated with malignant pleural mesothelioma, particularly regarding the staging process, treatment decisions, and adherence to evolving clinical guidelines. The disease's rarity and long latency period continue to make early detection difficult. Many patients, including the one discussed here, are diagnosed only after presenting with non-specific symptoms and substantial disease burden, leaving few curative options available. In this instance, the absence of definitive radiographic findings early in the diagnostic workup, combined with the lack of known asbestos exposure, delayed the suspicion of MPM.

A key limitation in this case was the lack of a documented occupational history, which, if positive for asbestos exposure, might have raised earlier suspicion of MPM. This reflects a recurring issue in real-world clinical settings, where time constraints and non-specific presentations may lead to incomplete histories. Particularly in patients presenting with pleural effusion or atypical thoracic symptoms, even a brief occupational history could steer diagnostic thinking in a more targeted direction.

Staging in this case was not exhaustive, as PET-CT imaging and mediastinal lymph node evaluation via EBUS or mediastinoscopy were not performed. However, since the patient was not treated at a specialized mesothelioma center and was not considered for surgery, the

limited staging approach was appropriate for systemic therapy. While this may have been acceptable under the circumstances, the absence of comprehensive staging restricted the ability to evaluate potential eligibility for clinical trials or other treatment strategies.
Therapeutically, the patient's treatment followed a structured sequence of systemic therapies, which was the standard regimen per the ESMO 2015 guidelines in effect at that time. First-line platinum-based chemotherapy was appropriately selected, followed by subsequent lines of gemcitabine and docetaxel as disease progression occurred. Radiotherapy was not administered in this case, which was also in line with the guidelines. Its omission was reasonable given the absence of localized pain or other indications for palliative radiation.
The later initiation of nivolumab reflects how evolving guidelines and approvals shape treatment decisions in practice, and how patients treated longitudinally may benefit from updated standards of care that were not available at the time of initial diagnosis.
The intensive care management of this patient followed several SSC recommendations but revealed some gaps in adherence to guidelines, particularly in antimicrobial stewardship, hemodynamic support, infection monitoring, and documentation. Although many aspects of supportive care were implemented according to current standards, retrospective evaluation of the patient's ICU course was limited by gaps in the clinical record. It remains unclear whether these reflect true deficiencies in care or incomplete access to documentation. In critically ill cancer patients, distinguishing between sepsis and malignancy-associated inflammation is notoriously difficult. This case highlights how careful documentation and daily reassessment are essential not only for patient care, but also for understanding what may have contributed to clinical deterioration.
A comparison with another MPM case illustrates the variability in disease progression and treatment response, even among patients with similar histology. Although both patients had the same tumor subtype and a similar clinical presentation at the time of diagnosis, their divergent courses reveal how treatment response can vary significantly. While one case stabilized with first-line therapy, the other required multiple treatment changes before immunotherapy finally achieved temporary disease control. This demonstrates the importance of tailoring therapy to individual factors such as staging depth, comorbid conditions, overall physical status, and early signs of treatment effectiveness.
Several clinical lessons emerge from this case. Taking a thorough exposure history should be standard practice in all patients with pleural symptoms, regardless of age or known risk profile. Comprehensive staging may not have altered the therapeutic approach in this case due to advanced disease and lack of surgical intent, but it could have improved prognostic clarity

and informed potential eligibility for clinical trials or future care planning. In the ICU, meticulous documentation and regular evaluation of antimicrobial use should be prioritized, especially in complex oncologic patients where the source of inflammation may be multifactorial. In addition, early involvement of multidisciplinary teams may improve continuity of care and ensure that treatment decisions are made with full awareness of both oncologic and critical care perspectives.

In summary, this case confirms that real-world management of MPM often operates at the interface between guideline recommendations and practical limitations. Thorough exposure history, guideline-based staging, and flexible treatment strategies aligned with updated evidence are essential to optimizing patient outcomes. Ultimately, malignant pleural mesothelioma remains a complex disease that demands individualized, multidisciplinary approach throughout all stages of diagnosis, treatment, and supportive care. As the disease is relatively rare and often presents at an advanced stage, continued clinical and biomedical research is essential to improve early detection, treatment efficacy, and overall patient survival.

8. LIST OF REFERENCES

1. Brims F. Epidemiology and Clinical Aspects of Malignant Pleural Mesothelioma. Cancers (Basel). 20. August 2021;13(16):4194.

