Pathophysiological background and perioperative outcome of thymus removal with spontaneous ventilation by intubation. Moving forward with minimal invasiveness.

Ph.D. Thesis

Tibor Németh M.D.

Szeged

2023

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Ph.D. Program:

Clinical and Experimental Research for Reconstructive an Organ-sparing Surgery

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List of abbreviations

AC – Ambenonium Clorid

ACh – Acetylcholine

ALI – Acute Lung Injury

APC – Antigen Presenting Cell

ARDS – Acute Respiratory Distress Syndrome

ASA – American Society of Anaesthesiologists

AZA – Azathioprine

BIS – Bispectral Index

BMI – Body Mass Index

CARS – Compensatory Anti-inflammatory Immune Response

CD – Cluster Of Differentiation

CEA = Carcinoembryonic Antigen

COVID – Coronavirus Disease

CRP – C - Reactive Protein

CRC = Colorectal Cancer

CS – Corticosteroid

CT – Computed Tomography

DAMPS – Damage-associated Molecular Patterns

DFS – Disease Free Survival

DFI – Disease Free Interval

DIC – Disseminated Intravascular Coagulation

ECG – Electrocardiogram

ENB – Electromagnetic Navigation Bronchoscopy

ESTS – European Society of Thoracic Surgeons

EtCO2 – End-tidal Carbon Dioxide

FiO2 – Fraction of Inspired Oxygen

FEV1 – Forced Expiratory Volume in 1s

GCS – Glasgow Coma Scale

HPV – Hypoxic Pulmonary Vasoconstriction

ICI – Immune Checkpoint Inhibitor

IFN – Interferon

Ig – Immunoglobulin

IL – Interleukin

IVIG – Intravenous Immunoglobulin

MG – Myasthenia Gravis

MHC – Major Histocompatibility Complex

MITS – Minimally Invasive Thoracic Surgery

MODS – Multiple Organ Dysfunction Syndrome

MOF – Multi Organ Failure

mOLV – mechanical One-Lung Ventilation

NSCLC – Non-Small Cell Lung Cancer

NITS – Non-Intubated Thoracoscopic Surgery

NIV – Non-Invasive Ventilation

NK – Natural Killer

OS – Overall Survival

PAMPS – Pathogen-associated Molecular Patterns

PB – Pyridostigmine Bromide

PaO2 – Partial Pressure for O2 in arterial blood

PaCO2 – Partial Pressure for CO2 in arterial blood

PCO2 – Partial Pressure for CO2

PD-1 – Programmed Death Inhibitory Receptor

PDL-1 – Programmed Death Ligand 1

PEEP – Positive End-Expiratory Pressure

PET/CT – Positron Emission Tomography/Computed Tomography

PFS – Progression Free Survival

PSV – Pressure Support Ventilation

RATS – Robot Assisted Thoracoscopic Surgery

RIX – Rituximab

SI – Systemic Inflammation

SIRS – Systemic Inflammatory Response Syndrome

SOFA – Sepsis-related Organ Failure Assessment

sOLV – spontaneous One-Lung Ventilation

SPSS – Statistical Package for the Social Sciences

SV – Spontaneous Ventilation

SVI – Spontaneous Ventilation with Intubation

TCI – Target Controlled Infusion

TEA – Thoracic Epidural Anaesthesia

TGF – Transforming Growth Factor

Th – T helper

TIVA – Total Intravenous Anaesthesia

TIL – Tumour-Infiltrating Lymphocyte

TLR – Toll-like Receptor

TNF – Tumour Necrosis Factor

TPE – Therapeutic Plasma Exchange

TOF – Train-On-Four

VAS – Visual Analog Scale Score

VATS – Video-Assisted Thoracoscopic Surgery

V/Q – Ventilation/Perfusion Ratio

List of original papers

List of papers relating to the subject of the thesis

1. **Németh T,** Szabó Z, Pécsy B, Barta ZV, Lázár Gy, Torday L, Maráz A, Zombori T, Furák J. Changes in the surgical treatment of pulmonary metastases during the last 12 years. [A tüdőmetastasisok sebészi kezelésében történt változások az elmúlt 12 évben]. Orv Hetil. 2020 Jul;161(29):1215-1220. Hungarian. doi: 10.1556/650.2020.31770. PMID: 32628621. **IF: 0.54**
2. Furák J, **Németh T,** Lantos J, Fabó C, Géczi T, Zombori-Tóth N, Paróczai D, Szántó Z, Szabó Z. Perioperative Systemic Inflammation in Lung Cancer Surgery. Front Surg. 2022 May 20;9:883322. doi: 10.3389/fsurg.2022.883322. PMID: 35669251; PMCID: PMC9163434. **IF: 1,8**
