Comparison of outcomes of surgical and other invasive treatment modalities for malignant pleural effusion in patients with pleural carcinosis

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Master's thesis / Diplomski rad

2022

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Split, School of Medicine / Sveučilište u Splitu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:171:563174

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Joshua Schramm

COMPARISON OF OUTCOMES OF SURGICAL AND OTHER INVASIVE TREATMENT MODALITIES FOR MALIGNANT PLEURAL EFFUSION IN PATIENTS WITH PLEURAL CARCINOSIS

Diploma Thesis

Academic year:
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Coburg, August 2022

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ACKNOWLEDGEMENT

"One chance is all you need"- Jesse Owens. This quote resembles my journey and dream of becoming a doctor quite well. Being a physician is not just a job, not just another avenue, it is a calling. For me, practicing medicine is a privilege and I am very grateful that this exceptional opportunity has been given to me. Therefore, I want to deeply thank everyone responsible and involved in the newly established cooperation between the Medical School Regiomed and the University of Split School of Medicine (USSM) for making this possible and giving me the chance to accomplish my dream. Being one of the first "pioneers", graduating from this program, makes me really proud and I hope this cooperation will only prosper and remain for the future.

I want to express my special gratitude to Prof. Dr. med. Johannes Brachmann, not only for being one of the main initiators of the Medical School Regiomed, but also for being my mentor as well as always having an open ear during the entire journey and someone I look up to as a role model.

Furthermore, I especially want to thank Dr. med. Zsolt Sziklavari, PhD as my mentor, who always had time for my issues and helped me resolve them in every possible way. He is an essential contributor to the completion of this work.

Additionally, I want to thank Luise Gehring, MD. She was the first one telling me about the Medical School Regiomed and because of her support and belief, I was able to apply to this program. She is one of the cornerstones of my professional career.

Noteworthy to mention is also Prof. dr. sc. Dragan Primorac, who inspired me from day one of my medical education. Because of him and his quote "Excellence is not a matter of chance, it is a matter of choice", he helped me study hard and realize what is at stake. Patients will put their lives into my hands in the future and therefore I owe them, to give them, my very very best.

I also want to express my appreciation to Prof. Dr. med. Gerhard Grabenbauer, who was the first introducing me to scientific work and made me realize what it really means. Besides this,

I perceive him as an excellent physician, who embodies medical tradition, knowledge and virtues and is able to translate this into patient care.

I would also like to thank Elina Eslauer for her support. She is currently a resident of anaesthesiology at the REGIOMED-clinics in Coburg.

Another person not to forget to mention, is my dearest Judith. I want to thank her, for all the support, inspiration, her belief in me as well as for the strength she gave me in all aspects of my life and during my studies.

Lastly, but very importantly, there are not enough words able to express my deepest gratitude to my parents, who made it possible for me to achieve my goal and dream of becoming a doctor. I want to thank them for every imaginable support through all these years, their sacrifices, motivation, patience, their trust in me as well as their unconditional love.
Danke Mama, danke Papa, für Alles, was ihr für mich getan habt!

LIST OF ABBREVIATIONS

AE – Adverse event

ALK – Anaplastic lymphoma kinase

ANG – Angiopoietin

BC – Breast cancer

CCL – Chemokine (C-C motif) ligand

CEA – Carcinoembryonic antigen

CI – Confidence interval

CRC – Colorectal cancer

CT – Computed tomography

CUP – Cancer of unknown primary

ECOG – Eastern Cooperative Oncology Group

EGFR – Epidermal growth factor receptor

ER – Estrogen receptor

FDG – Fluorodeoxyglucose

FIGO – International Federation of Gynecology and Obstetrics

HER – Human epidermal growth factor receptor

HL – Hodgkin lymphoma

IFN – Interferon

IL – Interleukin

INR – International normalized ratio

IPC – Indwelling pleural catheter

IRB – Institutional review board

LC – Lung cancer

LDH – Lactate dehydrogenase

LOS – Length of stay

mCRC – metastatic colorectal cancer

MMP – Matrix-metalloproteinase

MPE – Malignant pleural effusion

MPM – Malignant pleural mesothelioma

MRI – Magnetic resonance imaging

MT – Medical thoracoscopy

NHL – Non-Hodgkin lymphoma

NSCLC – Non-small cell lung cancer

OC – Ovarian cancer

OPN – Osteopontin

OR – Odds ratio

PA – Posteroanterior

PDGF – Platelet-derived growth factor

PET – Positron-emission tomography

PR – Progesterone receptor

QoL – Quality of life

RCC – Renal cell carcinoma

RCT – Randomized controlled trial

SCC – Squamous cell carcinoma

SCLC – Small-cell lung cancer

TGF – Transforming growth factor

TIMP – Tissue inhibitor of metalloproteases

TLC – Total lung capacity

TNBC – Triple-negative breast cancer

TNF – Tumor necrosis factor

TPC – Tunneled pleural catheter

US – Ultrasound

VATS – Video-assisted-thoracoscopic surgery

VEGF – Vascular endothelial growth factor

WBC – White blood cell

1. INTRODUCTION

1.1. Epidemiology

With the exception of cardiovascular diseases, malignant neoplasia is the most common cause of death not only in Germany, but also globally (1,2). Even though all malignancies have the propensity to involve the pleural cavity, some of them are more likely to affect the chest (3). Characteristic for a malignant pleural effusion (MPE) is the existence of malignant neoplastic cells (3,4). Metastatic tumors are much more frequent than primary pleural tumors, however an increasingly common cause of MPE, especially in industrialized nations, is malignant pleural mesothelioma (MPM) (5). Because of the lungs' close anatomical proximity to the pleura, lung cancer is the most common cause of malignant pleural effusion (accounting for approximately 40%) of all cases (6). The second most frequent cause is metastatic breast cancer (approximately 25%), followed by lymphoma (approximately 10%), ovarian cancer (approximately 5%), gastro- intestinal cancers (approximately 5%) and MPM (4%) (2,5). In nearly 5-10% of malignant pleural effusions, no primary tumor is discovered. These cases are described as CUP (cancer of unknown primary) (7). Malignant pleural effusion due to pleural carcinosis is one of the most common findings in oncology (2).

The annual incidence of malignant pleural effusion is approaching 150 000 cases in the United States and 100 000 cases in Europe (2,8,9). Approximately 22% of all effusions have a malignant etiology (10). About half of patients with tumor develop a pleural effusion and, as the cancer incidence rises and the overall survival improves, the prevalence of MPE is expected to increase (11). Usually, effusions signalize progressed malignant disease, with expected survival times approaching 3-12 months after first diagnosis (12,13). Pleural carcinosis found in patients suffering from lung cancer displays an estimated 5-year survival rate of approximately 3% (13). Frequently encountered symptoms in patients suffering from malignancy-related pleural effusions include pain in the chest, sensation of breathlessness and cough. The severity degree of symptomatology is dependent on rapidity of development and volume of the effusion as well as the general cardiopulmonary status of the patient (4).

1.2. Pleural Effusion

1.2.1. Anatomy and Physiology of Pleural Effusion

Formation of the pleural space occurs during embryogenesis between weeks four to seven. Both, the visceral and parietal pleura are derived from the lateral plate mesoderm, splitting the somatopleuric mesoderm into two distinct layers, one giving rise to the parietal membrane and the other one to the splanchnopleuric mesoderm of the visceral membrane. Both play a critical role in regulating homeostasis within the pleural space (13,14). The mesothelium, lining the pleural cavity, engulfs the inner aspects of the thoracic wall and parietal as well as visceral surfaces of the lung. It is a monolayer of mesothelial cells and derived from the embryonic mesoderm (13). Those cells are pavement-like and resemble the cytological properties of other cells found in cavitary linings of the body (13,15). Mesothelial cells found in the pleura constitute the majority of prevailing cells and are chiefly responsible for the initiation of reactions to harmful substances or stimulation (13,14). A wide variety of molecules are produced by those cells including glycoproteins, hyaluronic acid, growth factor beta 1 as well as nitrous oxide to name a few (13,16).

Figure 1a presents a basic representation of the anatomical situation within the thorax (4). The pleural space is located between the parietal portion and the visceral portion of the pleura. The lining of the parietal pleura spans the entire chest wall from the inside, ranging from the medial mediastinum bilaterally over both leaflets of the diaphragm subcostally, all the way to the inner aspect of the ribs and associated musculature, while the visceral pleura forms a closely approximated covering around the lung parenchyma. Both pleural membranes are joined at the hilar region (13,17). The normal pleural space is approximately 18 to 20 μm in width, although it widens at its most dependent areas. It has been shown that the pleural membranes do not touch each other and that the pleural space is not just a potential space, but a real gap (6). Strong adherence of visceral to parietal pleura is achieved by maintaining slight negative pressure within the intrapleural space (13,16).

Figure 1b shows the forces balancing and regulating the volume and rate of fluid turnover in the pleural space. Key regulators of pleural fluid resorption are lymphatic vessels of the pleura (4). The flow in these vessels can increase by a factor of 20 if more than the usual amount of pleural fluid is produced, which means the pleural lymphatic resorbing system has a large reserve capacity (18). Physiologically, 0.26 mL/kg body weight of fluid accumulates in the pleural space with an hourly exchange of 11% (2,13,16). Before passing into the pleural space, pleural fluid must pass through the systemic capillaries, pleural interstitium and pleural membrane (19). The distance between the intercostal arteries, providing blood supply to the parietal pleura, and the pleural membrane is 10-12 μm, whereas the distance between pleural membrane and bronchial arteries, supplying blood to the visceral pleura, is 20-50 μm (19). Additionally, the filtration pressure found in the intercostal arteries is higher than the filtration pressure of the bronchial arteries (17). Since the parietal pleura thickness is less than that of the visceral pleura, it is believed, that most of the fluid originates from the parietal pleura (14,17). Therefore, the parietal pleura is regarded as the most effective surgical target for controlling an MPE (14,16,17) .

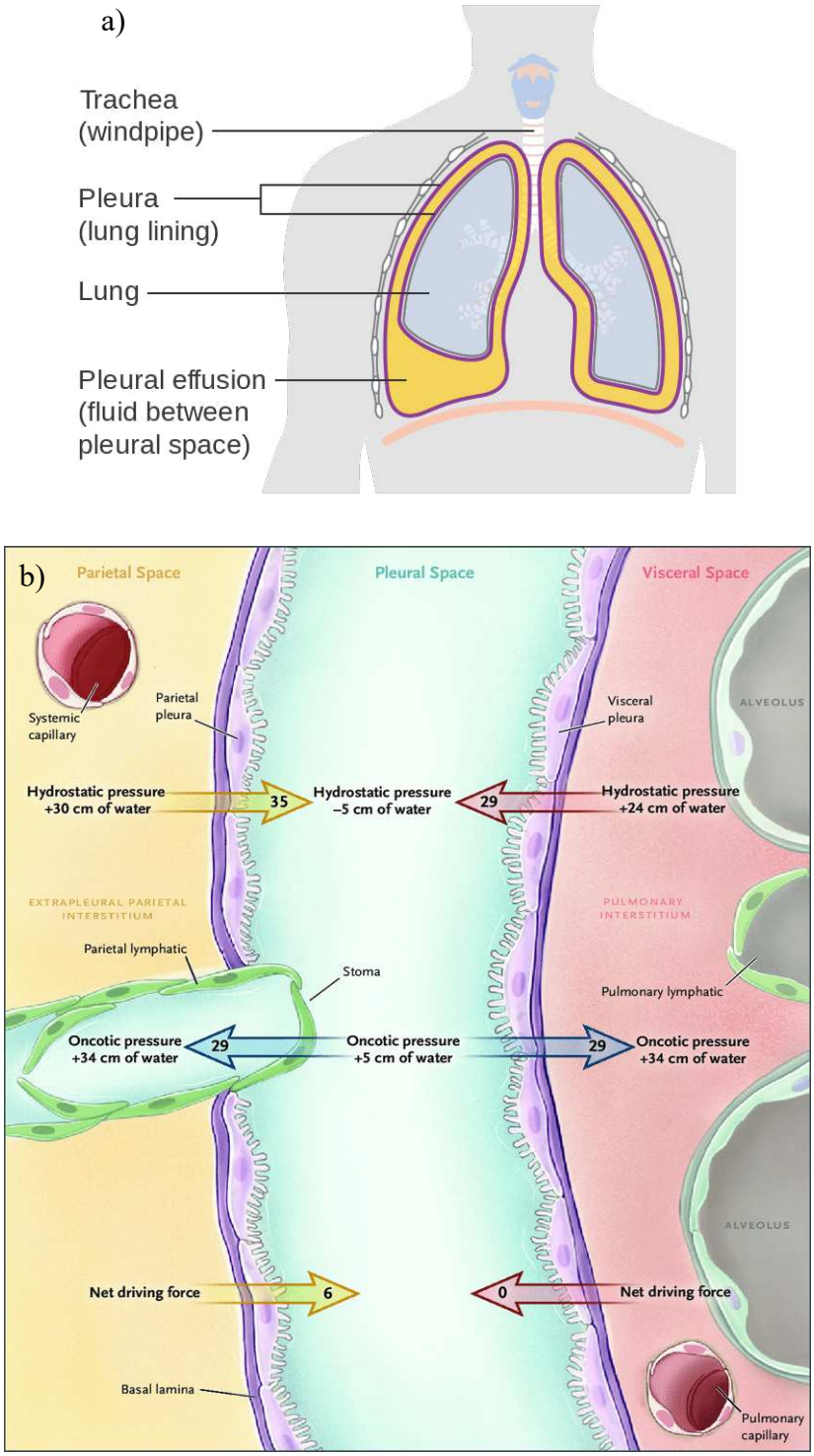


Figure 1. Basic illustration of pleural effusion in the pleural space (a) and the physiologic aspects of fluid turnover (b).
(a) Simplified anatomic representation of the lungs, the parietal and visceral pleura, surrounding them with depiction of pleural fluid accumulation in the pleural cavity (4); (b) Shown is the visceral, pleural as well as parietal space. Equilibrium of fluid production and reabsorption is achieved and balanced through forces generated by hydrostatic and colloid-osmotic (oncotic) pressures. Elastic recoil of the thoracic wall and lung and surface tension from alveolar fluids create slightly negative pressure (~–5 mmHg) within the pleural space. This prevents collapse of the lung and facilitates inflation. Pleural fluid is mainly produced from the parietal pleura as a result of hydrostatic pressure differences between parietal pleura and visceral pleura (4). The colloid-osmotic pressure is in a steady state. Lymphatics in the parietal pleura are the chief regulators and mainly responsible for fluid re-absorption and transport (4,13). Figure (a) is accessible via web and marked as »reusable by changing«. Author: By Cancer Research UK, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=34332978. (b) adapted from Feller-Kopman D, Light R. Pleural disease. New England Journal of Medicine. 2018;378:740-51.