2. Kim J, Bhagwandin S, Labow DM. Malignant peritoneal mesothelioma: a review. Ann Transl Med. Juni 2017;5(11):236.

3. Schumann SO, Kocher G, Minervini F. Epidemiology, diagnosis and treatment of the malignant pleural mesothelioma, a narrative review of literature. J Thorac Dis. April 2021;13(4):2510–23.

4. Geltner C, Errhalt P, Baumgartner B, Ambrosch G, Machan B, Eckmayr J, u. a. Management of malignant pleural mesothelioma - part 1: epidemiology, diagnosis, and staging : Consensus of the Austrian Mesothelioma Interest Group (AMIG). Wien Klin Wochenschr. September 2016;128(17–18):611–7.

5. Świątkowska B, Szeszenia-Dąbrowska N. Mesothelioma continues to increase even 40 years after exposure - Evidence from long-term epidemiological observation. Lung Cancer. Juni 2017;108:121–5.

6. Wang Q, Xu C, Wang W, Zhang Y, Li Z, Song Z, u. a. Chinese expert consensus on the diagnosis and treatment of malignant pleural mesothelioma. Thorac Cancer. September 2023;14(26):2715–31.

7. Røe OD, Stella GM. Malignant pleural mesothelioma: history, controversy and future of a manmade epidemic. Eur Respir Rev. März 2015;24(135):115–31.

8. Kerger BD. Longevity and pleural mesothelioma: age-period-cohort analysis of incidence data from the Surveillance, Epidemiology, and End Results (SEER) Program, 1973-2013. BMC Res Notes. 23. Mai 2018;11(1):337.

9. Oddone E, Bollon J, Nava CR, Consonni D, Marinaccio A, Magnani C, u. a. Effect of Asbestos Consumption on Malignant Pleural Mesothelioma in Italy: Forecasts of Mortality up to 2040. Cancers (Basel). 3. Juli 2021;13(13):3338.

10. Brustugun OT, Nilssen Y, Eide IJZ. Epidemiology and outcome of peritoneal and pleural mesothelioma subtypes in Norway. A 20 year nation-wide study. Acta Oncol. Oktober 2021;60(10):1250–6.

11. Brims F, Kumarasamy C, Menon L, Olsen N, de Klerk N, Franklin P. The Western Australian Mesothelioma Registry: Analysis of 60 years of cases. Respirology. April 2024;29(4):288–94.

12. Marinaccio A, Binazzi A, Bonafede M, Corfiati M, Di Marzio D, Scarselli A, u. a. Malignant mesothelioma due to non-occupational asbestos exposure from the Italian national

surveillance system (ReNaM): epidemiology and public health issues. Occup Environ Med. September 2015;72(9):648–55.
13. Khella MS, Salem AM, Abdel-Rahman O, Saad AS. The Association Between the FTO rs9939609 Variant and Malignant Pleural Mesothelioma Risk: A Case-Control Study. Genet Test Mol Biomarkers. Februar 2018;22(2):79–84.
14. Tunesi S, Ferrante D, Mirabelli D, Andorno S, Betti M, Fiorito G, u. a. Gene-asbestos interaction in malignant pleural mesothelioma susceptibility. Carcinogenesis. Oktober 2015;36(10):1129–35.
15. Wadowski B, De Rienzo A, Bueno R. The Molecular Basis of Malignant Pleural Mesothelioma. Thorac Surg Clin. November 2020;30(4):383–93.
16. Bueno R, Stawiski EW, Goldstein LD, Durinck S, De Rienzo A, Modrusan Z, u. a. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet. April 2016;48(4):407–16.
17. Karpathiou G, Stefanou D, Froudarakis ME. Pleural neoplastic pathology. Respir Med. August 2015;109(8):931–43.
18. Goto Y, Shinjo K, Kondo Y, Shen L, Toyota M, Suzuki H, u. a. Epigenetic profiles distinguish malignant pleural mesothelioma from lung adenocarcinoma. Cancer Res. 1. Dezember 2009;69(23):9073–82.
19. Faversani A, Favero C, Dioni L, Pesatori AC, Bollati V, Montoli M, u. a. An EBC/Plasma miRNA Signature Discriminates Lung Adenocarcinomas From Pleural Mesothelioma and Healthy Controls. Front Oncol. 2021;11:643280.
20. de Reyniès A, Jaurand MC, Renier A, Couchy G, Hysi I, Elarouci N, u. a. Molecular classification of malignant pleural mesothelioma: identification of a poor prognosis subgroup linked to the epithelial-to-mesenchymal transition. Clin Cancer Res. 1. März 2014;20(5):1323–34.
21. Mei W, Yang SJ, Zhang YP, Fu QS, Xiong W, Zhao Y. [Analysis of clinicopathological features of 68 cases of malignant pleural mesothelioma]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 20. August 2023;41(8):588–93.
22. Lee HS, Jang HJ, Choi JM, Zhang J, de Rosen VL, Wheeler TM, u. a. Comprehensive immunoproteogenomic analyses of malignant pleural mesothelioma. JCI Insight. 5. April 2018;3(7):e98575, 98575.
23. Ceruti P, Lonni S, Baglivo F, Marchetti G. Endoscopic diagnosis and management of pleural effusion in malignant pleural mesothelioma. J Thorac Dis. Januar 2018;10(Suppl 2):S269–75.