3. Furák J, **Németh T**, Budai K, Farkas A, Lantos J, Romy Glenz J, Fabó Cs, Shadmanian A, Buzás A. Spontaneous ventilation with double-lumen tube intubation for video-assisted thoracic surgery thymectomy: a pilot study. Video-assist Thorac Surg 2023. https://dx.doi.org/10.21037/vats-23-37. **IF:0,2**

Cumulative impact factor of the publications on which this thesis is based: 2.54

List of papers not-relating to the subject of the thesis

1. Fabó Cs, Oszlányi A, Lantos J, Rárosi F, Horváth T, Barta ZV, **Németh T**, Szabó Zs. Non-intubated Thoracoscopic Surgery-Tips and Tricks From Anesthesiological Aspects: A Mini Review. Front Surg. 8 Paper: 818456 , 8 p. (2022) **IF:1,8**
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Cumulative impact factor: 25,061

1. INTRODUCTION

Scientific and technical progress has led to the development of newer and less demanding types of surgery in many areas of surgery compared to previous types. The progressively expanding range of available tests, increasingly detailed examinations, patients' demand for procedures with the least possible surgical burden, the shortest possible post-operative recovery and the fullest possible life have led to the development of many surgical techniques that were previously unfeasible or required a revision of the previous surgical indication criteria. Detailed laboratory diagnostics of previously difficult to access, but more recently becoming more widespread, immunological abnormalities have become routinely testable.

During our thoracic surgical procedures, even with our most careful and tissue-friendly surgical techniques, tissue damage occurs which activates the body's natural immune response, upsetting its homeostasis and leading to a condition known as inflammatory response. The intensity of the inflammatory response depends on several factors, some of which depend on the parameters of the actual surgical intervention and others on the anaesthetic impact.

In the first part of our thesis, we will review how the surgical management of metastatic tumours in the lung has changed, how the range of surgical options and the available anaesthetic methods have expanded at the beginning of the millennium. How this influenced the techniques that emerged and were introduced later.

We will then look at how the inflammatory response develops, how it is affected by surgical stress, the type of airway protection used during anaesthesia, how this affects complications in the post-operative period, and what options are available to influence the inflammatory response.

In the third part, a possible variation of video-assisted thoracoscopic thymectomy is presented, using the same technique as previously studied for lung resections, in an intubated but spontaneously breathing patient.

1.2. Setting of objectives

(1) In our study, we sought to answer the question of what surgical and anaesthetic changes and technical developments in the surgical management of resectable pulmonary metastases have taken place over 12 years, in relatively distant periods, comparing two five-year periods. The shift in the type of lung resection and the mode of anaesthesia towards minimally invasive has resulted in what outcomes for patients in terms of the postoperative parameters studied.

(2) During minimally invasive lung resections, we investigated the processes involved in the development and maintenance of the perioperative inflammatory response and how these are influenced by thoracic surgery - mainly the degree of surgical intervention and the degree of the anaesthetic factors, such as the administration of local anaesthetics, the type of ventilation, including a review of the physiological and pathophysiological differences between mechanical ventilation involving one lung and spontaneous unilateral ventilation. We have examined how and what options we have to prevent and influence the inflammatory response that has already developed, and we review the early and late negative effects on postoperative outcomes and further patient management, and ultimately patient recovery.