1.2.2. Pathophysiology of MPE

In a classical description, pleural effusion is the build-up of fluid in the pleural space that may be caused by any reason (6). If there is a proof of invasion by the tumor or any evidence of malignant cells in this fluid, then it is described as malignant pleural effusion. Pleural fluid is resorbed via lymphatic vessels in the parietal pleura (6). The capacity of pleural fluid reabsorption is 28 times higher than the rate at which it is produced. For this reason, accumulation of excess fluid in the pleural cavity is extremely difficult under normal conditions (19). Under regular instances, balance of fluid influx into and resorption from the pleural space is maintained. Disruption of this balance has to occur, for an effusion to manifest. There either has to be an enhanced rate of production/entry or a diminished reabsorption/exit rate, respectively. Interplay of both mechanisms is most likely the reason for the formation of an effusion (4,17). Intrinsic factors (disruption of normal anatomy, direct invasion of malignant cells, and distorted hormonal equilibrium) as well as extrinsic factors (decrease in respiratory movement and compression by mechanical force) interfere with the normal effective functionality of the lymphatic system of the pleura. Together, intrinsic and extrinsic factors mount their effect to decrease pleural fluid reabsorption capacity resulting in excessive accumulation of fluid within the pleural cavity (13,17). The same mechanisms translate into the understanding of MPE formation. Via the hematogenous, lymphatic or direct route, tumor cells invade the pleural space. As the consequence of a growing tumor, the lymphatic drainage system might get blocked, resulting in build-up of pleural fluid (13,20). Up to 55–60% of patients affected by metastases involving the pleura or lymphatics develop MPE (13,21). There is still controversy about the question why some patients with pleural metastases develop MPE and others do not. What is well known however, is that “wet” disease of the pleura compared to “dry” pleural disease shows poorer prognosis and more limited possibilities of therapy (13,22).

The development of molecular medicine, really impacted the understanding of tumor-host cell interactions and made those evident. Physiological factors – Attributable to both, increased production and decreased reabsorption take part in the development of MPE (13,23). Molecular factors – Three different classes of chemical molecules can be distinguished based on their mechanisms of action responsible for pleural fluid accumulation due to pleural vessel hyperpermeability (13,24). The first class are the inflammatory cytokines including interleukin 2- IL2, TNF, and IFN (13). The second class consist of molecules promoting angiogenesis such as angiopoietin 1 (ANG-1) and angiopoietin 2 (ANG-2). Additionally,

the third subset comprises molecules including VEGF, CCL, MMP, and OPN, which directly take part in the pathophysiological mechanism of vascular hyperpermeability (13). Furthermore, there is evidence of mastocytes, significantly impacting the development of malignant pleural effusions. Liberation of tryptase α and β-1 and IL-1β has been connected to increased permeability of the pulmonary vessels and induction as well as stimulation of the transcription factor NF-ϰB, further promoting fluid aggregation and tumor growth (4). Genetic factors - Mutations in EGFR, KRAS, BRAF, MET, RET, PIK3CA, and EML4/ALK have been identified by researchers, using genome analysis of tumor cells, to be associated with MPE development (4). For distant metastases KRAS mutations are commonly detected and tumors which metastasize via direct infiltration often harbor EGFR mutations. Interestingly, the genetic profile of mutations in the primary tumor can be different from the metastases causing the pleural effusion (13). This research finding is directly connected to the area of targeted therapy.

Impact on Respiratory Physiology - Hypoxemia and a reduced partial pressure of oxygen has been associated with the development of pleural effusion. In addition, the occurring intrapulmonary shunt, is another predisposing factor which leads to a reduction of arterial oxygenation. More emphasis has also been added on the effect of MPE on respiratory dynamics since successfully performed thoracentesis leads to a drastic relief in the sensation of dyspnea. The underlying pathophysiological mechanisms of dyspnea in MPE have been shown to be activation of mechanoreceptors due to stimulation by accumulating pleural fluid, in response to stretching, coughing, and alterations in pulmonary volumes (13,25).

1.3. Clinical Presentations

A succinct clinical history is necessary in order to differentiate between the various etiologies of malignant pleural effusions. Having insight into all underlying comorbidities such as renal, pulmonary, hepatic or cardiac can not only help in predicting the patients physiological reserves and general health status but might dictate management implications as well (13).

Symptoms - The magnitude and speed or rate of development of an effusion, as well as general overall health condition and reserves of a patient, dictate the clinical presentation (13,26).

Dyspnea - Dyspnea represents the most frequently reported symptom. It is seen in over 50% of patients suffering from a pleural effusion (13). Various mechanisms are responsible for its development including reduction of chest wall compliance representing a mechanical factor, alterations in biomechanics as a result of contralateral mediastinal shift, decreased lung vol-

umes and capacities, stimulation of chest wall receptors resulting in activation of compensatory reflexes, as well as caudal diaphragmatic displacement (25). A disproportionally large sensation of breathlessness with respect to the volume of drained fluid may also be explained by a mismatch in ventilation-perfusion ratio, coexistence of a collapsed lung and pulmonary arterial hypertension (13,16).

Pain - Thoracic pain can signify that the chest wall might be involved by local tumor infiltration and rib fractures or MPM (13,27). Visceral pain from pleural involvement, often describes as pleuritic, may also increase upon deep inspiration (13). Sometimes, instead of the classically described pleuritic pain, the character is described as dull and aching. Pointing towards diaphragmatic involvement might be radiating pain to the right shoulder (13).

Cough - Can manifest as productive or may be accompanied by hemoptysis. It signalizes underlying irritated or inflamed pleura, which may be associated with pleural or bronchial tumor involvement. Constitutional symptomatology includes reduction in appetite, cachexia, weight loss, fever, night sweats, easy fatiguability, and lethargy and are potential indicators of an advanced stage of the disease (13,28).

1.4. Cancer and Malignant Pleural Effusion

Almost exclusively (95%) responsible for all malignant pleural effusions are metastases involving the pleural space. Adenocarcinomas constitute two-thirds (70-77%) of the histological classification at diagnosis (29). In the majority of all cases, pleural effusion is the first presenting sign of the disease. Half of these are caused by LC. Prognosis tends to be better for hematological malignancies and gynecological cancers in which MPE occurs as initial presenting complaint compared to those developing MPE at later stages of their disease. In breast cancer, the longest time intervals from cancer diagnosis until malignant pleural effusion development can be observed (4). Regardless of the time of formation however, malignancy related effusions remain universal pointers towards a dismal prognosis (4,17).

1.4.1. Lung Cancer

Lung cancer is representative of the most common malignancy world-wide (4). Lung cancer can be classified into several subtypes on the basis of histopathological characteristics. The most widely used and broadest division is into small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The vast majority of lung cancer cases (85%) are NSCLCs, which can be further grouped into Adenocarcinomas accounting for 25–30%, Squamous cell carcinomas (SCC) constituting 40%, and Large cell carcinomas in 5–10% of cases (30). LC

subtypes greatly differ in molecular characteristics, despite certain similarities in histological appearance (31). Responsible for these changes are expression of mRNA, microRNA or alteration and methylation of DNA as well as different mechanisms of protein expression (4). EGFR mutations and ALK translocations are the most common biological markers (31).

Effusions occur with all histological types, most frequently with adenocarcinoma due to its peripheral location and therefore close proximity to the pleura in most of the cases (29). In roughly a quarter of all lung cancer patients, MPE already manifests at an early point of their disease, whereas in 40-50% of patients it is not discovered until progression of their disease (4). In squamous cell carcinoma (SCC) tumor cells directly invade the pleural membrane (32). The 5-year survival rate is 3% of these patients with MPE (4). MPE in SCLC presents in 10–38%, and forms due to indirect infiltration of the lymph vessels (33).

1.4.2. Breast Cancer

BC is the second most common cancer worldwide, ranked first in incidence in women living either in developed (794,000/year) or developing countries (883,000/year). Isolated occurrence of BC is increasing in the world, since preventive public health mechanisms have been successfully implemented with a resulting decrease in disseminated and progressed disease incidence as well as lower mortality rates (4).

Histopathological and molecular properties help in the differentiation of the numerous types of breast cancer. BC can be classified as invasive and non-invasive types. 75% are invasive ductal carcinomas of the breast, lobular carcinomas account for 5-10% of cases, 5-7% are classified as medullar, mucinous type is seen in 3-5% of cases, 1-4% are of tubular origin and the rest are rarely seen subtypes (4,34). The molecular categorization arises from the presence or absence hormonal receptors. This receptor status refers to the estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor (HER2) as it conveys prognosis and possible targets of therapy (4). This is the basis for the division of breast cancer into four distinct subtypes: Luminal A (ER+ and PR+), luminal B (ER+, PR+ and HER2+), triple-negative (ER-, PR- and HER2-), as well as HER2 positive (ER- and PR-, HER2+) (4,35). Predilection sites for BC metastases are bone, brain, liver and lungs (36).

Occurrence rate of MPE is 2–11% of patients with BC and manifestation can occur even years after the first diagnosis. Dissemination of breast cancer into the pleural cavity occurs most frequently via the lymphatic route (4). Patients with BC and MPE have an overall survival ranging from 5 to 13 months (37). Due to its aggressiveness, rapid progression as well as quick and frequent metastases, malignant effusions are most commonly encountered

in triple-negative breast cancer (TNBC), among all breast cancer subtypes (4). Occurrence of metastases usually happens between two and three years after the first diagnosis (4). There is less association between Luminal A and B subtypes when compared to TN breast cancer in the development of malignant pleural effusion (4,38). It is not uncommon for metastases to undergo subsequent molecular changes and mutations. For this reason, bimolecular assessment should be additionally performed, to select the most appropriate treatment (39). For prognostic purposes, the proliferation marker Ki-67 is quantified in pleural effusions of malignant etiology, with its presence predicting an inferior prognosis. Raised values can be seen in over 60% of malignant effusions (4).

1.4.3. Gynecological Malignancies

In women, cancer of the ovaries is accountable for 2.5% of all diagnosed malignancies. Nevertheless, ovarian cancer (OC) accounts for 5% mortality rate related to cancer in females (4,40). OC ranks fifth on the list of malignancies affecting the pleura (41). On the basis of histopathological and molecular analysis, we can divide OC into five major categories: High-grade serous carcinoma accounting for the majority of the cases (70%), endometrioid carcinoma (10%), clear cell carcinoma (10%), low-grade serous carcinoma (5%) and mucinous carcinoma (3%) (4). Classification of malignancies involving the ovaries is performed according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines (42). A positive cytological finding in the pleural effusion, by definition of the FIGO, is classified as stage IV disease (IVA). The overall 5-year survival for patients with localized disease is over 90%, contrasting patients with disseminated disease having a 5-year survival rate of less than 20% (4).

The most common clinical manifestation of epithelial OC with 33-53% is MPE (4,42). Infiltration of OC cells into the pleural cavity occurs primarily by direct spread via the diaphragm, pleuroperitoneal or by hematogenous dissemination (43). Survival rate of 21 months after initial diagnosis in patients with MPE due to OC appears to be relatively long when compared to other types of cancer (44). Unfortunately, around 70% of all ovarian cancers are detected in an advanced stage, where disease has already progressed or disseminated (45). MPE appears to be the first clinical sign of disease in 15% of all newly diagnosed patients (4, 43).

1.4.4. Hematological Malignancies

Lymphomas constitute a diverse collection of hematological malignancies distinguished by uncontrolled proliferating lymphatic tissue (4). Lymphomas can be broadly categorized into two principal classes: Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL) (4). While there is a decrease in the incidence of HL, the incidence of NHL is rising.

In men, non-Hodgkin disease is ranked on the ninth place by cancer incidence and tenth in women (4,46). NHL causes MPE in 16–20% of patients. The subtypes most commonly responsible for causing MPE, due to NHL, are diffuse giant B-cell lymphoma (60%) and in 20% of cases follicular lymphoma (4). Possible underlying processes of pathogenesis are the following: (1) Contiguous spread into the pleural cavity; (2) Blockage of lymphatics from direct invasion of pulmonary and mediastinal lymph nodes as well as; (3) Thoracic duct obstruction resulting in the emergence of chylothorax (4).

Occurrence of Hodgkin lymphoma is bimodally distributed. One surge occurring from puberty until age of 40 and the other beyond age of 50 (4). In 10-30% of patients with HL, MPE presents initially when diagnosis is established, but in more than half of cases not until the disease progresses (47). Dearth of cellular components in the pleural fluid, makes diagnosis of malignant effusion in the case of lymphoma a real challenge. It definitely signalizes a bad prognosis, with an overall survival after the occurrence of 3–6 months (4).

Multiple myeloma is an infrequent cause of malignant pleural effusion, which occurs in 6% of cases (48). High pleural protein values, in the range of 8–9 g/dL, are suggestive of this diagnosis. Diagnosis can be achieved by electrophoresis and immunoelectrophoresis of pleural fluid (48). Infiltration of the chest wall is usually present, due to invasion from adjacent skeletal lesions (ribs, sternum, and vertebrae), but pleuropulmonary infiltration may also originate from soft tissue plasmacytoma of the chest wall or from direct involvement. With pleural immunocytoma from Waldenstrom macroglobulinemia, pleural effusion is a rare manifestation (7).

1.4.5. Malignant Mesothelioma of the Pleura

Representing a malignancy with a high degree of aggressiveness, originating from the mesothelium, is malignant mesothelioma, often affecting the lung serosa, peritoneal cavity, the pericardium or even the tunica vaginalis of the testes (4). Exposure to mineral fibers (e.g., asbestos) is known to be the most important risk factor for its development. The still increasing incidence can be explained by the typical delay of onset of this disease (30–50 years after exposure), but heavy variations exist depending on geographic location (4).

Histopathology enables classification of malignant mesotheliomas as epithelioid, mixed or biphasic and sarcomatoid type (4). The most commonly diagnosed class is epithelioid (60–80%) which shows highest overall survival of over one year. In contrast, sarcomatoid subtypes, depict the worst prognosis with survival times of 4–6 months (4,49). Even at an early stage, all malignant pleural mesotheliomas manifest with MPE in 54–90% of cases (4). Biological activity of the effusion offers malignant cells protection against chemotherapy and facilitates cancer expansion (4,50).

1.4.6. Gastro-Intestinal Cancers

Malignant pleural effusions from metastatic disease involving the pleura resulting from primary tumors of the gastrointestinal-tract account for approximately 5% of cases. Characteristic for malignancies involving the colon or rectum in a progressed phase of the disease are predominantly distant pulmonary and hepatic metastatic lesions. Involvement of the pleura is uncommon and preserved for end-stage metastatic colorectal cancer (mCRC) (41). Since colonic drainage occurs via portal circulation, occurrence of metastases in other organ-systems should not be anticipated unless there is hepatic tumorous involvement. Malignant tumors of the rectum however, have the ability to disseminate via the portal-circulation as well as the systemic-circulation, making them prone to affecting the pleural cavity in a large proportion of advanced-stage cancer patients suffering from rectal cancer (41). In theory, malignant cells can also be distributed through the pulmonary circulation to invade the pleural space. Very limited information exists, addressing MPE in gastric cancer patients. Dissemination occurs predominantly via the hematogenous route, followed by direct involvement of the pleura and through lymphatic spread. In very rare circumstances even pancreatic cancer has the propensity to accumulate excess pleural fluid (41,48).