24. Mansour MSI, Huseinzade A, Seidal T, Hejny K, Maty A, Taheri-Eilagh F, u. a. Comparison of immunohistochemical mesothelial biomarkers in paired biopsies and effusion cytology cell blocks from pleural mesothelioma. Cytopathology. September 2023;34(5):456–65.
25. Sundaralingam A, Bedawi EO, Rahman NM. Diagnostics in Pleural Disease. Diagnostics (Basel). 4. Dezember 2020;10(12):1046.
26. Kindler HL, Ismaila N, Armato SG, Bueno R, Hesdorffer M, Jahan T, u. a. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 1. Mai 2018;36(13):1343–73.
27. Nabeshima K, Hamasaki M, Kinoshita Y, Matsumoto S, Sa-Ngiamwibool P. Update of pathological diagnosis of pleural mesothelioma using genomic-based morphological techniques, for both histological and cytological investigations. Pathol Int. August 2022;72(8):389–401.
28. Viscardi G, Di Natale D, Fasano M, Brambilla M, Lobefaro R, De Toma A, u. a. Circulating biomarkers in malignant pleural mesothelioma. Explor Target Antitumor Ther. 2020;1(6):434–51.
29. Sun HH, Vaynblat A, Pass HI. Diagnosis and prognosis-review of biomarkers for mesothelioma. Ann Transl Med. Juni 2017;5(11):244.
30. Schillebeeckx E, van Meerbeeck JP, Lamote K. Clinical utility of diagnostic biomarkers in malignant pleural mesothelioma: a systematic review and meta-analysis. Eur Respir Rev. 31. Dezember 2021;30(162):210057.
31. Pass HI, Lott D, Lonardo F, Harbut M, Liu Z, Tang N, u. a. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. N Engl J Med. 13. Oktober 2005;353(15):1564–73.
32. Cavallari I, Urso L, Sharova E, Pasello G, Ciminale V. Liquid Biopsy in Malignant Pleural Mesothelioma: State of the Art, Pitfalls, and Perspectives. Front Oncol. 2019;9:740.
33. Matboli M, Shafei AE, Ali MA, Gaber AI, Galal A, Tarek O, u. a. Clinical significance of serum DRAM1 mRNA, ARSA mRNA, hsa-miR-2053 and lncRNA-RP1-86D1.3 axis expression in malignant pleural mesothelioma. J Cell Biochem. März 2019;120(3):3203–11.
34. Ferrari L, Carugno M, Mensi C, Pesatori AC. Circulating Epigenetic Biomarkers in Malignant Pleural Mesothelioma: State of the Art and critical Evaluation. Front Oncol. 2020;10:445.