(3) A pilot study was performed in a video-assisted thoracoscopic technique for minimally invasive thymectomy to investigate whether the anaesthetic aspects of spontaneously breathing double lumen tube intubation can be performed as safely as isolated tube intubation and mechanical ventilation. Can patients with certain thymic abnormalities benefit to an extent not previously possible.

2. CHANGES IN SURGICAL AND ANAESTHESIA CARE FOR PULMONARY METASTASES BETWEEN 2004 AND 2016

Metastases are responsible for 90% of cancer mortality [1]. For metastatic tumours in the lung, if they meet the criteria for resectability, intact resection [2] can result in complete tumour-free survival, improving long-term survival. Lung resection for metastasis can be performed if the following criteria are met: primary tumour is under control, metastasis is technically resectable, good overall status and functional capacity, no extrathoracic metastasis - except for example resectable liver metastasis, no other more effective treatment modality [3]. According to data from the Korányi Yearbook, 316 resections were performed in Hungary in 2013 with indication of lung metastasis, of which 107 were performed with Video-Assisted Thoracoscopic Surgery (VATS) technique [4]. According to European Society of Thoracic Surgeons (ESTS) Database data in 2015, 14.2% (n = 8891) of lung resections were metastasectomies and 21.7% of all lung resections were performed with VATS technique [5]. Lung metastasis resection accounts for 15-50% of the interventions performed by some European thoracic surgery working groups [6]. For unilateral involvement, VATS-technique approaches may be used in addition to anterior, axillary and posterolateral thoracotomy, while for bilateral metastases, sternotomy and 'clamshell' exploration [7], but also subxyphoid and transcervical exploration may be effective.

In 1973, Morton et al. still performed pulmonary metastasectomies from one or bilateral thoracotomies, which in their study meant either a wedge resection, lobectomy or pulmonectomy. In their case, preoperative diagnosis of intrapulmonary lesions smaller than 1 cm was not possible, intraoperative diagnosis - palpation of the lung was of paramount importance, performed by both the operator and the assistant, even with collapsed and expanded lungs [8].

Van der Veen et al. proposed median sternotomy for the surgical treatment of pulmonary metastases because it allowed bilateral staging, intraoperative diagnosis of occult metastases, and complete surgical treatment in one session with low morbidity [9].

In 1996, McCormack et al. performed a prospective study in which they performed resection of 1 or 2 intrapulmonal nodules found during preoperative evaluation, followed by open thoracotomy, palpation of the lung, and found malignant nodules in 56% of patients that were not detected during VATS. In this study, VATS was proposed for diagnostic purposes [10].

In 2011, Cerfolio et al. investigated patients undergoing pulmonary metastasectomy from thoracotomy with preoperative 60-slice helical computed tomography (CT) and 5mm slice thickness. In 34% of their patients, they found an intraperitoneal nodule that was not imaged preoperatively [11]. This highlighted that the lower intrapulmonary nodule finding rate observed during the VATS technique is not a deficiency of the early VATS technique alone. Improvements in imaging tools and surgical technique are necessary for a higher intraoperative detection rate equivalent to thoracotomy.

In an 8-year study, Nakas et al. performed a 1mm slice-thickness CT scan as part of a preoperative examination, during which they were able to detect even small nodules, finding no difference in the number of undetected nodules between VATS and open thoracotomy [12].

In a meta-analysis of 8 studies by Meng et al., they investigated the outcomes of open thoracotomy and VATS metastasectomy and found better survival in the VATS group, although not significantly better than in the open group, and no difference in recurrence-free survival [13].

In a study by Murakawa et al. 1999-2014, data from 1047 patients were analysed and found that VATS metastasectomy for colorectal tumours (CRC) had better overall survival (OS) compared to open surgery [14].