1.4.7. Renal Cell Carcinoma (RCC)

Of all malignancy-related effusions, only 1-2 % are caused by renal cell carcinomas. In these cases, development of MPE results from pleural metastases originating from metastatic lesions in the lung (19). A very rare phenomenon are solitary pleural metastases without the presence of lung metastases. One explanation for isolated pleural metastases to occur, is the hematogenous spread through the Batson venous plexus, which comprises a network of valveless veins surrounding the spinal cord and vertebral column (19). There are connections to the azygos vein, hemiazygos vein, bronchial vein as well as intercostal veins (19). Papillary

and clear cell tumors, which tend to be high grade, are the more frequently seen subtypes causing MPE due to RCCs (51,52).

1.4.8. Cancer of Unknown Primary (CUP)

At times, malignant pleural effusions develop in the setting of a cancer of unknown primary (CUP). The term is applied when a patient is diagnosed with metastatic cancer, in which the origin could not be identified after extensive evaluation and investigations. Rapidly developing metastases, bad responsiveness to treatment and dismal prognosis are typical for this diagnosis (53).

1.4.9. Rare Primary Tumors of the Pleura

Primary sarcomas are rare tumors occurring in the pleural cavity, causing MPE. For the diagnosis, ultrastructural and molecular examinations as well as immunohistochemical tests may help, even though it remains a challenge to correctly diagnose most spindle cell tumors found in the pleural cavity. Since the majority of these neoplasms display different prognosis and require distinct treatment regimens and modalities, it is imperative to set an accurate diagnosis (19). Despite the difficulties in treatment, similar principles apply to most: complete excision with large safety margins (2 cm) is required for localized tumors, and radiotherapy and adjuvant chemotherapy are the recommendation for insufficient margins or incomplete resection (19).

1.5. Evaluation

1.5.1. Imaging

Chest radiograph – The principal method to initially investigate patients showing signs or malignancy-related symptomatology of pleural effusion, is a posteroanterior chest radiograph (4). At least 200 ml of pleural fluid accumulation has to be present in the pleural cavity to make the diagnosis on a PA chest x-ray. In contrast, only 50 ml of fluid may be visualized in a lateral-view X-ray of the thorax (54). However, less than 500 ml of pleural fluid volumes (detected in roughly 10-15% of effusions) have not been associated with symptoms (13,55).

Radiographic findings that might point to a diagnosis are costophrenic angle blunting, shift of the mediastinum, crowding of the ribs or an elevated hemidiaphragm (13,56). By definition, a massive effusion has to occupy the entire hemithorax and is frequently associated with shifted mediastinum and inverted diaphragm (13,56). Signs, raising the suspicion of an

underlying malignant process are massive effusions, loculations, and decrease of ipsilateral lung volume on the involved site (13).

Thoracic Ultrasound – Ultrasonographic examination of the thorax provides a higher sensitivity than conventional chest radiography (13,57). Not only does ultrasonography help in diagnosing smaller amounts of fluids, but it also acts as a guide for the performance of diagnostic and therapeutic interventions (13). Optimal spatial resolution and good penetration depth can be provided by the use of 3.5-5 MHz transducer probes. Furthermore, even to distinguish between effusions, consolidations and pleural thickening, ultrasound can also be used (13,56). The characteristic appearance of pleural metastases are relatively small lenticular hypoechoic masses, which are in close proximity to the thoracic wall or they can appear as masses with complex echogenicity (13).

Other hints suggestive of malignancy may be the presence of pleural thickening in excess of 1 cm, pleural nodularity or irregularity, thickened visceral pleural, and more than 7mm of diaphragmatic thickening (13).

Contrast-Enhanced Chest Computed Tomography – The gold standard approach used for screening in the case of suspected underlying malignancy is the contrast-enhanced CT scan, because it permits more accurate visualization of parenchymal disease as well as lymph node involvement (4,13). Pointers of a diagnosis of malignant etiology are circumferential thickening encasing the lung, pleural nodularity, parietal pleural thickening of more than 1 cm, and involvement of the mediastinal pleura (4,13). Inability to differentiate between pleural metastases and malignant pleural mesothelioma is a potential limiting factor (13).

Porcel *et al.* proposed a CT scoring system for differentiating between benign and malignant conditions, including several parameters: Detection of pleural lesions larger than 1 cm, hepatic metastasis, any pulmonary mass/nodule in excess of 1 cm, presence of pericardial effusion, absence of loculations and no enlargement of cardiac silhouette. A score exceeding 7 out of 10 has the capability of detecting malignancy with a sensitivity of 88% and specificity of 94% (4,13).

Magnetic Resonance Imaging - MRI is superior to a CT scan in the way, that it offers a higher soft tissue resolution. This is why MRI can detect diaphragmatic and chest wall involvement with a higher sensitivity (13). MRI-based imaging is currently not included in the standard diagnostic algorithms, which is attributable to limited availability, higher costs and difficulty in lung parenchyma imaging. Diffusion-weighted imaging has also put value in the differentiation between malignant and benign diseases of the pleura (13,58).

PET Imaging

Positron-emission-tomography utilizes radioisotopes such as fluorodeoxyglucose (FDG) for staging of a malignant disease. Its role to differentiate between malignant and benign etiology of pleural effusion is however subsidiary. Particularly useful are PET scans to perform pleural biopsy in order to target certain anatomical areas. Furthermore, the importance becomes evident in cases of pleural asbestosis, malignant mesothelioma or other mixed diseases (13).

1.5.2. Histopathological Diagnosis

Diagnostic Thoracentesis – Usually, aspiration of 40-60 ml of pleural fluid is necessary to diagnose MPE, which is tested for glucose and protein content, pH, concentration of lactate dehydrogenase (LDH) and microbiological as well as cytological analysis is also performed (4). Diagnostic yield differs for tumor etiology with reported sensitivity of 6-32% for malignant mesothelioma and comparatively higher sensitivity of 80% for Adenocarcinomas (13). Most MPE are categorized as exudates, even though transudates can also be observed in 5-10% of cases (4). By repeating the procedure, diagnostic yield may increase by a third (13).

Pleural Fluid Analysis – Physical and chemical pleural fluid characteristics under normal conditions are pH values ranging from 7.60 to 7.64, less than 2g/dl of protein content, glucose concentration similar to plasma, LDH levels of less than 50% found in plasma and WBC count below 100 per cubic millimeter. Useful parameters for establishing the diagnosis of malignant pleural effusion are pH values below 7.30, reduction of pleural fluid glucose content (30-50 mg/dl), a lymphocyte predominance of more than 50-70% and lactate dehydrogenase levels exceeding 1000 U/l (4,13).

The tumor marker level elevation of CEA, Leu 1 and mucin have been shown in MPE, which may help guiding the diagnosis (4,13). Apart from distinguishing an exudative from a transudative effusion with the standard Light's criteria by using protein content and LDH levels of pleural fluid, more extensive criteria can additionally be used. They include the general gross appearance (turbid/clear/cloudy), specific weight of pleural fluid (>1.020), level of cholesterol content as well as attenuation parameters on CT scan and albumin gradient between serum and pleural fluid (13).

Cytology - It is often used as initial test providing approximately 60% of sensitivity. This is dependent on several factors including etiology of the primary tumor, quality of sample preparation as well as experience and expertise of the cytologist (4,13). The minimal invasiveness and rapidity of effectiveness as well as easy availability makes cytology an effective method in the diagnosis of MPE. The combined usage of cytology together with pleural biop-

sy increases sensitivity of diagnostic yield to 74% (4,48). When after a diagnostic thoracentesis, the diagnosis remains uncertain, the procedure is repeated in conjunction with a blind needle pleural biopsy (4). Diagnosis of malignant effusion can be confirmed by detecting the presence of neoplastic cancer cells in the pleural fluid on cytologic examination (4,59).

Pleural Fluid Cell Block - Cell-block technique has the advantage of retaining tissue fragments over conventional cytology, accentuating the need for cellular material in order to obtain the diagnosis (13). Preparation of a cell block can be done by various methods. Same mechanisms apply to all of them. Proteins form cross-links resulting in the formation of a gel, which can be processed without the sample of tissue to dissolve (13). Cytomorphological characteristics and antigenicity remain preserved as another advantageous factor of this technique. Reason for the enhanced sensitivity of this procedure could be attributable to the preserved cellular architecture and morphological patterns of malignant cells as well as increased cellularity (13). The cell block specimen can further be immunohistochemically analyzed and special staining methods can also be applied (13,60).

Pleural Biopsy- This procedure should be considered in cases of negative cytology results as the diagnostic yield of conventional cytology is low and cell block technique is rarely used routinely (4,13). By using Cope, Abrams, Vim Silverman or a cutting needle, closed pleural biopsy is usually performed (13). Uneven or non-homogenous distributed tumors as well as malignancies in an early stage result in lowered diagnostic yields (13). Combination with conventional cytology yields higher diagnostic accuracy (Figure 2) (48). Closed pleural biopsy alone, can achieve a diagnostic sensitivity of up to 60%. If additional imaging techniques are used (CT and US), diagnostic yield can further be improved (4,13).

Image-Guided Biopsies – Both, biopsies under CT guidance and US guidance can be performed for diagnostic purposes to obtain representative samples of the pleura (4,13). The reported sensitivity of both procedures to diagnose MPE ranges between 70-90% (13).

Thoracoscopy: Medical Thoracoscopy (MT) and Video-Assisted Thoracoscopic Surgery (VATS) – Direct visualization of areas of interest with simultaneous ability of tumor tissue sampling provides improved diagnostic accuracy (as shown in Figure 2). Adhesions, nodules, ulcers as well as plaques and hyperemia are commonly encountered major pathological changes in the observation of pleural diseases (13). Thoracoscopy has been shown to have a minor extent of morbidity and mortality rate despite the invasiveness of the intervention (4,61). Reported adverse events following thoracoscopy include cough, sensation of discomfort in the chest as a result of pulmonary re-expansion and transient chest pain (4,13).

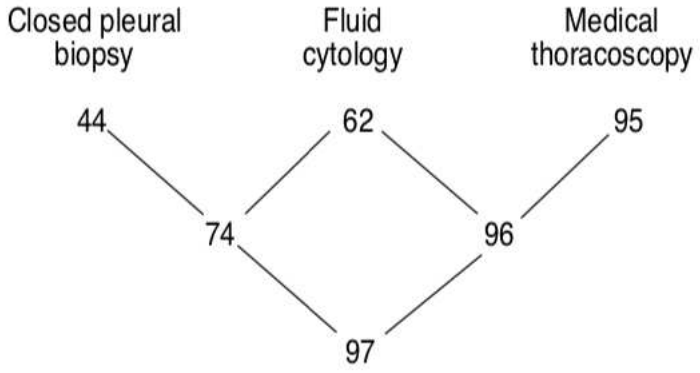


Figure 2. Malignant pleural effusions: sensitivity (%) of different biopsy methods (cytological and histological results combined). Adapted from Antony VB, Loddenkemper R, Astoul P, Boutin C, Goldstraw P, Hott J, et al. Management of malignant pleural effusions. European Respiratory Journal. 2001;18:402.

1.6. Treatment / Management

The definition of a definitive procedure is one aiming to provide long-term relief from effusion-related symptomatology. It is led by an assessment of the patient's prognosis and driven by a balance of the expected benefit and morbidity of the proposed procedure (5). The treatment of malignant pleural effusions should be oriented and tailored to the patient's general health status including performance status and symptoms, etiology of primary tumor and tumor response to systemic therapy, pulmonary re-expansion after drainage of pleural fluid, as well as estimated survival time and individual wishes or desires. The objective in palliative treatment and care is the permanent elimination of pleural fluid (4).

While asymptomatic effusions only require observation, management options for symptomatic MPEs, in conjunction with oncologic therapies directed to the underlying cancer, include (22): thoracentesis, pleurodesis via medical thoracoscopy, video-assisted thoracoscopic surgery (VATS) or chest tube (slurry), insertion of indwelling pleural catheter (IPC),

combination of pleurodesis and IPC, and other methods such as pleurectomy/decortication (P/D) as well as pleuroperitoneal shunt (4,8,22).

1.6.1. Thoracentesis

Thoracentesis is the first approach to any new onset pleural effusion and has diagnostic and therapeutic value. While it can provide immediate relief of acute symptoms, it is associated with a high recurrence rate (4). Incidence of recurrence approaches 98 percent within 30 days after the procedure. Aim of the thoracentesis is not the prevention of fluid re-accumulation or enabling continued drainage but rather symptom alleviation (13).

Recurrence of MPE is defined as either radiographic documented reaccumulation of pleural fluid or clinically bothersome symptoms such as dyspnea. Pleural effusions tend to increase the volume of the hemithorax more than they compress the lung tissue (10). Therefore, after thoracentesis, total lung capacity (TLC) increases by one third of the drained fluid. Patients with high lung compliance have the greatest improvement of their lung function and lung capacity (13).

Contraindications for thoracentesis include bleeding disorders, anticoagulation, elevated INR or platelets <20,000, infection of the chest wall, pneumothorax, hemothorax, and pain (62). Repeated thoracentesis carries the risk of infection leading to adhesions between the lung and chest wall, loculation of fluid and tumor implantation as well as hypoproteinemia (63).

Complications of thoracentesis include pneumothorax, bleeding, infection, and internal organ laceration (62). Evacuation of large pleural effusions requires caution and controlled drainage, not exceeding 1.5 l at a time or titration of evacuated pleural fluid volume to a rate of 500ml per hour. Drainage of a massive pleural effusion and rapid pulmonary re-expansion can lead to hypotension, chest discomfort and bothersome cough. Re-expansion pulmonary edema is described as a rare complication after rapid drainage of pleural effusion. The pathophysiological mechanisms of re-expansion pulmonary edema include reperfusion injury of the underlying hypoxic lung, increased capillary permeability, share injury of pulmonary capillaries, and local production of chemotactic factors such as interleukin-8 (62).

1.6.2. Pleurodesis

The word “pleurodesis” is originated from the Greek words pleurá (pleura) and desmos (bond) (64). Pleurodesis confers to the artificial obliteration of the pleural space to prevent effusion recurrence. Pleural symphysis can be accomplished surgically by a mechanical

procedure (e.g. partial parietal pleurectomy or abrasion) or by instillation of chemical sclerosants and irritants via thoracoscopy or chest tube (13). A complex interplay of various molecules underlies the mechanism by which the intrapleural instillation of sclerosant agents induces pleurodesis. There is no doubt, that the induced pleural injury activates the inflammation cascade through molecules and cytokines such as IL-8, promotes angiogenesis by producing VEGF and fibrogenesis mediated by TGF beta and leads to a reduction in the activity of the fibrinolytic system, which all eventually leads to pleural fibrosis and development of pleural adhesions (13,65).