35. Iadevaia C, D'Agnano V, Pagliaro R, Nappi F, Lucci R, Massa S, u. a. Diagnostic Accuracy of Ultrasound Guided Percutaneous Pleural Needle Biopsy for Malignant Pleural Mesothelioma. J Clin Med. 29. April 2024;13(9):2600.
36. Zhang Y, Tang J, Zhou X, Chen W, Zhang S, Li Y, u. a. Diagnostic ability and its influenced factors of ultrasound-guided percutaneous pleural needle biopsy diagnosis for malignant pleural mesothelioma. Front Surg. 2022;9:1022505.
37. Ghigna MR, Crutu A, Florea V, Soummer-Feulliet S, Baldeyrou P. The role of endobronchial ultrasound-guided fine needle aspiration in the diagnosis of pleural mesothelioma. Cytopathology. August 2016;27(4):284–8.
38. Cardinale L, Ardissone F, Gned D, Sverzellati N, Piacibello E, Veltri A. Diagnostic Imaging and workup of Malignant Pleural Mesothelioma. Acta Biomed. 23. August 2017;88(2):134–42.
39. Fortin M, Cabon E, Berbis J, Laroumagne S, Guinde J, Elharrar X, u. a. Diagnostic Value of Computed Tomography Imaging Features in Malignant Pleural Mesothelioma. Respiration. 2020;99(1):28–34.
40. Usuda K, Iwai S, Funasaki A, Sekimura A, Motono N, Matoba M, u. a. Diffusion-Weighted Imaging Can Differentiate between Malignant and Benign Pleural Diseases. Cancers (Basel). 12. Juni 2019;11(6):811.
41. Falaschi F, Romei C, Fiorini S, Lucchi M. Imaging of malignant pleural mesothelioma: it is possible a screening or early diagnosis program?-a systematic review about the use of screening programs in a population of asbestos exposed workers. J Thorac Dis. Januar 2018;10(Suppl 2):S262–8.
42. Barbieri PG, Mirabelli D, Magnani C, Brollo A. On the diagnosis of malignant pleural mesothelioma: A necropsy-based study of 171 cases (1997-2016). Tumori. August 2019;105(4):304–11.
43. Neilly MDJ, Pearson J, Thu AW, MacRae C, Blyth KG. Contemporary management of mesothelioma. Breathe (Sheff). Juni 2024;20(2):230175.
44. Lapidot M, Sattler M. The Role of Surgery in Pleural Mesothelioma. Cancers (Basel). 28. April 2024;16(9):1719.
45. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, u. a. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 15. Juli 2003;21(14):2636–44.
46. John A, O'Sullivan H, Popat S. Updates in Management of Malignant Pleural Mesothelioma. Curr Treat Options Oncol. Dezember 2023;24(12):1758–89.

47. Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, u. a. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol. August 2011;12(8):763–72.
48. Bellini A, Mazzarra S, Sterrantino S, Argnani D, Stella F. Second Surgery for Recurrent Malignant Pleural Mesothelioma after Multimodality Treatment: A Systematic Review. J Clin Med. 10. Juni 2022;11(12):3340.
49. Macleod N, Price A, O'Rourke N, Fallon M, Laird B. Radiotherapy for the treatment of pain in malignant pleural mesothelioma: a systematic review. Lung Cancer. Februar 2014;83(2):133–8.
50. Manegold C. Pemetrexed (Alimta, MTA, multitargeted antifolate, LY231514) for malignant pleural mesothelioma. Semin Oncol. August 2003;30(4 Suppl 10):32–6.
51. Taylor P, Castagneto B, Dark G, Marangolo M, Scagliotti GV, van Klaveren RJ, u. a. Single-agent pemetrexed for chemonaïve and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. J Thorac Oncol. Juli 2008;3(7):764–71.
52. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, u. a. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2. April 2016;387(10026):1405–14.
53. Cedres S, Assaf JD, Iranzo P, Callejo A, Pardo N, Navarro A, u. a. Efficacy of chemotherapy for malignant pleural mesothelioma according to histology in a real-world cohort. Sci Rep. 1. November 2021;11(1):21357.
54. Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, u. a. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 30. Januar 2021;397(10272):375–86.
55. McNamee N, Harvey C, Gray L, Khoo T, Lingam L, Zhang B, u. a. Brief Report: Real-World Toxicity and Survival of Combination Immunotherapy in Pleural Mesothelioma-RIOMeso. J Thorac Oncol. April 2024;19(4):636–42.
56. Piha-Paul SA, Oh DY, Ueno M, Malka D, Chung HC, Nagrial A, u. a. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies. Int J Cancer. 15. Oktober 2020;147(8):2190–8.