2.1. Patients and method

The patients were divided into two groups. The first group consisted of patients operated on between 2006 and 2010, and the second group between 2014 and 2018. In the first group, 55 patients underwent 57 operations. The first metastasis removal was performed in 94.7% of patients (n = 54) and the repeated metastasis removal in 6.3% of patients (n = 3). 54.5% of patients (n = 30) were male, 45.5% (n = 25) were female, and the mean age was 57.9 years (24-80 years). The second group consisted of 115 patients, 69 male (60%) and 46 female (40%), with an average age of 62.2 years (26-82 years). During this period, 85.1% (n = 114) of the operations were for the removal of the first metastasis, while 14.9% (n = 20) were for repeated metastasectomy. Figure 1.

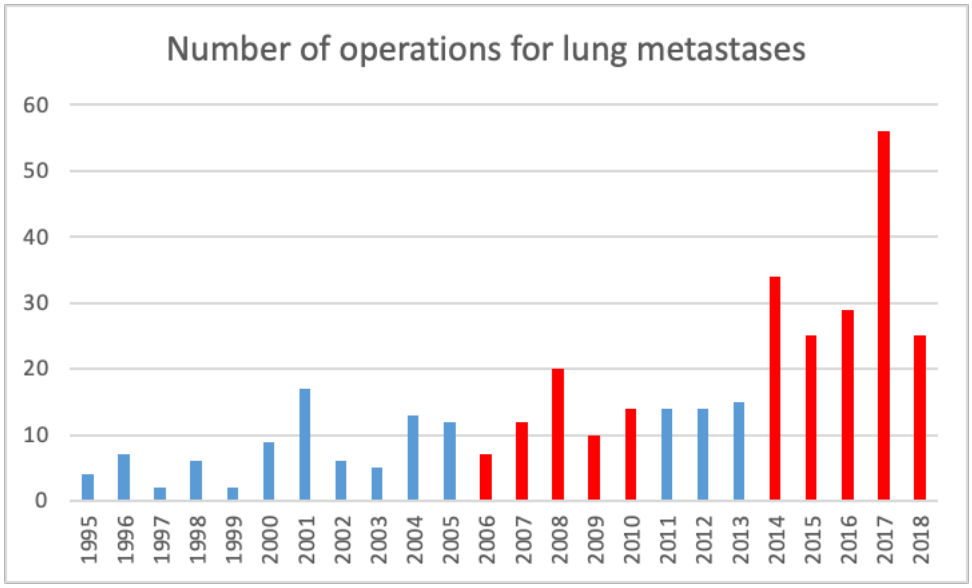

Figure 1. Number of patients undergoing surgery for metastases in the lungs during the analysed periods.

All patients will have a chest CT scan, bronchoscopy, plethysmography as part of the preoperative examination. The prolonged preoperative 'staging' tests have recently been replaced by positron emission tomography/computed tomography (PET/CT) scans.

Patients are intubated with a 2-lumen isolated tube to perform surgery. For non-intubated thoracoscopic surgery (NITS), patients are not intubated and relaxed. Patients are positioned in a lateral position on the operating table. Resections performed from the posterolateral thoracotomy include segmentectomy, lobectomy, pulmonectomy and atypical resection. At the end of the operation, the thoracotomy wound is closed in layers after leaving 1 or 2 chest drains and 1 subpleural analgesic cannula.

NITS surgery can be performed on patients who comply with the following criteria: body mass index (BMI) ‹ 28 kg/m2, American Society of Anaesthesiologist (ASA) I.-II., absence of sleep apnoea, perioperative blood gas results free of abnormalities, absence of intrapleural adhesions, no surgical reason for isolation of the operated side - protection of the opposite side, haemodynamically stable, no bleeding disorders or anticoagulant therapy, adequate Forced Expiratory Volume in 1s (FEV1), no potentially difficult airway provision expected, no persistent cough or large amounts of airway secretions, minimal chance of regurgitation, no increased intracranial pressure, patient is able to cooperate and accept this type of anaesthesia [15].