The goal of this procedure is to allow the adhesion of both pleural layers and eliminate the pleural space to prevent pleural fluid from reaccumulating or terminate further air leak (64). Through direct infliction of pleural injury by physical or mechanical techniques including pleural abrasion during VATS or formation of intrapleural adhesions by means of chemical irritating agents like talc, povidone iodine, bleomycin and Corynebacterium parvum, active pleurodesis can be achieved (13). Very diverse groups of agents have been investigated for performing chemical pleurodesis with a high degree of variability of effectiveness including antibiotics (tetracycline, doxycycline, erythromycin, minocycline) as well as chemotherapeutic agents (bleomycin, cytarabine, mitomycin, doxorubicin and mitoxantrone), antiseptics (silver nitrate, povidone iodine), microorganisms (Corynebacterium parvum, Streptococcus pyogenes (OK432), and autologous blood (13). Thoracoscopy as well as pleural catheters, can be ways of administering the sclerosing agents into the pleural cavity (13). Acceptability of those procedures is determined by life expectancy and other patient factors (44) . The presence of a non-expendable or trapped lung together with loculated pleural effusions are considered major contraindications to pleurodesis (13,66). Determination of degree of effectiveness regarding pleurodesis outcome is influenced by extensiveness of pleural involvement, cancer type and utilized sclerosing agent, as well as modality of administration (13,63).

Effectiveness of pleurodesis can be classified as total success when there are no signs of pleural fluid re-accumulation or partial success in the case of residual effusion persistence or fluid re-accumulation which remained asymptomatic and not requiring another invasive procedure for drainage, and failure where pleural effusion related symptoms persisted or reoccurred with additional procedures being required, up to six months (10,13).

Procedure

Having replaced open thoracotomy to access the thorax almost completely, thoracoscopy, offering a less invasive approach, can be used for a wide variety of surgical procedures in the chest (Figure 3). Thoracoscopy can be performed via two different methods. One is video-assisted thoracoscopic surgery (VATS) and the other medical thoracoscopy (MT) (61).

Medical Thoracoscopy (MT)

It is also known as pleuroscopy and can be performed by internists as well as surgeons. With some premedication, MT is generally performed under local anesthesia (61). During the procedure, special attention has to be paid to dangerous anatomical areas such as the internal mammary artery, in the axillary region to the lateral thoracic artery and in the infraclavicular region to the subclavian artery (61). Risk of injury to intra-abdominal organs and to the diaphragm can be drastically reduced with the help of ultrasonographic examination of the thorax for selecting the insertion site (61). During the procedure, the patient is usually positioned in lateral decubitus position with the examined hemithorax facing upward (61).

Depending on the treatment indication, the level of entry point is in line somewhere between the middle and anterior axillary line, at the level of third to fourth intercostal space in the management of pneumothorax, whereas a lower level of access is used for pleural effusions at the level of fifth to seventh intercostal space (61). After generous application of local anesthesia and respective residence time, skin is opened with a small incision and followed by atraumatic blunt dissection until chest wall is reached. Subsequent introduction of a trocar allows for insertion of the thoracoscope (61).

Video Assisted Thoracoscopic Surgery (VATS)

VATS is generally performed under general anesthesia with either single-lumen or double-lumen intubation. The preferred option for pleural effusion and biopsy of the parietal pleura is the intubation with a single-lumen tube (61). Following proper positioning of the patient on the operating table, prepping and draping, insertion of the thoracoscope allows optimal visualization of intrathoracic structures when the lung is completely collapsed. In the next step, thorough exploration and detailed examination of the thoracic cavity is performed (Figure 4) and followed by obtaining further intercostal access under direct thoracoscopic vision (61). Usually, three incisions (each 1 cm) are made to accommodate the corresponding ports and allow for free movability and triangulation of instruments in minor operations. The camera is usually positioned in the central port to allow best visualization, whereas the rest of the ports are mainly used for instruments taking biopsies or for retracting of structures (61).

Advantages include the fact that it permits the complete deflation of a lung, hence superior visualization and access for interventions, while allowing assessment of the underlying lung's ability to fully expand while being inflated with positive pressure (67). The latter, if adequate, is often followed by pleurodesis. Other potential benefits are the ability to perform mechanical abrasion of the visceral and parietal surfaces, and even parietal pleurectomy (68). Some centers even perform decortication in order to expand a lung that is trapped by malignant infiltration of the visceral pleura, although this is associated with a higher complication rate including persistent air leak (69). Revision of VATS into open thoracotomy can easily be achieved by joining the incisions. Chest tube placement into the pleural cavity occurs at the end of the procedure (61).

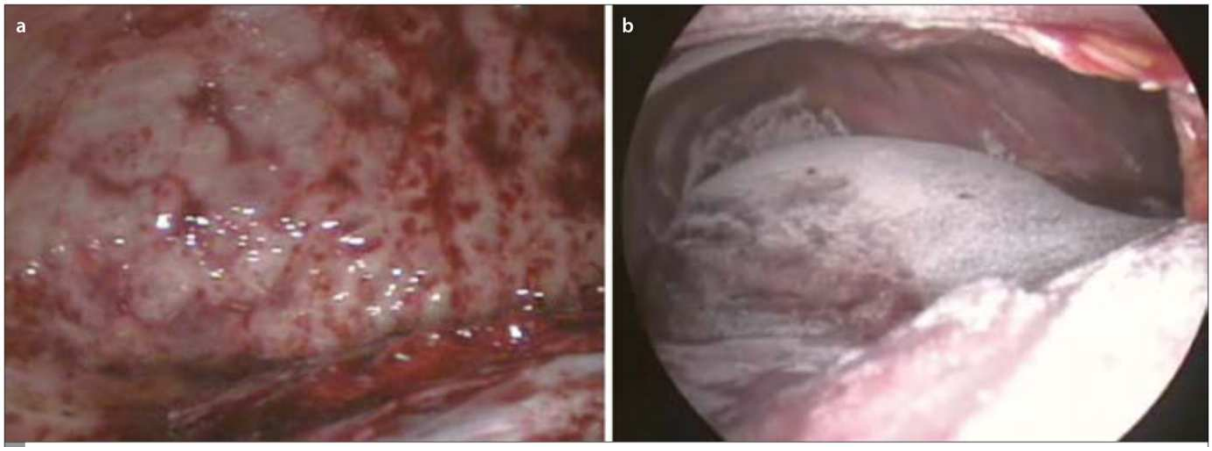


Figure 3. a, b. Lung cancer involving the parietal pleura. (a); Intraoperative view after talc poudrage during videothoracoscopy (VATS) (b). Adapted from Laçin T, Topçu S. Surgical procedures performed in management of malignant pleural effusions. Eurasian J Pulmonol. 2015;17:10-4.

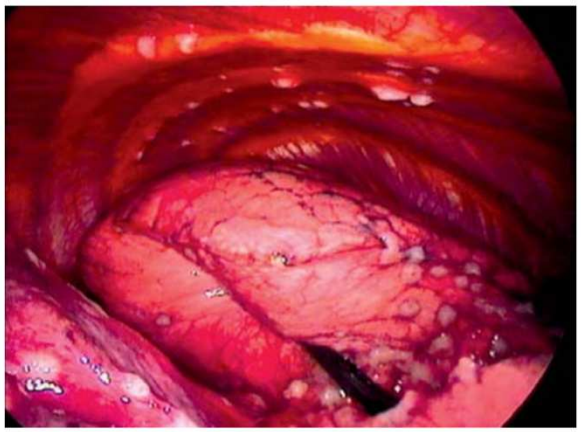


Figure 4. Thoracoscopic evidence of pleural carcinosis in a cytologically confirmed malignant pleural effusion prior to talc pleurodesis. Adapted from Ried M, Hofmann H-S. The treatment of pleural carcinosis with malignant pleural effusion. Dtsch Arztebl International. 2013;110:313-8.

Contraindication

Despite a good tolerability of thoracoscopy, some contraindications to this procedure exist. Since patients who are unable to tolerate a complete or partial unilateral pulmonary collapse, it delineates an absolute contraindication to thoracoscopy. Cardiopulmonary instability and presence of dense pleural space adhesions are also regarded as contraindications (61). Posing major difficulties on the performance of thoracoscopy are patient factors such as narrow rib spaces, small size of the thorax, bleeding diathesis as well as increased chest wall thickness and severe obesity (61,70,71).

1.6.3. Indwelling Pleural Catheter

The Device and Indications

Indwelling pleural catheters constitute an effective and relatively safe approach in the treatment of pleural effusions, allowing intermittent drainage. This procedure is also well tolerated by cancer patients with MPE at an advanced stage (13). Not only does the IPC aid in lung re-expansion, which is further facilitated by the negative pressure occurring from suction, when vacuum bottles are attached, but as a foreign body, it also promotes inflammation, eventually leading to auto-pleurodesis (13,72).

By draining pleural fluid without the side effects of mechanical or chemical pleurodesis, IPC addresses patient symptoms, even allowing fluid removal in the ambulatory setting, leading to a reduction in hospitalization and less costs in an economic sense (32). Without instillation of a chemical agent, pleurodesis occurs spontaneously in 50% even up to 70% of cases, allowing removal of the IPC. If however needed, the IPC can remain *in situ* for the remaining lifespan of the patient (32,66). Mainly used initially in MPE treatment for patients unsuitable for pleurodesis or in situations of trapped lung or pleurodesis failure with recurrence of pleural effusions, IPC is now rapidly replacing conventional pleurodesis as the first-line definitive management for MPE (13,32,66). Multiloculated effusions, infection or malignant infiltration of the skin at insertion site as well as bleeding disorders are considered as potential contraindications to IPC placement (13). Commonly encountered potential complications include drain blockage or malfunction, development of pleural infections such as pleural empyema or accidental dislodgement (13,73).

The indwelling pleural catheter used in the United States is PleurX™ catheter system (Becton, Dickinson and Company, Franklin Lakes, United States). It is a 66 cm long, 15.5 F flexible catheter made out of silicone (Figure 5,7) (1,74). The proximal end of the IPC contains a valve, allowing only unidirectional fluid flow. On the other end, at the distal side, the catheter contains multiple fenestrations (1). Adhesion of the IPC under the skin, to prevent dislodgement, is provided by the polyester cuff, positioned 14 cm away from the proximal end (1). With the Seldinger method under sterile conditions, the IPC is introduced under sedation. The first step is advancement of a guide wire together with a needle into the thorax. One incision (1cm) is performed in this region and another one is made in approximately 5 cm distance to the first one in the medial costal arch to create the subcutaneous tunnel (1). The cuff can be subcutaneously tunneled by passing the catheter through the incisions. (Figure 6) (1,2). After passing a sheath dilator over the guide wire, both can be removed and consequently insertion of the IPC through a sheath, which is then removed by tearing, can occur. After that, the catheter is fixated on the skin and skin incisions are closed (1). All pleural effusions can be drained intermittently even after hospital discharge by connecting the IPC to a disposable vacuum bottle (Figure 7) (1,74).

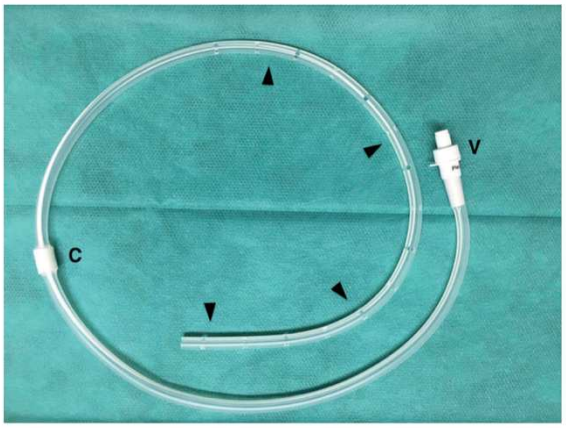


Figure 5. The indwelling pleural catheter is a soft 15.5 F silicone catheter, having fenestrated side holes at the distal end (pleural cavity) (arrowheads), and a midway polyester cuff (C), subcutaneously tunneled, and an external portion with a one-way safety valve (V) (1). Adapted from Porcel JM, Lui MM, Lerner AD, Davies HE, Feller-Kopman D, Lee YC. Comparing approaches to the management of malignant pleural effusions. Expert Rev Respir Med. 2017;11:273-84.

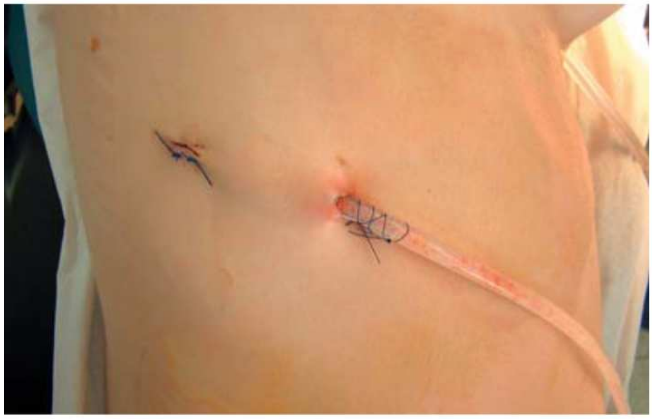


Figure 6. Indwelling pleural catheter (IPC) subcutaneously tunneled. Adapted from Ried M, Hofmann H-S. The treatment of pleural carcinosis with malignant pleural effusion. Dtsch Arztebl International. 2013;110:313-8.

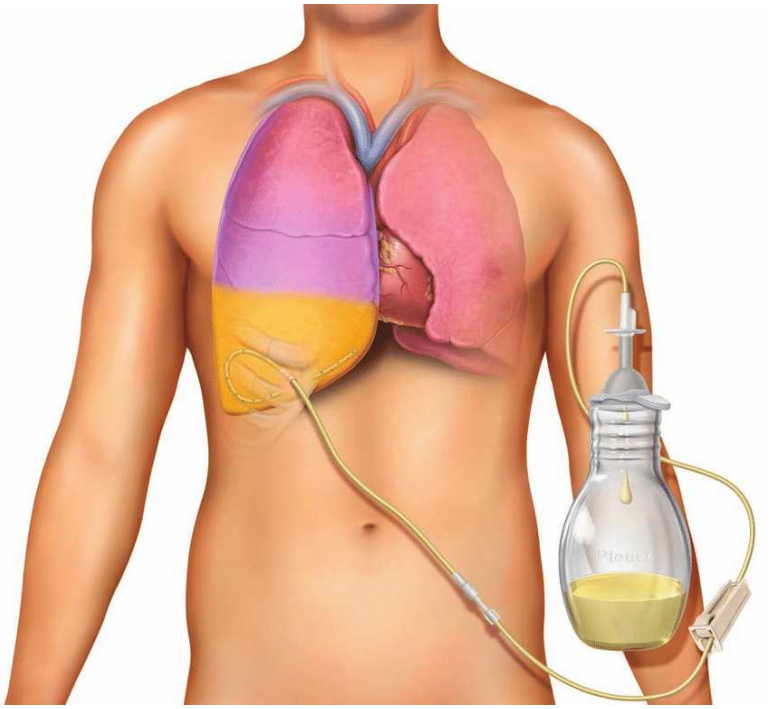


Figure 7. Schematic presentation of PleurXTM indwelling pleural catheter Courtesy and © Becton, Dickinson and Company. Adapted from Vrtis MC, DeCesare E, Day RS. Indwelling pleural catheters for malignant pleural effusion: A time for action. Home Healthc Now. 2021;39:302-9.