57. Banna GL, Addeo A, Zygoura P, Tsourti Z, Popat S, Curioni-Fontecedro A, u. a. A prognostic score for patients with malignant pleural mesothelioma (MPM) receiving second-line immunotherapy or chemotherapy in the ETOP 9-15 PROMISE-meso phase III trial. Lung Cancer. Juli 2022;169:77–83.
58. Fennell DA, Casbard AC, Porter C, Rudd R, Lester JF, Nicolson M, u. a. A randomized phase II trial of oral vinorelbine as second-line therapy for patients with malignant pleural mesothelioma. JCO. 20. Mai 2021;39(15_suppl):8507–8507.
59. Scherpereel A, Mazieres J, Greillier L, Lantuejoul S, Dô P, Bylicki O, u. a. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol. Februar 2019;20(2):239–53.
60. Pinto C, Zucali PA, Pagano M, Grosso F, Pasello G, Garassino MC, u. a. Gemcitabine with or without ramucirumab as second-line treatment for malignant pleural mesothelioma (RAMES): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. Oktober 2021;22(10):1438–47.
61. Bertin B, Zugman M, Schvartsman G. The Current Treatment Landscape of Malignant Pleural Mesothelioma and Future Directions. Cancers (Basel). 12. Dezember 2023;15(24):5808.
62. Belderbos RA, Baas P, Berardi R, Cornelissen R, Fennell DA, van Meerbeeck JP, u. a. A multicenter, randomized, phase II/III study of dendritic cells loaded with allogeneic tumor cell lysate (MesoPher) in subjects with mesothelioma as maintenance therapy after chemotherapy: DENdritic cell Immunotherapy for Mesothelioma (DENIM) trial. Transl Lung Cancer Res. Juni 2019;8(3):280–5.
63. Rintoul RC, Ritchie AJ, Edwards JG, Waller DA, Coonar AS, Bennett M, u. a. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet. 20. September 2014;384(9948):1118–27.
64. Batirel HF. Extrapleural pneumonectomy (EPP) vs. pleurectomy decortication (P/D). Ann Transl Med. Juni 2017;5(11):232.
65. Lewis GD, Dalwadi SM, Farach A, Brian Butler E, Teh BS. The Role of Adjuvant Radiotherapy in the Treatment of Pleural Mesothelioma. Ann Surg Oncol. Juni 2019;26(6):1879–85.
66. Lim E, Darlison L, Edwards J, Elliott D, Fennell DA, Popat S, u. a. Mesothelioma and Radical Surgery 2 (MARS 2): protocol for a multicentre randomised trial comparing

(extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma. BMJ Open. 1. September 2020;10(9):e038892.
67. Cao C, Tian D, Manganas C, Matthews P, Yan TD. Systematic review of trimodality therapy for patients with malignant pleural mesothelioma. Ann Cardiothorac Surg. November 2012;1(4):428–37.
68. Bellini A, Dell'Amore A, Terzi S, Zambello G, Zuin A, Pasello G, u. a. Relapse Patterns and Tailored Treatment Strategies for Malignant Pleural Mesothelioma Recurrence after Multimodality Therapy. J Clin Med. 8. März 2021;10(5):1134.
69. Bertoglio P, Ambrogi MC, Chella A, Aprile V, Dini P, Korasidis S, u. a. Is less also better? A single-institution experience on treatment of early stage Malignant Pleural Mesothelioma. Eur J Surg Oncol. Juli 2017;43(7):1365–71.
70. Banks KC, Ossowski S, Hung YY, Hsu DS, Ashiku SK, Patel AR, u. a. Comparison of Survival by Multimodal Treatment Regimen Among Malignant Pleural Mesothelioma Patients in an Integrated Health System. Clin Lung Cancer. Dezember 2022;23(8):694–701.
71. MacLeod N, Chalmers A, O'Rourke N, Moore K, Sheridan J, McMahon L, u. a. Is Radiotherapy Useful for Treating Pain in Mesothelioma?: A Phase II Trial. J Thorac Oncol. Juni 2015;10(6):944–50.
72. Bayman N, Ardron D, Ashcroft L, Baldwin DR, Booton R, Darlison L, u. a. Protocol for PIT: a phase III trial of prophylactic irradiation of tracts in patients with malignant pleural mesothelioma following invasive chest wall intervention. BMJ Open. 27. Januar 2016;6(1):e010589.
73. Clive AO, Taylor H, Dobson L, Wilson P, de Winton E, Panakis N, u. a. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. Lancet Oncol. August 2016;17(8):1094–104.
74. Stahel RA, Riesterer O, Xyrafas A, Opitz I, Beyeler M, Ochsenbein A, u. a. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial. Lancet Oncol. Dezember 2015;16(16):1651–8.
75. Rimner A, Zauderer MG, Gomez DR, Adusumilli PS, Parhar PK, Wu AJ, u. a. Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) As Part of Lung-Sparing Multimodality Therapy in Patients With Malignant Pleural Mesothelioma. J Clin Oncol. 10. August 2016;34(23):2761–8.