The preoperative examination was performed according to protocol. Patients were premedicated with a benzodiazepine (midazolam 0.02- 0.05 mg/kg) prior to surgery. Regional

(intercostal and paravertebral) analgesia was provided (bupivacaine 0.5%, lidocaine 2%) and intrathoracic blockade of the vagus nerve on the operated side was performed to abolish the cough reflex. Under routine monitoring: electrocardiogram (ECG), invasive blood pressure measurement, pulsoximetry, the bispectral index (BIS)-guided (target 40-60), target-controlled intravenous (TCI) propofol sedation was started, with opioid (fentanyl 1-2 mcg/kg body weight) administration. After reaching the target BIS, a laryngeal mask was inserted, through which end-expiratory carbon dioxide (EtCO2) and respiratory rate were monitored with continuous oxygen supplementation and regular arterial blood gas monitoring. It is also possible to ventilate the patient as needed, depending on the course of the surgery [16].

Surgical technique

Initially, VATS surgery was performed through multiple incisions. In uniportal VATS, the skin incision and soft tissue dissection is performed in the fifth intercostal space, using a so-called Alexis ring. If there are no adhesions, the lung will gradually collapse. Subsequently, intercostal anaesthesia is administered between the second and sixth ribs with 20 ml of bupivacaine 0.5% solution, divided proportionally. After waiting a few minutes, the lungs become moveable without the patient developing a reflex cough. After gentle elevation of the lungs, vagal blockade is applied by injecting 3 ml of bupivacaine 0,5 % solution: on the right side of the trachea, approximately 2 cm from the vena azygos in the upper mediastinum, and on the left side in the aortopulmonary window. The lung then becomes moveable without the patient coughing, leaving only the mediastinum and the diaphragm to move, which may cause some technical difficulties. The procedure to remove the involved lung areas is then identical to the steps of conventional surgery in an intubated patient [16]. The extent of the resection is the same as indicated for open surgery.

Statistical analysis was performed using SPSS v. 15 with the Kaplan-Meier method (IBM®, Armonk, NY, USA).

2.2. Results

Looking at the distribution of primary tumour localisation, we can see that in both periods colorectal tumours were the most common source of lung metastasis (36.8% vs. 38.8%), followed by kidney (14% vs. 9%) and then skin - melanoma malignum (14% vs. 7.5%). The detailed data are summarised in Figure 2.