1.6.4. Other Approaches

Pleurectomy

Pleurectomy can be performed as radical total or subtotal approach with decortication. Occasionally it is done in cases of relapsing MPE due to pleurodesis failure (4). Patients should be able to tolerate surgery and have a prognostic longer life expectancy. Subtotal pleurectomy can be performed with a thoracoscopic approach. The subtotal procedure itself is almost always effective in obliterating the pleural space (55).

Pleuroperitoneal Shunt

A pleuroperitoneal shunt is rarely used in patients with trapped lungs, malignant chylothorax, or after unsuccessful pleurodesis. The reason for the rare use of a shunt are problems, characteristic of established communication (blockage, infections, etc.) and the relative aggressiveness of the intervention compared to IPC. The procedure is performed during thoracoscopy. Utility of this approach remains controversial as it is neither included in routine care nor in clinical guidelines or recommendations (55).

1.7. Prognosis

Advanced cancer with MPE is generally regarded as bad prognostic sign (4,44). This is displayed by the observation, that patients with MPE due to metastatic cancer show higher mortality rates than those without MPE (4,44). Several factors impact the prognosis of patients suffering from MPE ranging from general health and performance status, etiology and stage of the tumor, age, comorbidities over composition of pleural fluid and response to therapy up to nutritional status, weight loss and decreased serum albumin values (4,63). As an outlook for the future, and in the face of increasing number of cancer patients with improving survival, prevalence and incidence of MPE can be expected to rise (4,22). Generally, MPE often manifests as sign of disseminated metastatic malignancy and advanced stage disease with a dismal prognosis with a life expectancy of 3-12 months, under the influence of general condition of the patient and tumor factors (4,22).

Different scoring systems such as the LENT score, modified LENT score, and the PROMISE score can help in the prediction of survival of patients suffering from MPE (13). The LENT score consists of four parameters: **L**-pleural fluid LDH levels, **E**-ECOG performance status, **N**-neutrophil to lymphocyte ratio, and **T**-tumor entity (13). Each of these prognostic factors is associated with a certain numerical value. After calculation the respective scores, patients can be stratified into low (score 0–1), moderate (score 2–4), or high-risk

groups (score 5–7) (4). Patients belonging to the low risk group have expected survival times of almost one year, whereas patients with intermediate risk are expected to have a median survival of 130 days and in contrast to that, median survival in the high-risk group accounts for 44 days (4,16,75).

The PROMISE-score utilizes a broader repertoire of biological markers in predicting mortality within a three-month period and success rate of pleurodesis. It includes seven variables (chemotherapy, radiotherapy, hemoglobin, white blood cell count, C-reactive protein, ECOG performance status, and cancer type) in addition to tissue inhibitor of metalloproteases – 1(TIMP1), cadherin 1, PDGF, VEGF, and interleukin 4 (13). This score stratifies patients based on 3-month mortality risk into one of four groups (A < 25%, B 25% to <50%, C 50% to <75%, and D≥75%) (63).

The SELECT score also uses different markers to predict the 90-day survival in those patients. It includes Sex, ECOG performance status, leucocyte count, EGFR status, chemotherapy, and etiology of underlying primary tumor (13,76). Suggestions have been made to individualize the prognostication process, with special emphasis on patient preferences, psychological strain and disease burden as well as recognizing the advancements in immunotherapy and targeted therapy (4,13). The palliative prognostic index is just one of many tools that could be used to establish the prognosis for advanced stage disease. It covers the palliative performance scale, dyspnea, edemas, delirium and reduction in oral intake. In this scoring system, a value of 4.5 translates into an expected survival of less than six weeks (13,76).

Unfortunately, there is no definitive cure to MPE and treatment goals should primarily aim at the palliation of symptoms. The financial difficulties arising from cancer treatment and repeated procedures is another burden for patients suffering from cancer and their families, which must not be overlooked (13).

2. OBJECTIVES

2.1. Aims

The aim of the presented study was to analyze clinical data of patients with symptomatic malignant pleural effusion due to pleural carcinosis hospitalized at the REGIOMED Clinics and to evaluate and compare outcomes of different surgical treatment modalities with regards to effectiveness, survival, morbidity and mortality as well as duration of hospital stay.

2.2. Hypotheses

1. The use of VATS pleurodesis with IPC placement compared to sole VATS pleurodesis therapy is more effective in the treatment of malignant pleural effusion by decreasing the frequency of symptomatic pleural fluid reaccumulation and resulting in comparable improvement in quality of life without affecting overall mortality.

2. The use of VATS pleurodesis combined with an IPC has a significantly higher complication rate than IPC placement alone.

3. The type of interventional approach has a significant impact on survival of the patient.

4. Achieving successful pleurodesis positively correlates with survival time of patients.

5. Patients treated with an IPC have a considerable shorter duration of hospital stay compared to those treated with VATS pleurodesis.

3. MATERIALS AND METHODS

3.1. Design and Description of the Study

Patients with symptomatic malignant pleural effusion due to pleural carcinosis, hospitalized at any of the REGIOMED Clinics facilities in Germany, from January 2018 to December 2020, were included in this retrospective observational chart-based study. The REGIOMED Clinics institutional review board (IRB) reviewed and approved the present study on March 18th, 2022, and informed patient consent was waived because of the retrospective nature. The study was conducted in accordance with the Declaration of Helsinki.

Data retrieval was carried out by reviewing and analyzing medical case records. Additionally, questionnaires were sent to respective oncologists and/or primary care physicians, in case of missing important information. Eligible patients were required to be over 18 years of age, receiving treatment in the time span from 2018 to 2020, furthermore there had to be an established diagnosis of symptomatic malignant pleural effusion due to pleural carcinosis in order to be included into the current study. Patients not meeting these criteria or patients with non-malignant effusions and interventions other than the ones of interest as well as incomplete data were excluded from the analysis. Different surgical interventions for the treatment of malignant pleural effusion were compared regarding survival and mortality as well as duration of hospital stay (LOS) as primary outcomes. Additionally, secondary end points assessed effectiveness of treatment and associated morbidity and adverse events (AE). The aforesaid treatment options were the following: VATS pleurodesis (mechanical or chemical) alone or in combination with an indwelling pleural catheter (IPC) [PleurX™ catheter system] (Becton, Dickinson and Company, Franklin Lakes, United States), combination of VATS and IPC placement, or sole management with an IPC. Effectiveness of the different treatment modalities was evaluated based on clinical, sonographic and radiological investigations. Pleurodesis was deemed successful if there was no evidence of significant pleural fluid on the chest imaging and if there was symptom relief. Pleurodesis failure was defined as recurrent or persisting symptoms related to pleural effusion and/or fluid on chest imaging.

Survival times were calculated and assessed from the time of intervention until death or, for patients who were still alive at the end of data entry, the time of the last medical record of the patient was taken as the cut-off time. Morbidity included all complications and adverse events occurring after and related to the intervention. Any hospital admission involving 1 or more days was included. One day referred to a hospital stay crossing midnight. Day-case procedures (e.g. chemotherapy) were excluded. Data on all hospital admissions were collected

from electronic databases and case records. Hospitalization times were calculated and assessed from day of admission until discharge or in-hospital death.

3.2. Data Collection

Data collection from patient medical records was carried out at the department of thoracic surgery of the REGIOMED Clinics in Coburg, by using Orbis, an internal, institution specific hospital information system. Moreover, questionnaires were sent to the respective primary care physicians and/or specialists for additional or incomplete information.

Initially, a list of patient record numbers, who were diagnosed with a cytologically or histopathologically proven pleural carcinosis and malignant pleural effusion, was generated. Subsequently, the existence of all inclusion criteria was verified and data of interest were collected. All medical case records of every patient meeting the criteria for diagnosis of pleural carcinosis and malignant pleural effusion, hospitalized between January 2018 to December 2020, were retrieved and reviewed to obtain necessary data.

Eligible patients were required to have symptomatic pleural effusion resulting from an underlying malignant process of any type and stage, which was either cytologically or histopathologically proven. Sociodemographic information such as age and gender, baseline patient characteristics, date of death or the most recent date at which the patient was confirmed alive, tumor entity, comorbid conditions, duration of hospital stay, readmissions and need for further interventions, clinical findings, complications, diagnostic approach, date and modalities of intervention were extracted from their case records. In addition, physical examination findings at admission, serum albumin, receipt of systemic therapy and histopathological results were obtained. Patients with nonmalignant effusions and interventions other than the ones of interest as well as incomplete data were excluded from the analysis. The documentation of clinical information was carried out by using a cryptographically secured Excel spreadsheet. The number of included patients accounted for 91. Thereupon, statistical analysis and evaluation was performed in a completely anonymous fashion.

3.3. Statistical Analysis

The data were explored and analyzed using IBM SPSS Statistics for Macintosh, Version 28.0.1.1 (IBM Corp., Armonk, NY, USA). Normality testing of data has been done analytically, by Shapiro Wilk hypothesis testing and graphically, by analysis of histograms and Q-Q plots. Baseline characteristics of patients from the dataset were presented as frequencies (N) and percentages (%) for categorical variables and as means and standard deviations or

medians and interquartile ranges for continuous variables according to normality of distribution of data. Descriptive and frequency statistics were obtained for the variables of interest. The chi-square ($\chi 2$) test was used to determine differences between groups in terms of categorical variables. For determining differences between the groups, one-way ANOVA or independent samples t-test was used for continuous variables with normal distribution, whereas the Kruskal-Wallis test or the Mann-Whitney U test was used for continuous variables with non-normal distribution, respectively. Overall survival was calculated from the date of surgery to the date of death. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test for dichotomous variables, while for continuous or ordinal variables the Cox regression analysis was performed. Pearson correlation coefficient (r) was used to identify correlation of variables of interest with survival time. Subsequently, multiple linear regression was used to determine significant independent predictors of survival from the final model with the significant variables. The level of statistical significance was set at p-value < 0.05 for all comparisons.

4. RESULTS

4.1. Demographics and Patient Characteristics

Since this is a retrospective study, it was investigated, whether the treatment groups were comparable regarding important patient characteristics such as gender, age and tumor entity. Thereby, the tests show a homogeneity among those parameters ($p>0.05$). The study included a total of 91 patients, with fairly equal gender distribution, 48 patients being male (53%) and 43 female (47%). The mean age of the total group of patients at the time of intervention was 66 years, ranging from 38 to 90 years.

When the frequency of organ site or primary tumor type in the 91 patients was tabulated without respect to the sex of the patients, the lung was the most common organ of tumor origin (45.1%). The next neoplastic groups or organ sites encountered in order of descending frequency were breast (23.1%), genitourinary tract (13.2%), and gastrointestinal tract (7.7%). In 2 patients (2.2%), the primary site of the neoplasm was never determined. Only one mesothelioma was recognized. All parameters describing main characteristics of study population are presented in Table 1.

Table 1. Demographics and patient characteristics

	Number of patients (N = **91**)	Percentage (%)
Age at intervention (years) mean± SD, [range]	65.83±12.33 [38-90]	
Gender		
Male	48	52.7
Female	43	47.3
Comorbidities		
Cardiovascular	65	71.4
Renal	21	23.0
Primary malignancy		
Lung	41	45.1
Breast	21	23.1
Genitourinary	12	13.2
Upper Gastrointestinal	5	5.5
Lower Gastrointestinal	2	2.2
Hematological	1	1.1
Liver	1	1.1
Mesothelioma	1	1.1
Other	5	5.5
Unknown (CUP)	2	2.2
Treatment group		
VATS[a] + Pleurodesis	22	24.2
VATS[a] + IPC[b]	21	23.1
VATS[a] + Pleurodesis + IPC[b]	22	24.2
IPC[b]	26	28.6
Systemic Therapy	74	81.3
Hypoalbuminemia[c]	43	47.2

Data are presented as number (%) and as mean±standard deviation

[a] Video-assisted-thoracoscopic-surgery

[b] Indwelling pleural catheter

[c] Hypoalbuminemia was defined as serum albumin value below 35g/L

The VATS pleurodesis group comprised 22 patients, with 12 patients of male (54.5 %), and 10 of female sex (45.5%), respectively. The mean age was 67 years. The VATS IPC group consisted of 21 patients, of which 13 were male (61.9%) and 8 female (38.1%), respectively. Another 22 patients were treated by a combination of VATS pleurodesis and IPC placement. This group consisted of 12 male (54.5%) and 10 female (45.5%) patients. Mean

age of this group was 62 years. The last group was managed by sole IPC placement and comprised 26 patients, of which 11 were male (42.3%) and 15 female (57.7%). For this group, mean age was 65 years. There were no statistically significant differences between type of surgical treatment modality with respect to gender (P=0.593). Demographics and patient characteristics of treatment groups are shown in Table 2.