76. Nakanishi-Imai M, Murai T, Onishi M, Mouri A, Komiyama T, Omura M, u. a. Survey of malignant pleural mesothelioma treatment in Japan: Patterns of practice and clinical outcomes in tomotherapy facilities. J Radiat Res. 17. März 2022;63(2):281–9.
77. Shin JY, Offin M, Simone CB, Zhang Z, Shepherd AF, Wu AJ, u. a. Clinical outcomes of stereotactic body radiation therapy for malignant pleural mesothelioma. Radiother Oncol. Februar 2024;191:110057.
78. Pease DF, Kratzke RA. Oncolytic Viral Therapy for Mesothelioma. Front Oncol. 2017;7:179.
79. Ebinç S, Oruç Z, Kalkan Z, Karhan O, Urakçı Z, Küçüköner M, u. a. Prognostic factors and the prognostic role of inflammation indices in malignant pleural mesothelioma. Turk Gogus Kalp Damar Cerrahisi Derg. Januar 2023;31(1):105–15.
80. Van Gerwen M, Alpert N, Wolf A, Ohri N, Lewis E, Rosenzweig KE, u. a. Prognostic factors of survival in patients with malignant pleural mesothelioma: an analysis of the National Cancer Database. Carcinogenesis. 10. Juni 2019;40(4):529–36.
81. Ergönül AG, Aydın S, Kahraman Aydın S, Akçam Tİ, Özdil A, Turhan K, u. a. Survival of pleurectomy-decortication and hyperthermic chemotherapy in mesothelioma. Turk Gogus Kalp Damar Cerrahisi Derg. Juli 2023;31(3):381–7.
82. Marshall AD, Bayes HK, Bardgett J, Wedderburn S, Kerr KM, Currie GP. Survival from malignant mesothelioma: where are we now? J R Coll Physicians Edinb. 2015;45(2):123–6.
83. Guzmán-Casta J, Carrasco-CaraChards S, Guzmán-Huesca J, Sánchez-Ríos CP, Riera-Sala R, Martínez-Herrera JF, u. a. Prognostic factors for progression-free and overall survival in malignant pleural mesothelioma. Thorac Cancer. April 2021;12(7):1014–22.
84. Ringgaard Petersen T, Panou V, Meristoudis C, Weinreich UM, Røe OD. Clinical prognostic factors in pleural mesothelioma: best supportive care and anti-tumor treatments in a real-life setting. Acta Oncol. April 2021;60(4):521–7.
85. Billé A, Krug LM, Woo KM, Rusch VW, Zauderer MG. Contemporary Analysis of Prognostic Factors in Patients with Unresectable Malignant Pleural Mesothelioma. J Thorac Oncol. Februar 2016;11(2):249–55.
86. Rahouma M, Aziz H, Ghaly G, Kamel M, Loai I, Mohamed A. Survival in Good Performance Malignant Pleural Mesothelioma Patients; Prognostic Factors and Predictors of Response. Asian Pac J Cancer Prev. 27. August 2017;18(8):2073–8.
87. Sun HH, Vaynblat A, Pass HI. Diagnosis and prognosis-review of biomarkers for mesothelioma. Ann Transl Med. Juni 2017;5(11):244.