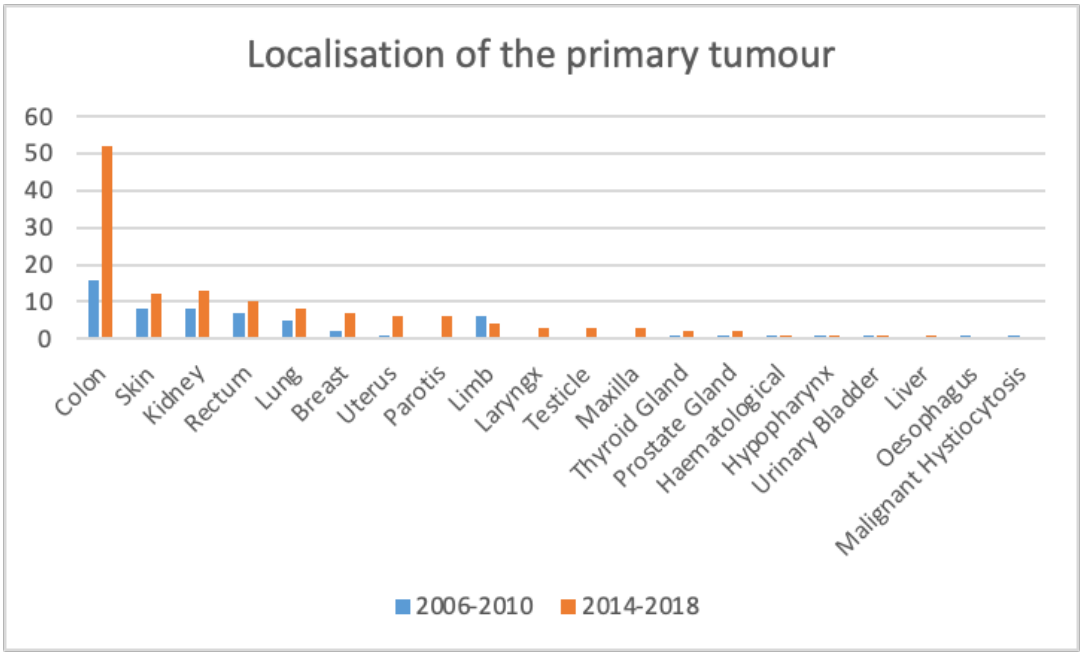

Figure 2. Distribution of lung metastases by tumour location.

Between 2006 and 2010, 57 surgeries were performed, 49.1% (n = 28) from the left side, 49.1% (n = 28) from the right side, and 1.8% (n = 1) from both sides in one session. In single-session bilateral surgery, posterolateral thoracotomy was performed on both sides. Solitary lesions were found in 54.4% (n = 31) and multiple lesions in 45.6% (n = 26).

Between 2014 and 2018, 134 surgeries were performed, 52.2% (n = 70) from the left side and 44.8% (n = 60) from the right side. In 3% (n = 4) metastasectomies were performed from both sides in one session, including 2 patients from sternotomy and 2 patients from single-session bilateral VATS insertion. Solitary lung metastases were detected in 58.2% (n = 78) and multiple metastases in 41.8% (n = 56).

When reviewing the distribution of the performed surgeries, we found that the most frequently performed intervention was atypical mechanical wedge resection (38.6% vs. 46.3%), followed by lobectomy (31.6% vs. 26.9%), pulmonectomy (10.5% vs. 1.5%) and segmentectomy (7% vs. 9.7%). Figure 3.

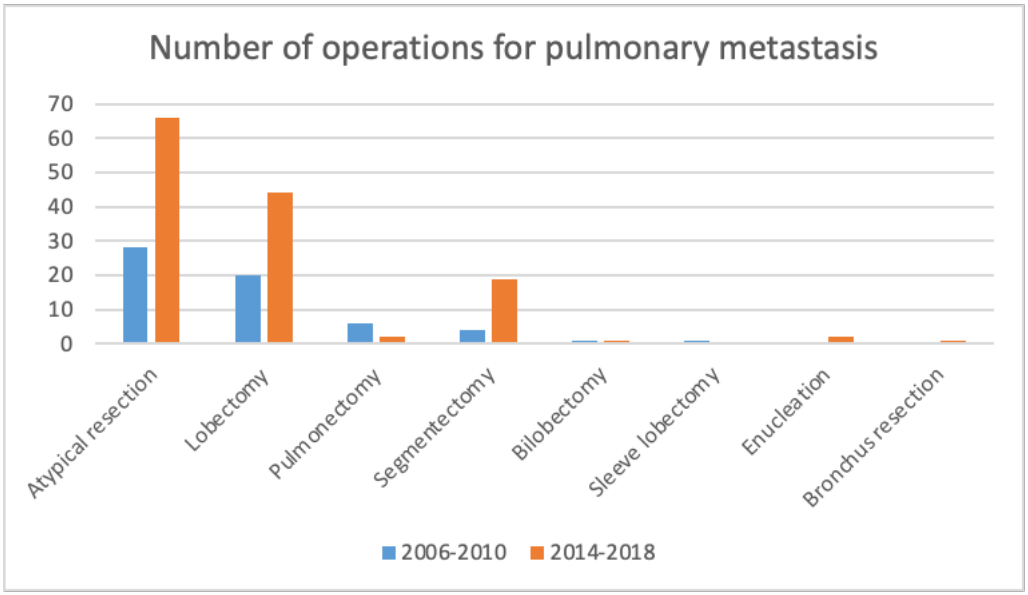

Figure 3. Distribution of the number of operations for metastatic lung tumours.