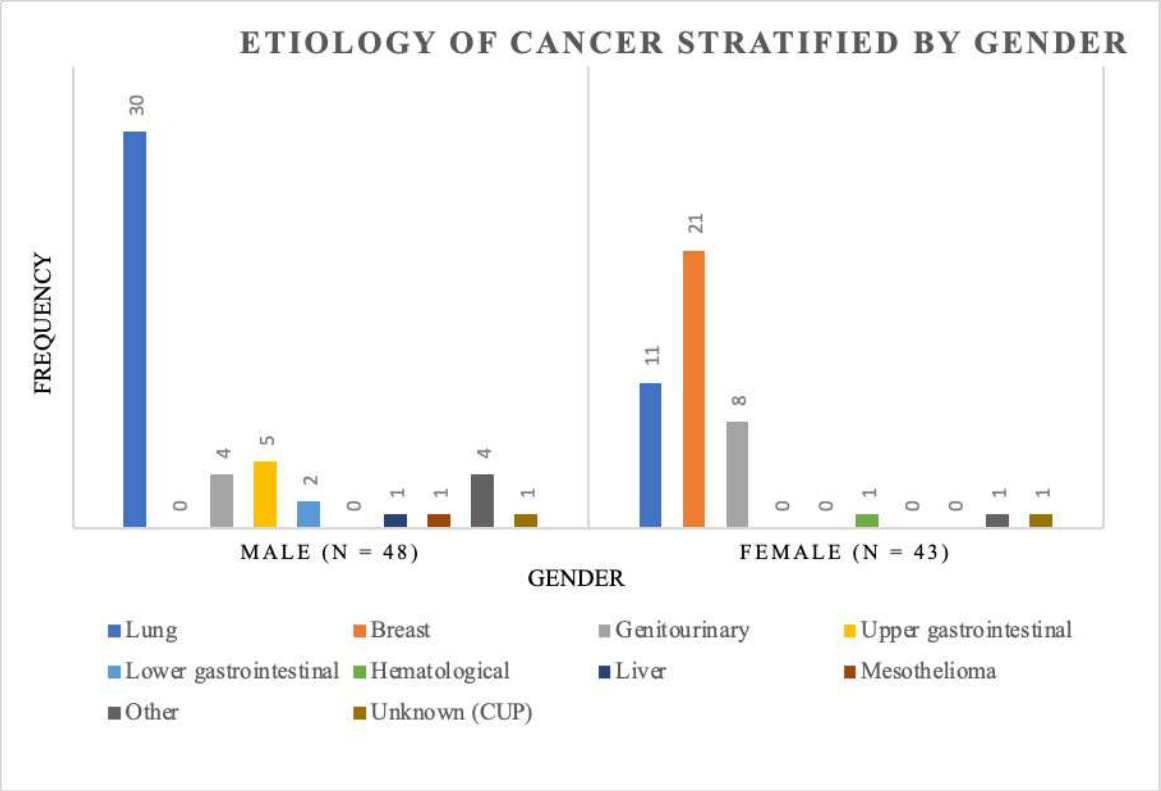
Table 2. Demographics and patient characteristics within treatment groups

	Intervention				
Variables	**VATS[a] + Pleurodesis (N = 22)**	**VATS[a] + IPC[b] (N = 21)**	**VATS[a] + Pleurodesis + IPC[b] (N = 22)**	**IPC[b] (N = 26)**	***P****
Gender					**0.593**
Male (N = 48) (%)	12 (54.5)	13 (61.9)	12 (54.5)	11 (42.3)	
Female (N = 43) (%)	10 (45.5)	8 (38.1)	10 (45.5)	15 (57.7)	
Age at intervention (years) mean± SD, [range]	66.94±12.08 [38-84]	68.88±10.23 [52-85]	62.20±13.46 [38-87]	65.48±12.95 [47-90]	
Primary Malignancy					
Lung (N = 41) (%)	11 (50.0)	12 (57.1)	8 (36.4)	10 (38.5)	
Breast (N = 21) (%)	4 (18.2)	4 (19.1)	6 (27.3)	7 (26.9)	
Genitourinary (N = 12) (%)	2 (9.1)	1 (4.8)	4 (18.2)	5 (19.2)	
Upper Gastrointestinal (N = 5) (%)	1 (4.5)	2 (9.5)	2 (9.1)	0 (0.0)	
Lower Gastrointestinal (N = 2) (%)	1 (4.5)	0 (0.0)	1 (4.5)	0 (0.0)	
Hematological (N = 1) (%)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	
Liver (N = 1) (%)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Mesothelioma (N = 1) (%)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Other (N = 5) (%)	0 (0.0)	0 (0.0)	1 (4.5)	4 (15.4)	
Unknown (CUP) (N = 2) (%)	1 (4.5)	1 (4.8)	0 (0.0)	0 (0.0)	

All the data is presented as whole numbers (percentage) or mean ± SD.
***** Chi-square test
[a] Video-assisted-thoracoscopic-surgery
[b] Indwelling pleural catheter

A further understanding of the frequency distributions of neoplastic organ site causing malignant pleural effusions is gained, by separating the malignant effusions due to pleural carcinosis as they occurred in males and in females (Figure 8). Among 48 male patients, cancer of the lung accounted for nearly 65%. Upper gastrointestinal tumors were the second most common cause and comprised 10.4% of the male population. Cancers metastatic from the genitourinary tract (8.3%) completes the list of the three most common sites of origin of the malignancies in males. In the females with malignant pleural effusions, the three most common cancers were metastatic carcinoma from the breast (48.8%), metastatic carcinoma from the lung (25.6%) and metastatic carcinoma from the female genital tract (18.6%).

Figure 8. Etiology of cancer stratified by gender



4.2. Treatment Outcomes

As shown in Table 3, a total of 83 patients (91.2%) had initial successful pleurodesis after the intervention. This was defined as no symptoms related to malignant pleural effusion and/or no fluid on radiologic images of the chest. In 19 patients (86.4%) of the VATS pleurodesis group, treatment was initially successful. Same applied for the VATS IPC group with 18 (85.7%) initial treatment successes. Furthermore, similar initial success rates could be observed in the VATS pleurodesis IPC group and sole IPC group with 21 patients (95.5%) and

25 patients (96.2%) respectively. Adversely, 8 patients (8.8%) did not initially respond to the treatment they received. There was however no statistically significant difference between treatment groups and initial pleurodesis failure (P=0.436).

Also included in Table 3 are the late treatment outcome success rates for all 69 patients (75.8%) and late failure rates for all 22 patients (24.2%) as well as late success and failure rates for the respective treatment groups. Late pleurodesis failure was defined as either reoccurrence of symptoms related to malignant pleural effusion and/or fluid detected on chest imaging. Similarly, no statistically significant difference could be observed between treatment groups with regards to late pleurodesis failure (P=0.068).

Table 3. Pleurodesis outcomes among different therapeutic interventions

Outcomes	**Intervention**				**Total**	**p***
	VATS[a] + Pleurodesis (N = 22)	**VATS[a] + IPC[b] (N = 21)**	**VATS[a] + Pleurodesis + IPC[b] (N = 22)**	**IPC[b] (N = 26)**		
Initial pleurodesis failure (%)	3 (13.6)	3 (14.3)	1 (4.5)	1 (3.8)	8 (8.8)	0.436
Initial pleurodesis success (%)	19 (86.4)	18 (85.7)	21 (95.5)	25 (96.2)	83 (91.2)	
Late pleurodesis failure (%)	8 (36.4)	2 (9.5)	8 (36.4)	4 (15.4)	22 (24.2)	0.068
Late pleurodesis success (%)	14 (63.6)	19 (90.5)	14 (63.6)	22 (84.6)	69 (75.8)	

Data are presented as number (%) of patients.
Pleurodesis success was defined as no symptoms and/or fluid on chest-imaging.
Pleurodesis failure was defined as symptoms related to pleural effusion and/or fluid on chest-imaging.
Initial was defined as before discharge from hospital or less than 30 days.
Late was defined as after discharge from initial hospitalization or after 30 days.
* Chi-square test
[a] Video-assisted-thoracoscopic-surgery
[b] Indwelling pleural catheter

4.3. Morbidity and Adverse Events

An overview of number and rate of adverse events within treatment groups is provided in Table 4. A total of 21 adverse events (23.1%) were recorded among all 91 patients. In the VATS pleurodesis group, 4 patients (18.1%) experienced an adverse event. Patients treated with VATS and IPC placement had a total of 5 complications (23.8%). In the VATS pleurodesis and IPC group, 9 adverse events (40.9%) were noted. Patients, which underwent IPC placement suffered from 3 complications (11.5%). There was a statistically significant difference between groups regarding occurrence of adverse events, with patients treated by a combination of VATS pleurodesis and IPC placement, experiencing complications more frequently (P=0.026, OR = 3.288, 95% CI [1.147 - 9.430]).

Table 4. Adverse events according to treatment groups

Treatment groups	**Adverse events (N = 21)**	**OR (95% CI)**	***P****
VATS[a] + Pleurodesis (%) (N =22)	4 (18.1)	0.679 (0.202-2.29)	0.533
VATS[a] + IPC[b] (%) (N = 21)	5 (23.8)	1.055 (0.334-3.327)	0.927
VATS[a] + Pleurodesis + IPC[b] (N = 22) (%)	9 (40.9)	3.288 (1.147-9.430)	**0.026**
IPC[b] (N = 26) (%)	3 (11.5)	0.341 (0.091-1.275)	0.109

Data are presented as number (%) of patients.

Abbreviations: OR- odds ratio; **95% CI-** 95% confidence interval.

***** Chi-square test

[a] Video-assisted-thoracoscopic-surgery

[b] Indwelling pleural catheter

Details of adverse events are shown in Table 5. The three most common complications occurring were IPC dysfunction (N = 5, 23.8%), 1 in the VATS IPC group, 2 in the VATS pleurodesis IPC group and 2 in the IPC group, followed by Pneumonia (N = 3, 14.3%), all occurring in the VATS pleurodesis IPC group as well as respiratory insufficiency after intervention (N = 3, 14.3%), of which 2 occurred in the VATS pleurodesis and 1 in the VATS pleurodesis IPC group, respectively. No statistically significant differences were seen between treatment groups and type of adverse event (P=0.103).

Table 5. Type of adverse event according to treatment group

	Treatment groups				
	VATS[a] + Pleurodesis (N = 22)	**VATS[a] + IPC[b] (N = 21)**	**VATS[a] + Pleurodesis + IPC[b] (N = 22)**	**IPC[b] (N = 26)**	***P****
Type of adverse event (N = 21)					**0.103**
IPC[b] dysfunction (N = 5)	0	1	2	2	
Pneumonia (N = 3)	0	0	3	0	
Respiratory insufficiency (N = 3)	2	0	1	0	
Pleural empyema (N = 2)	0	1	0	1	
Wound healing disorder (N = 2)	0	0	2	0	
Cardiovascular instability (N = 2)	1	1	0	0	
Subcutaneous emphysema (N = 1)	0	0	1	0	
Pulmonary edema (N = 1)	0	1	0	0	
Hemorrhagic shock (N = 1)	0	1	0	0	
Acute dyspnea (N = 1)	1	0	0	0	

Data are presented as numbers.

* Chi-square test; [a] Video-assisted-thoracoscopic-surgery; [b] Indwelling pleural catheter

4.4. Survival Analysis

Out of 91 patients, 67 died (73.6%) and 24 were still alive (26.4%) at the end of the study. The mean survival time after the surgical intervention was 138 days (4.6 months). 18 patients (19.8%) died within 30 days. Another 18 patients (19.8%) survived for 30 to 90 days. 10 patients (11%) had survival times of more than 90 days up to 180 days. 21 patients (23%) survived more than 6 months. The mean survival time in the VATS pleurodesis group was shortest with 75 days. This was followed by mean survival of 81 days in patients managed by sole IPC placement. In the VATS pleurodesis IPC group, mean survival time was 125 days. Longest mean survival time achieved patients in the VATS IPC group with 130 days. However, statistically significant differences with respect to survival could not be observed between groups (P=0.554). Table 6 gives an overview of mortality and survival times of the study population.

Table 6. Survival overview

	Survival						
	Days mean ± SD	**<30 days**	**31 to 90 days**	**91 to 180 days**	**>180 days**	**Alive**	***P****
Intervention							0.554
VATS[a] + Pleurodesis (N = 22) (%)	**74.95**±97.46	6 (27.3)	5 (22.7)	3 (13.6)	4 (18.2)	4 (18.2)	
VATS[a] + IPC[b] (N = 21) (%)	**129.76**±218.69	6 (28.6)	2 (9.5)	2 (9.5)	5 (23.8)	6 (28.6)	
VATS[a] + Pleurodesis + IPC[b] (N = 22) (%)	**125.05**±176.80	3 (13.6)	3 (13.6)	1 (4.5)	7 (31.8)	8 (36.4)	
IPC[b] (N = 26) (%)	**81.46**±85.48	3 (11.5)	8 (30.8)	4 (15.4)	5 (19.2)	6 (23.1)	
Total (N = 91) (%)	**138.31**±160.82	18 (19.8)	18 (19.8)	10 (11.0)	21 (23.0)	24 (26.4)	

Data are presented as number (%) of patients and days as mean±standard deviation
* Chi-square test
[a] Video-assisted-thoracoscopic-surgery
[b] Indwelling pleural catheter

To identify prognostic factors for survival, univariate analysis and multiple linear regression model was used. Univariate analyses revealed that hypoalbuminemia significantly correlated negatively with survival (Pearson correlation coefficient (r)=-0.322, P=0.008), whereas receipt of systemic therapy and successful pleurodesis were associated with significantly longer survival (Pearson correlation coefficient (r)=0.310, P=0.011; Pearson correlation coefficient (r)=0.247, P=0.044),respectively (Table 7).

Table 7. Bivariate correlation between different parameters and survival.

Parameters	**Survival**	
	Pearson correlation coefficient (r)	**p value** (2-tailed)
Type of intervention	0.030	0.811
Tumor entity	0.082	0.508
Age	0.116	0.350
Gender	-0.062	0.616
Hypoalbuminemia[a]	-0.322**	**0.008**
Systemic therapy	0.310*	**0.011**
Pleurodesis failure	-0.015	0.907
Pleurodesis success	0.247*	**0.044**
Adverse events	-0.099	0.426

**. Correlation is significant at the 0.01 level (2-tailed)
*. Correlation is significant at the 0.05 level (2-tailed)
[a] Hypoalbuminemia was defined as serum albumin value of less than 35g/L

These variables were examined by multivariate analysis, and hypoalbuminemia (b = -83.33, P=0.031) persisted as independent and significant unfavorable predictor of survival in patients with malignant pleural effusion due to pleural carcinosis (Table 8).

Table 8. Multiple linear regression analysis; Dependent variable: Survival in days

Predictors	Unstandardized beta coefficients	Standard Error	Standardized beta coefficients	t	*P*
(Constant)	46.060	64.251		0.717	0.476
Hypoalbuminemia	-83.333	37.783	-0.260	-2.206	**0.031**
Systemic therapy	74.797	46.408	0.195	1.612	0.112
Pleurodesis success	91.100	57.566	0.185	1.583	0.119

$R^2 = 0.190$; $adjR^2 = 0.151$; $F(3;63) = 4.918$; $p = 0.004$

Survival curves for hypoalbuminemia using the Kaplan-Meier method are shown in Figure 9. Comparison was made using the log-rank test (P=0.008).