88. Fournel L, Charrier T, Huriet M, Iaffaldano A, Lupo A, Damotte D, u. a. Prognostic impact of inflammation in malignant pleural mesothelioma: A large-scale analysis of consecutive patients. Lung Cancer. April 2022;166:221–7.
89. Tanrikulu AC, Abakay A, Komek H, Abakay O. Prognostic value of the lymphocyte-to-monocyte ratio and other inflammatory markers in malignant pleural mesothelioma. Environ Health Prev Med. September 2016;21(5):304–11.
90. Otoshi T, Kataoka Y, Kaku S, Iki R, Hirabayashi M. Prognostic Impact of Inflammation-related Biomarkers on Overall Survival of Patients with Inoperable Malignant Pleural Mesothelioma. In Vivo. 2018;32(2):445–50.
91. Dick IM, Lee YCG, Cheah HM, Miranda A, Robinson BWS, Creaney J. Profile of soluble factors in pleural effusions predict prognosis in mesothelioma. Cancer Biomark. 2022;33(1):159–69.
92. Zhang A, Cao S, Jin S, Cao J, Shen J, Pan B, u. a. Elevated aspartate aminotransferase and monocyte counts predict unfavorable prognosis in patients with malignant pleural mesothelioma. Neoplasma. 2017;64(1):114–22.
93. Berardi R, Fiordoliva I, De Lisa M, Ballatore Z, Caramanti M, Morgese F, u. a. Clinical and pathologic predictors of clinical outcome of malignant pleural mesothelioma. Tumori. 2016;102(2):190–5.
94. Akgun H, Metintas S, Ak G, Demirkol Canlı S, Isbilen M, Gure AO, u. a. Prognostic value of midkine, syndecan-1, hyaluronan synthase-2, sestrin-1, laminin subunit alpha-4 and fibulin-3 for malignant pleural mesothelioma. Arch Med Sci. 2023;19(2):355–64.
95. Klotz LV, Casjens S, Johnen G, Taeger D, Brik A, Eichhorn F, u. a. Combination of calretinin, MALAT1, and GAS5 as a potential prognostic biomarker to predict disease progression in surgically treated mesothelioma patients. Lung Cancer. Juni 2024;192:107802.
96. Marcq E, Siozopoulou V, De Waele J, van Audenaerde J, Zwaenepoel K, Santermans E, u. a. Prognostic and predictive aspects of the tumor immune microenvironment and immune checkpoints in malignant pleural mesothelioma. Oncoimmunology. 2017;6(1):e1261241.
97. Kadota K, Villena-Vargas J, Nitadori JI, Sima CS, Jones DR, Travis WD, u. a. Tumoral CD10 expression correlates with aggressive histology and prognosis in patients with malignant pleural mesothelioma. Ann Surg Oncol. September 2015;22(9):3136–43.
98. Mansfield AS, Peikert T, Vogelzang NJ, Symanowski JT. Effects of Reduction in Tumor Burden on Survival in Epithelioid Malignant Pleural Mesothelioma. Mayo Clin Proc. August 2018;93(8):1026–33.

99. Rosen LE, Karrison T, Ananthanarayanan V, Gallan AJ, Adusumilli PS, Alchami FS, u. a. Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study. Mod Pathol. April 2018;31(4):598–606.
100. Habougit C, Trombert-Paviot B, Karpathiou G, Casteillo F, Bayle-Bleuez S, Fournel P, u. a. Histopathologic features predict survival in diffuse pleural malignant mesothelioma on pleural biopsies. Virchows Arch. Juni 2017;470(6):639–46.
101. Proto C, Signorelli D, Mallone S, Prelaj A, Lo Russo G, Imbimbo M, u. a. The Prognostic Role of TNM Staging Compared With Tumor Volume and Number of Pleural Sites in Malignant Pleural Mesothelioma. Clin Lung Cancer. November 2019;20(6):e652–60.
102. Popat S, Baas P, Faivre-Finn C, Girard N, Nicholson AG, Nowak AK, u. a. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Annals of Oncology. 1. Februar 2022;33(2):129–42.
103. Baas P, Fennell D, Kerr KM, Schil PEV, Haas RL, Peters S. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up †. Annals of Oncology. 1. September 2015;26:v31–9.
104. Zauderer MG, Kass SL, Woo K, Sima CS, Ginsberg MS, Krug LM. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. Lung Cancer. Juni 2014;84(3):271–4.
105. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, u. a. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine. November 2021;49(11):e1063.
106. Timsit JF, Azoulay E, Schwebel C, Charles PE, Cornet M, Souweine B, u. a. Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure: The EMPIRICUS Randomized Clinical Trial. JAMA. 18. Oktober 2016;316(15):1555–64.
107. Leone M, Bechis C, Baumstarck K, Lefrant JY, Albanèse J, Jaber S, u. a. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med. Oktober 2014;40(10):1399–408.
108. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, u. a. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med. September 2011;39(9):2048–58.

109. Layios N, Lambermont B, Canivet JL, Morimont P, Preiser JC, Garweg C, u. a. Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. Crit Care Med. August 2012;40(8):2304–9.
110. Najafi A, Khodadadian A, Sanatkar M, Shariat Moharari R, Etezadi F, Ahmadi A, u. a. The Comparison of Procalcitonin Guidance Administer Antibiotics with Empiric Antibiotic Therapy in Critically Ill Patients Admitted in Intensive Care Unit. Acta Med Iran. 2015;53(9):562–7.
111. Hylands M, Moller MH, Asfar P, Toma A, Frenette AJ, Beaudoin N, u. a. A systematic review of vasopressor blood pressure targets in critically ill adults with hypotension. Can J Anaesth. Juli 2017;64(7):703–15.
112. Alphonsus CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. Anaesthesia. Juli 2014;69(7):777–84.
113. Rygård SL, Butler E, Granholm A, Møller MH, Cohen J, Finfer S, u. a. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. Juli 2018;44(7):1003–16.
114. Arabi YM, Al-Hameed F, Burns KEA, Mehta S, Alsolamy SJ, Alshahrani MS, u. a. Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis. N Engl J Med. 4. April 2019;380(14):1305–15.
115. Yatabe T, Inoue S, Sakaguchi M, Egi M. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. Intensive Care Med. Januar 2017;43(1):16–28.
116. Jaber S, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, u. a. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet. 7. Juli 2018;392(10141):31–40.
117. Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. Am J Surg. April 2002;183(4):390–8.
118. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. Nutr Clin Pract. 2009;24(3):305–15.
119. Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, u. a. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 13. Januar 2018;391(10116):133–43.

120. Rhazari M, Moueqqit O, Gartini S, El Morabit S, Diani S, Aharmim M, u. a. Unexplained Pleural Effusion Leads to the Revelation of a Malignant Mesothelioma: A Case Report. Cureus. April 2022;14(4):e24478.

9. ANNEXES

Annex 1: High-Level Timeline

Date	Event	Details
2020-08-03	Initial presentation	Patient experienced shortness of breath and chest pain. Diagnosed with somatoform dysfunction at VCKH
2020-08-21	Admission to hospital	Patient referred due to pleural effusion; admitted for further evaluation and treatment. Elevated D-dimers and CRP.
2020-08-21	Chest CT Angiography	Pulmonary embolism, left pneumothorax, pleural effusion, and basal segment atelectasis identified.
2020-08-25	Pleural drainage procedure	800 mL serous fluid drained. Cytology revealed reactive mesothelial changes; no malignant cells.
2020-09-11	Discharge	Condition improved: no dyspnea. Discharged under anticoagulation.
2020-10-08	Chest CT Angiography	No pulmonary thrombi; RV/LV ratio decreased.
2021-01-13	VATS pleural biopsy	Uneventful procedure. Biopsy performed for histological confirmation.
2021-01-19	Histological diagnosis	Epithelioid mesothelioma confirmed: Calretinin, BAP1, CK7, WT1 positive. Tumor tissue 2.2 × 1.8 × 0.6 cm.
2021-01-20	Tumorboard	Multidisciplinary decision: Cisplatin and Pemetrexed chemotherapy recommended.
2021-02-05	First chemotherapy session	First cycle of Cisplatin and Pemetrexed administered. Treatment completed without complications.

2021-09-02	Chest CT	Revealed disease progression: reduced paramediastinal masses but increased interlobar pleura lesions and new right lung lesion.
2021-09-06	Multidisciplinary team conclusions	Progression confirmed. Gemcitabine monotherapy recommended.
2021-09-21	First Gemcitabine chemotherapy cycle	Gemcitabine monotherapy initiated. No complications reported.
2021-11-19	Chest CT	Growth in left pleural masses, interlobar fissure lesions, and masses above the diaphragm. No new lesions observed. Radiological progression confirmed. Admission for Docetaxel chemotherapy planned.
2021-12-03	First Docetaxel cycle	First cycle of Docetaxel administered without complications.
2022-03-16	Chest CT	21% increase in target lesion size since Docetaxel discontinued; Nivolumab initiated.
2023-01-24	Nivolumab treatment ongoing	After 20 cycles, chest CT showed stable target lesions (51 mm) and reduced non-target lesions. Patient reports improved well-being.
2023-03-18	ICU admission	Treated for sepsis, bilateral pneumonia, UTI, and delirium. Oxygen therapy and antibiotics initiated.
2023-04-19	Neurologist consultation and LP	CSF findings consistent with systemic inflammation. No evidence of neuroinfection or carcinomatosis. MRI or head CT angiography suggested for thrombosis exclusion.
2023-04-19	Head CT and CT Angiography	Right internal carotid artery stenosis ~40%. No acute brain changes, hemorrhage, or perfusion defects.
2023-04-24	Hospital discharge	Stable condition. Palliative care recommended due to advanced oncological

		disease (ECOG 4). Transferred to palliative care facility.

Annex 2: Overview of MPM treatment timeline:

1. Cisplatin and Pemetrexed: 6 cycles administered, followed by disease progression.
2. Gemcitabine: 2 cycles administered, followed by disease progression.
3. Docetaxel: 4 cycles administered, followed by disease progression.
4. Nivolumab: 21 cycles administered, followed by ICU admission.