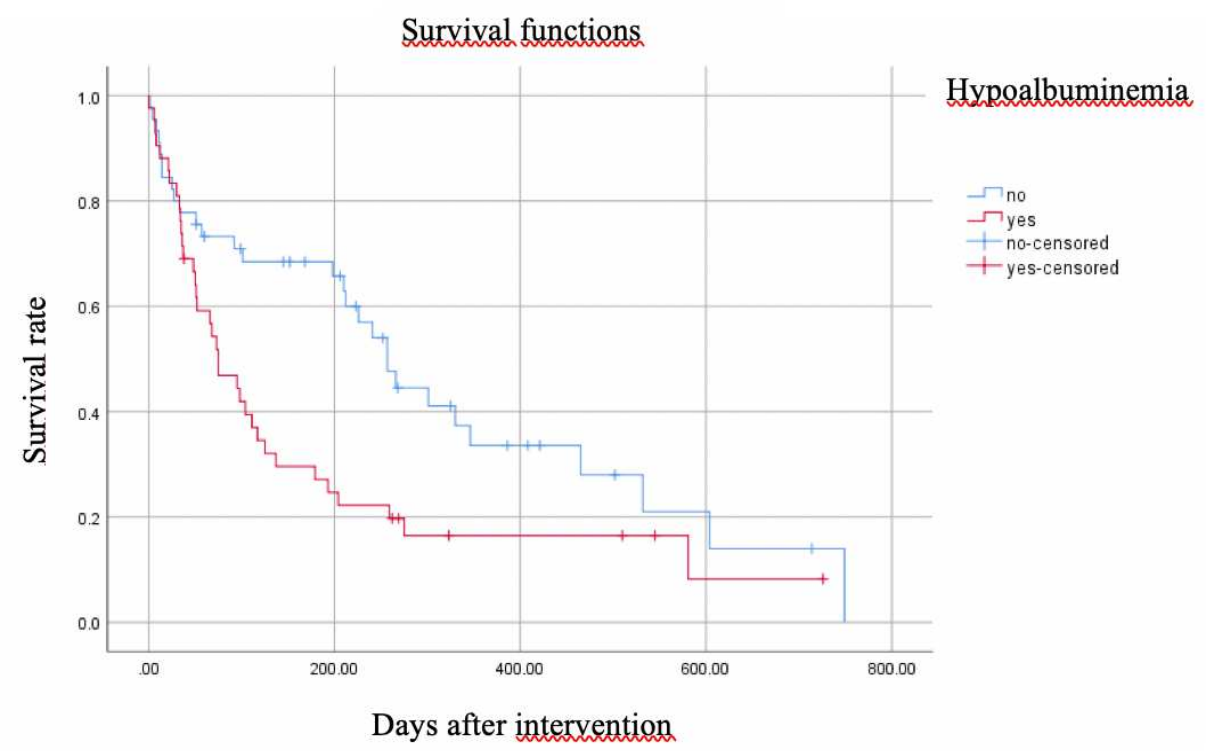


Figure 9. Kaplan-Meier survival curves for 91 patients with hypoalbuminemia (n = 43, 47.3%) and for patients without hypoalbuminemia (n = 48, 52.7%). Hypoalbuminemia was defined as serum albumin value below 35g/L.
*log-rank test, P = 0.008

4.5. Duration of Hospital Stay

The mean duration of total hospitalization time was 11.6 days for all treatment groups from day of admission. Length of total hospital stay (LOS) was further divided into initial length of stay with a mean of 10.1 days and length of stay at readmission with a mean of 1.5 days. For the VATS pleurodesis group, total length of stay accounted for a mean of 14.6 days, for the VATS pleurodesis IPC group 14.5 days and for the VATS IPC group, mean total length of stay was 12.5 days. Shortest duration of total length of stay could be seen in the IPC group with a mean of 6.7 days. Those differences regarding duration of hospital stay between treatment groups showed statistical significance (P=0.017). Table 9 illustrates the respective duration of hospitalization times.

Table 9. Duration of hospital stay

	LOS[a] initial admission in days [SD]	**LOS[a] readmission in days** [SD]	**LOS[a] total in days** [SD]	***P****
Intervention				**0.017**
VATS[b] + Pleurodesis (N = 22)	12.50±5.88	2.09±3.28	14.59±6.19	
VATS[b] + IPC[c] (N = 21)	11.71±6.26	0.81±2.60	12.52±6.68	
VATS[b] + Pleurodesis + IPC[c] (N = 22)	11.32±4.56	2.32±3.88	14.50±5.18	
IPC[c] (N = 26)	5.69±4.09	1.53±3.31	6.65±4.91	
Total	10.09±5.86	1.53±3.31	11.62±6.50	

Data are presented as mean±standard deviation
* Chi-square test
[a] Length of stay
[b] Video-assisted-thoracoscopic-surgery
[c] Indwelling pleural catheter

ANOVA with *post hoc* Tukey HSD test demonstrated statistically significant results with IPC placement, shortening initial length of hospital stay as well as total length of hospital stay compared to the other treatment modalities (Table 10). Specifically, IPC placement shortened mean length of hospital stay at initial admission for 6.8 days (P<0.001), 6.0 days (P=0.001) and 5.6 days (P=0.002) compared to VATS pleurodesis group, VATS IPC group and VATS pleurodesis IPC group, respectively. Same applied to total length of hospital stay with IPC placement, shortening mean total hospitalization time by 7.9 days (P<0.001), 5.9 days (P=0.004) and 6.9 days (P<0.001) compared to VATS pleurodesis, VATS IPC and VATS pleurodesis IPC group, respectively.

Multiple Comparisons

Table 10. Comparison of duration of hospitalization times between interventions.

						95% Confidence Interval	
	(I) Inter-vention	(J) Intervention	Mean Difference (I-J)	Std. Error	Sig.*	Lower Bound	Upper Bound
LOS[a] initial	IPC[c]	VATS[b] + Pleurodesis	-6.808*	1.511	**<0.001**	-10.76	-2.85
		VATS[b] + IPC[c]	-6.022*	1.530	**0.001**	-10.03	-2.01
		VATS[b] + Pleurodesis + IPC[c]	-5.626*	1.511	**0.002**	-9.58	-1.67
LOS[a] readmission	IPC[c]	VATS[b] + Pleurodesis	-1.129	.955	0.639	-3.63	1.37
		VATS[b] + IPC[c]	.152	.967	0.999	-2.38	2.68
		VATS[b] + Pleurodesis + IPC[c]	-1.357	.955	0.490	-3.86	1.14
LOS[a] total	IPC[c]	VATS[b] + Pleurodesis	-7.937*	1.662	**<0.001**	-12.29	-3.58
		VATS[b] + IPC[c]	-5.870*	1.683	**0.004**	-10.28	-1.46
		VATS[b] + Pleurodesis + IPC[c]	-6.983*	1.662	**<0.001**	-11.34	-2.63

*. The mean difference is significant at the 0.05 level.

* One-way analysis of variance (ANOVA) with *post hoc* Tukey HSD test

[a] Length of stay

[b] Video-assisted-thoracoscopic-surgery

[c] Indwelling pleural catheter

5. DISCUSSION

In men, lung cancer is the most common tumor metastatic to the pleura and breast cancer in women, together accounting for 60-65% of all malignant effusions, leading to a significant reduction in the quality of life of patients affected (77). Unfortunately, the prognosis for patients with MPE is usually poor, ranging between 3 and 12 months, and they therefore have a need for effective management of their respiratory symptoms (4). Treatment options are various, but in any case, palliative management of MPE involves treatment of the two major symptoms, especially dyspnea and chest pain, which most often result from a combination of pleural fluid accumulation and encasement of the lung from a growing tumor (13). Those general considerations were also taken into account by this study. The majority of patients in this study suffered from lung cancer approaching 50%, followed by breast cancer with almost 25 % and the third most common malignancies in our study population, accounting for almost 15 % were originating from the genitourinary tract.

Mean survival time in this study was rather at the lower end of reported survival times, which might partly be explained by the high proportion of advanced stage lung cancer patients. Special emphasis for the treatment of malignant pleural effusion due to pleural carcinosis in the presented study, was put on four major surgical treatment modalities, namely VATS for performing pleurodesis, VATS together with IPC placement, a combination of VATS pleurodesis and IPC placement as well as sole management with an indwelling pleural catheter.

Since no intervention so far has been able to prolong life, any attempt in the management of malignant pleural effusion will inevitably be of palliative nature (5, 78). High quality evidence on various therapeutic approaches is unfortunately lacking and therefore it is not surprising to find great variability in the management of this condition. Due to the development of a wider range of therapeutic options, diversity in daily practice increases, becoming particularly evident when comparing results of surveys, completed by pulmonologists and thoracic surgeons, which underlines this trend (79). While pulmonary specialists prefer placement of IPCs or rather offer pleurodesis as talc slurry to patients requiring treatment and only refer 20% for VATS, their surgical counterparts on the other hand, regard pleurodesis via VATS as the first-line and preferred therapeutic option (80).

Another point to criticize is the evaluation of outcome measures in the treatment of MPE since effectiveness if often judged, based on radiological assessment as the only determinant of success and pleurodesis occurrence is seen as a necessity (48, 67). Fortunately, patient-centered outcomes including time of hospitalization or avoidance of readmission to the hospital, quality of life (QoL) and relief of symptoms, have recently gained more impact as

main outcome measures and are increasingly used as measure of success instead of re-accumulation of pleural fluid as only measure of effectiveness of an intervention (75). Ultimately management should be tailored around the patient's general health status, individual needs and wishes, underlying malignancy and to some degree local expertise as well as availability (66).

VATS is generally regarded as more invasive and resource consuming than the other interventions commonly used in the treatment of MPE. It is mostly performed under general anesthesia with multiple ports of access and single-lung ventilation, which is possible with the use of double lumen endotracheal tubes (61). The lung can be partially or completely collapsed, offering superiority of view and enough accessible space to perform interventions in addition to the possibility of assessing the lung during re-expansion (61). In this case, pleurodesis is often subsequently performed. Other potential advantages include the possibility of mechanical abrasion of the pleural surfaces and, if necessary, even pleurectomy and decortication (4). Some centers even perform decortication in order to expand a lung that is trapped by malignant infiltration of the visceral pleura, even though this carries a higher risk of complications (69).

While there is major heterogeneity in practice, most centers only offer and perform VATS in patients with a general health condition stable enough to undergo surgery. Most studies report a success rate of over 90%, although this highly depends on patient selection as well as proposed definition of treatment success as outcome measure (78). VATS has a high potential of definitive elimination of MPE until death without the need for any further interventions. A promising alternative to conventional VATS, especially for patients with a poor performance status, who are mostly excluded from studies, is 'tubeless' VATS, which can be performed under moderate sedation and is increasingly offered to poor surgical candidates (78). So called 'mini-VATS', another recently developed approach, also provides an alternative by offering the advantages of conventional VATS but being less invasive at the same time due to smaller instruments (78).

Advocates of VATS pleurodesis will especially highlight one major advantage: The ability to perform adhesiolysis and even dispersion of talc in the pleural space. Similar success rates could be observed in this study by the use of VATS pleurodesis with initial treatment success of 86.4 % and even 95.5 % when combined with an IPC. Those results could also be observed in other studies, where VATS pleurodesis turned out to be effective in 82%, especially when malignant pleural effusion was caused by metastatic lung or breast cancer (81) as well as in other prospective randomized trials (82) or meta-analysis (83). Therefore,

VATS pleurodesis, especially with talcum as sclerosing agent, has been shown to be highly effective, with the prerequisite of an expandable lung (84). Also, with regards to long term effectiveness, VATS pleurodesis shows promising results with one-year recurrence-free interval of 67% (84, 85). Our study also underlines this finding with long term success rates of almost 65%.

In this study, we could also demonstrate an effective approach in the management of MPE by combining thoracoscopic pleurodesis and IPC insertion into a single procedure. Our initial pleurodesis success rates of 95% compare well with other studies like with TAPPS RCT trial (86), even though the long term success rates of 64% could not exactly reach their reported 71.1 and 78.8% at 3 and 6-months. For those patients whose pleurodesis was unsuccessful, TPC was a safety net that improved dyspnea despite need for continued placement.

More recently, a pilot study by Reddy *et al.* (87) demonstrated a reduction in hospital length of stay and TPC duration when PP was coupled with simultaneous TPC placement. Their approach effected pleurodesis in 92% of patients with a mean inpatient stay of 3.2 days (vs. a historical control of approximately 6 days) (88) and a median of 1.8 days. Rapid pleurodesis combines thoracoscopic-guided talc poudrage with IPC insertion during the same procedure. In a recently published single-center retrospective chart-based study, ambulatory thoracoscopic poudrage and IPC insertion were found to be a safe and effective option in the management of MPE, with a 77.8% pleurodesis rate at 6 months (89, 90).

A separate small study by Boujaoude *et al.* involving 29 patients reported a 92% pleurodesis success rate at 1 month and a median duration of hospitalization of 3 days as well as improvement in dyspnea scores (91). Compared to our approach, patients in these studies were routinely admitted post-procedure and underwent aggressive drainage of their IPC. Another crucial factor, different from this study was the exclusion of deceased from the final analysis. Nevertheless, these findings support the safety and efficacy of combinational approaches.

The high initial success rates of the combinational approach of VATS pleurodesis and IPC placement was also accompanied by a significantly higher rate of complications, compared to the other treatment groups with 40.9% of patients experiencing some sort of adverse event. This might be explained by mounting, not only the respective advantages of the individual treatment, but their complications as well. Similarly, high initial treatment success rates could be recognized for patients treated with indwelling pleural catheters, however with significantly lower number of adverse events. Patients undergoing VATS and IPC placement had an excellent response to therapy with 85.7 % and experienced complications in 23.8% of

cases. Patients managed with sole IPC placement, had initial treatment success of 91.2%, with 11.5% suffering from an adverse event, which is in accordance with results of a large meta-analysis of Van Meter *et al*. (92)

In a study by Pollak *et al*. (93), the effectiveness of IPCs was assessed in 28 patients suffering from MPE. Dyspnea could be improved in 94% of patients at 48 hours and in 91% on day 30 post procedure. MPE control was achieved in 90% of patients at the end of the study. They came to the conclusion, that IPCs require shorter duration of hospitalization and placement as well as management could be achieved in the outpatient setting. With regards to potential complications of pleural catheters, dislodgement and infections were observed most often. However, serious complications were uncommon (6).

Reflecting the findings of several other studies, including Markowiak *et al*. *(94)* and Dilkaute *et al*. (95), IPC placement drastically reduced the duration of time spent in the hospital for patients compared to the other, more invasive treatment options. The mean duration of hospital stay in the IPC group at initial admission accounted for 5.7 days. This reduced the mean duration of initial hospitalization time by 6.8 days, compared to VATS pleurodesis, 6.0 days when compared to the VATS IPC group and 5.6 days with regards to the VATS pleurodesis IPC group.

Furthermore, this means that 91.2% of patients could be safely discharged usually within 3 to 6 days, reducing reliance on hospital bed capacity which may be severely limited in situations such as the coronavirus pandemic, as well as decreasing the risk of infection for the patients. The short LOS is also likely to be important to patients given the limited survival time for individuals with MPE.

One major difference to other studies is the time point, at which duration of in hospital stay was assessed. In this study, this started from the day of admission in contrast to the time of intervention, often used as starting point in other research articles. This is the reason for longer total time spans given, as opposed to general shorter time intervals, seen in similar articles as mentioned above. Also, total hospitalization times could be contracted when patients were managed with sole IPC placement. Precisely, a 7.9 mean difference of total days spent in the hospital when compared to VATS pleurodesis, 5.9 days with respect to VATS IPC group and 7.0 days comparing it to VATS pleurodesis with IPC. However, most of the time spent in hospital for all groups, regardless of their treatment, was attributable to the initial duration of admission. Length of readmission did not differ significantly between treatment groups. It is noteworthy to mention and possibly explained by a high proportion of patients succumbing to their disease during the time of their readmission. Out of 22 patients (24.2%) who were read-

mitted due to recurrence of malignant pleural effusion related symptoms, only 3 (13.6%) survived, whereas 19 patients (86.4%) died.

In the VATS pleurodesis groups, late treatment failure was defined as recurrence of the effusion or symptoms related to effusion after an initially successful pleurodesis, whereas, in the pleural catheter groups, late failure was defined as the recurrence of the effusion or effusion related symptoms after its initial successful control. One possible criticism of the current study is the manner in which the efficacy of the two procedures was compared. Because a pleurodesis would have to occur for the treatment to be classified as successful in the IPC groups. However, we maintain that a treatment is successful as long as there is no pleural fluid re-accumulation or no pleural effusion related symptoms, whether or not a catheter is present. This, in part, explains the difference in outcomes regarding late treatment success. Finally, it is noteworthy that performing thoracoscopy without the use of any sclerosing agent or mechanical abrasion has a 50% chance of pleurodesis in patients with MPE (61). This finding, together with reported 40-70% auto-pleurodesis rates observed in patients treated with IPC, might further explain high late treatment success rates in this study, especially in those treated with a combination of VATS and IPC (3, 96).

According to the international literature there is a credible possibility that aggressive diseases are responsible for a rapid and plentiful recurrence of pleural effusion and limited life expectancy. Sahn and Good *et al*. (97) showed that this type of pleural effusion correlated with a pH of 7.28 or less or with a lower glucose concentration. These pleural fluid characteristics were not examined in our study. Nevertheless, this might be another contributing factor explaining the difference in late treatment success, since 50% of patients with advanced lung cancer, as an aggressive disease were treated with VATS pleurodesis, whereas lung cancer in the IPC group accounted for only 38% of treated patients. Opposingly, breast cancer as less aggressive tumor nearly constituted one third of cases in this group.

Long-term tunneled IPCs are effective in controlling recurrent and symptomatic MPE in selected patients, particularly those with a trapped lung. They are an option for symptom management in these patients and in those with short life expectancy, or significant operative risk factors (3). Spontaneous pleurodesis has been reported to occur in 40–70% of patients after IPC placement, and it may occur within 6 weeks, potentially allowing for pleural catheter removal (96). For that reason, some have proposed long-term IPC as primary MPE therapy (93). Chemical pleurodesis instilled through the IPC remains an option (86). The failure rate of IPCs is <4% and complication rates appear to be relatively low (98).

In this study, survival of patients was analyzed as well as predictive factors, correlating with survival. Overall mean survival time in our study population was expectedly low with 138.3 days (4.6 months), displaying the dismal prognosis. Reported survival times differ widely across studies. A study conducted by Stefani *et al*. (99) found an overall median survival of 7.7 months. Putnam *et al*. (100) on the other hand, reported overall median survival to be 3.48 months. Those observations translate also more into what we found in our study with respect to patient characteristics and primary tumor site. The type of surgical treatment modality used, did not affect survival significantly.

Studies that evaluated the primary site as an overall survival prognostic factor have shown controversial results, with our study displaying no correlation. However in other series, histology of the primary tumor was an independent prognostic factor, with breast being the histological type of better prognosis and lung, together with gastrointestinal cancer, the histological types of worse prognosis (101). Another study evaluated early mortality (3- month survival) and showed that breast cancer was also associated with longer survival (102). A lower concentration of pleural fluid protein has also been associated with a lower survival, in other studies. Bielsa *et al*. (103) showed a mean survival of 2.2 months when the pleural fluid total protein value was less than 3.85 g/dL, which proved statistical significance in multivariate analysis. This study included patients who had received previous oncologic treatment, in which MPE was a sign of disease progression. On the other hand, Anevlavis *et al*. (104) studied 90 patients who had received no systemic treatment for cancer and, therefore, had less advanced disease. In this sample, total protein concentration in the pleural fluid was not a factor related to patient survival. The explanation may be the advanced stage of cancer, which is strongly associated with hypoproteinemia and hypoalbuminemia (103).

In our study, univariate analysis could show significant positive correlation between successful pleurodesis and systemic therapy on the outcome survival. Interestingly, hypoalbuminemia defined as serum albumin value below 35g/L, also showed a significant, however negative correlation with survival. This result also persisted to be significant on multivariate analysis, showing that hypoalbuminemia was an independent negative predictor of survival for patients in our study. In this regard, the effect of regular loss of pleural effusion on the patient's nutritional status after IPC implantation may therefore also warrant further investigation. Hypoalbuminemia portends poor long-term prognosis in hospitalized patients regardless of the underlying disease and could be added to prognostic predictive models, which has also been proposed by Howard et al. (105), in a very recent study.

The results of a recently published systematic review by Hassan *et al*. (106) demonstrate a survival difference according to pleurodesis outcome in patients with MPE. Additionally, not only type of malignancy but also respective oncologic treatment has been shown to be associated with survival and even pleurodesis outcome. This was shown by several studies of different designs and on patients with different primary malignancies (106). In patients with MPE several factors affect pleurodesis outcome, survival, or both. In order to ascertain if there is true correlation between pleurodesis outcome and survival, it is crucial to control for possible confounders. Some of the studies reported multi-variate analyses, mostly by performing Cox proportional hazards model, to control for clinically relevant factors. Performance status was one of the most important factors affecting survival in such cohort of patients. Due to the retrospective nature of the study, we were unfortunately not able to determine the performance status for all our patients.

Different mechanisms have been proposed to explain the association between pleurodesis failure and poorer survival. One explanation might be the persistence of pleural fluid that can potentially act as a medium for further propagation of malignancy and as a barrier for oncological treatment to reach its target. This is supported by the observation that patients who failed pleurodesis and those who were treated with IPC had shorter survival times in comparison to patients who successfully achieved pleurodesis (106). There is *in vitro* data that show that MPE fluid allows perpetuation of cell lines from primary and secondary pleural malignancies. Additionally, the fluid also causes the malignant cells to resist the effects of cytotoxic medications (106). Alternatively, pleural inflammation, which is known to be associated with successful pleurodesis could have a role in the defense against cancer, and thus patients who fail pleurodesis might mount weaker inflammatory responses (107).

For future research, novel sclerosing agents and drug-coated IPCs will be under investigation during the next years, as well as the optimal manner of combining pleurodesis and IPCs with respect to correct timing and other practical considerations. Complementary therapeutic interventions tackling topics such as diet and exercise may also reveal to be beneficial adjuncts to standard pleural interventions in the holistic approach for patients with MPE (67). Future studies may very well include more patient-based outcomes. Supportive therapy such as nutritional interventions, exercise and psychological support have rarely been investigated, but could hold a significant role in MPE care for patients.

Ultimately, large multicenter RCTs stratified according to patient characteristics and comparing interventions ranging from surgical to minimally invasive methods of achieving pleurodesis or preventing fluid accumulation are needed to attain the ultimate goal of ‘person-

alized' management (78). An important limitation in general is the heterogeneous reporting of outcome measures across trials and limited data on patient-centered outcomes. This as well has important implications for future research. Selection of appropriate, clinically relevant, standardized outcome measures is essential. An internationally agreed definition of pleurodesis success and the timing at which it should be assessed would be hugely beneficial, along with a consensus about how to handle the inevitable patient attrition due to death (48).

One of the strengths of this research, was the ability to also include patients with evidence of a trapped lung, which is most commonly seen as an exclusion criterion by other studies, including the TAPPS RCT trial by Bhatnagar *et al*. (86). Beyond that, this study did not exclude patients with expected survival of less than three months, frequently encountered in other published papers, which potentially portraits the general condition and outcomes of patients in a wider and more applicable context.

There are however, potential limitations to our study. First, the retrospective chart-based approach of the study must be noticed. As with all retrospective study designs, a causal relationship between variables can therefore not be established. This design led to high rates of undocumented outcomes. This study tried to solve this issue by only including patients with completeness of medical case records. However, this also impacted the number of patients that could be accounted for in this study, resulting in somewhat lesser degree of generalizability. Another shortcoming, was the unavailability of records on the performance status of the patients, which may have introduced some degree of bias in the analysis. One point to criticize are the subjectively, patient reported outcomes without the use of standardized, validated and objective methods, which again, makes retrospective observational studies not the optimum study design. Those factors can be taken into account for further research on this evolving topic, in order to provide high quality evidence which can guide the clinical decision process in order to provide best patient-centered care and individualized therapy.

6. CONCLUSIONS

Treatment should be individualized and led by an assessment of the patient's prognosis and driven by a balance of the expected benefit and morbidity of the proposed procedure as well as individual desires of the patient. The ideal method for treating recurrent malignant pleural effusion should be simple, effective, and inexpensive, with minimal disturbance to the patient. The objective is to relieve distressing symptoms due to the effusion, to prevent further fluid re-accumulation, and to return the individual to a functioning state of health. The survival time is short and expressed in months for patients with MPE. The goal of the treatment is to decrease the severity of symptoms, disease burden and the duration of time spent in the hospital as well as to improve the quality of life of patients. Freedom from hospital admissions is an important goal for patients and their families. With the continued efforts to improve patient-centered endpoints, the combination of therapies offers promising alternatives over individual therapy alone.

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8. SUMMARY

Objectives: The aim of the presented study was to analyze clinical data of patients with symptomatic malignant pleural effusion due to pleural carcinosis hospitalized at the REGIOMED Clinics and to evaluate and compare outcomes of different local surgical treatment modalities with regards to effectiveness, survival, morbidity as well as duration of hospital stay.

Materials and methods: Patients with cytologically or histopathologically proven pleural carcinosis and malignant pleural effusion, hospitalized at any of the REGIOMED Clinics facilities in Germany, from January 2018 to December 2020, were included in this retrospective observational chart-based study. All patients were suffering from dyspnea. Patients were divided into groups according to the type of treatment they received. The aforesaid treatment options are the following: VATS (video-assisted thoracoscopic surgery) pleurodesis (mechanical or chemical) alone or in combination with an indwelling pleural catheter (IPC), combination of VATS and indwelling pleural catheter (IPC), or sole management with an indwelling pleural catheter (IPC).

Results: The study included 91 patients, aged between 38 and 90 years. Mean survival time was 138.3 days. No significant differences could be detected between treatment groups regarding the outcome treatment failure, neither initially (P=0.436), nor late treatment failure (P=0.068). In the VATS pleurodesis IPC group, patients experienced significantly more complications compared to the other treatment modalities (OR:3.288, P=0.026). Hypoalbuminemia, systemic therapy as well as successful pleurodesis (r=-0.322, P=0.008; r=0.310, P=0.011; r=0.247, P=0.044 respectively) significantly correlated with survival. In multiple linear regression, hypoalbuminemia persisted as independent predictor of survival (P=0.031). The type of intervention patients underwent showed significant difference regarding duration of hospital stay (P=0.017).

Conclusion: Treatment should be individualized and led by an assessment of the patient's prognosis and driven by a balance of the expected benefit and morbidity of the proposed procedure as well as individual desires of the patient. The ideal method for treating malignant pleural effusion should be simple, effective, and inexpensive, with minimal disturbance to the patient. The survival time is short and expressed in months for patients with MPE. With the continued efforts to improve patient-centered endpoints, the combination of therapies offers promising alternatives over individual therapy alone.

9. CROATIAN SUMMARY

Naslov: Usporedba ishoda kirurških i drugih invazivnih modaliteta liječenja malignog pleuralnog izljeva u bolesnika s pleuralnom karcinozom

Cilj: Cilj studije bio je analiza kliničkih podataka pacijenata s malignim pleuralnim izljevom zbog pleuralne karcinoze, hospitaliziranima u Klinici REGIOMED, te procjena i usporedba rezultata raznih modaliteta lokalnih kirurških tretmana u vezi djelotvornosti, preživljenja, smrtnosti, kao i trajanja hospitalizacije.

Materijali i metode: U ovu retrospektivnu opservacijsku temeljenu na karticama uključeni su pacijenti s citološki ili histopatološki dokazanom pleuralnom karcinozom i malignim pleuralnim izljevom, hospitalizirani u nekoj od jedinica Klinike REGIOMED u Njemačkoj od siječnja 2018. do prosinca 2020. Svi pacijenti patili su od zaduhe. Gore spomenute opcije tretmana su slijedeće: VATS (videoasistirana torakoskopska kirurška) pleurodeza (mehanička ili kemijska) sama ili u kombinaciji s tuneliranim pleuralnim kateterom (IPC), kombinacija VATS i tuneliranog pleuralnog katetera (IPC), ili samo tunelirani pleuralni kateter (IPC).

Rezultati: Studija je uključila 91 pacijenta, starosti između 38 i 90 godina. Srednje vrijeme preživljenja bilo je 138,3 dana. U skupini VATS pleurodeza IPC, pacijenti su imali značajno više komplikacija u odnosu na druge modalitete liječenja (OR:3,288, P=0,026). Hipoalbuminemija, sistemska terapija i uspješna pleurodeza (r=0,322, P=0,008; r=0,310, P=0,011; odnosno r=0,247, P=0,044) značajno su korelirali s preživljenjem. U višestrukoj linearnoj regresiji, hipoalbuminemija ustrajala je kao neovisan pretkazivač preživljenja (P=0,031). Vrsta tretmana kojem su pacijenti bili podvrgnuti pokazala je značajnu razliku u vezi trajanja hospitalizacije (P=0,017).

Zaključak: Liječenje mora biti individualizirano i vođeno procjenom pacijentove prognoze te ravnotežom očekivane koristi i smrtnosti predloženog postupka kao i pacijentovim individualnim željama. Idealna metoda liječenja malignog pleuralnog izljeva treba biti jednostavna, djelotvorna i ne skupa, s minimalnim uznemiravanjem pacijenta. Vrijeme preživljenja kod pacijenata s MPE je kratko i izraženo u mjesecima. Uz stalne napore k poboljšanju ciljeva usredotočenih na pacijenta, kombinacija terapija nudi obećavajuće alternative samo individualnim terapijama.

10. CURRICULUM VITAE

PERSONAL DATA

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EDUCATION

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09/2007 - 06/2015	Kaspar-Zeuß-Gymnasium, Kronach
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09/2003 - 07/2007	Elementary school Gehülz-Ziegelerden, Kronach

WORK EXPERIENCE

01/2022 - 01/2022	Clinical training at REGIOMED Klinikum, Coburg
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07/2016 - 09/2016	Nursing internship at REGIOMED Klinikum, Coburg
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ADDITIONAL SKILLS

Languages:	German (native), English (C1), French (basic skills),
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