Looking at the surgical techniques, between 2006 and 2010, 5.3% (n = 3) of surgeries were performed with VATS, no uniportal VATS or VATS NITS, while between 2014 and 2018, 64.9% (n = 87) of surgeries were performed with VATS, 21.7% (n = 29) with uniportal VATS, and 10.4% (n = 14) with VATS NITS metastasectomy.

During the study periods, mediastinal lymph node involvement was found in 19.3% (n = 11) and 9.7% (n = 13) of patients. The distribution of lymph node-positive cases by primary tumour origin by group for all patients was as follows: rectum: n = 3 (5.3%), kidney: n = 2 (3.5%), limb: n = 1 (1.8%), thyroid: n = 1 (1.8%), colon: n = 1 (1.8%), haematology: n = 1 (1.8%), bladder: n = 1 (1.8%), skin - melanoma malignant: n = 1 (1.8%), and colon: n = 5 (3.7%), kidney: n = 3 (2.2%), breast: n = 2 (1.5%), limb: n = 1 (0.7%), rectum: n = 1 (0.7%), skin - melanoma malignant: n = 1 (0.7%).

In two- or more-session repeated metastasectomies, in the first period, all three cases of contralateral metastasis were removed. The mean time between metastasectomies in these patients was 7.33 months (1-20 months). In the second period, 4 patients underwent same-sided metastasectomy and 16 patients underwent repeated opposite-sided metastasectomy, with an average time between metastasectomies of 6 months (1-31 months).

The disease-free period between primary tumour and lung metastasis removal in the first period averaged 45.2 months (0-168 months), 55.4 months (0-168 months) for solitary metastasis and 30.9 months (0- 144 months) for multiple metastases. In the second period, the average was 33.8 months (0-180 months), 39.3 months (0-174 months) for solitary metastasis and 25.8 months (0-180 months) for multiple metastases.

The median survival of 39 months observed in the first group increased to 59 months in the second group. The five-year survival was 41% in both groups, so no significant difference could be found ($p = 0.282$).

2.3. Discussion

The first pulmonary metastasectomy was performed by Weinlechner in 1882 [7]. Since the beginning of our computerized data recording in 1995, we have seen a similar upward trend. The lung is one of the most common target organs for metastases, which most often develop by haematogenous spread via venous drainage. This is followed by anterograde or retrograde spread via the lymphatic system. Metastases may be solitary or multiple. It is important to distinguish between the different forms of metastasis, as the diagnosis, treatment and prognosis differ significantly [17]. In colorectal cancer, approximately 20% of patients have metastatic tumours, including liver or lung metastases, at the time of diagnosis [18], with a combined incidence of 5-10% [7]. Colon and rectal tumours have a relatively different metastatic localisation: while liver metastases are more frequent in colon tumours, the incidence of lung metastases is higher in rectal tumours [18]. In osteosarcoma, 81% of patients have lung metastasis at diagnosis [19]. 80% of patients with melanoma of cutaneous origin have metastatic tumours, 40% have only solitary lung metastasis [20].

In our earliest case, we performed the single session bilateral resections from a 2-sided thoracotomy, that was followed by a median sternotomy and after than we have done it from 2-sided VATS exploration.

Depending on the origin of the primary tumour, mediastinal and hilar lymph node dissection or lymph node sampling may be necessary. In cases of pulmonary metastasis, same-site lymph node dissection is performed at the time of primary surgery. In the case of metastasis to the contralateral lung, contralateral hilar and mediastinal block dissection is also required. If the primary tumour and metastasis have no adequate treatment alternative to surgical resection (e.g., sarcomas), systemic mediastinal and hilar lymph node block dissection is indicated. In other cases, there is no evidence for mediastinal lymph node dissection for pulmonary metastases, but in all cases, it has prognostic significance. In cases in which the patient is tumour-free by resection of the lung metastasis and hilar and mediastinal lymph node dissection - R0 resection - lymph node removal is also recommended.

In CRC, block dissection or sampling of the N1 and N2 lymph node regions provides information on the degree of possible dissemination of the disease, but its therapeutic impact is not supported [7]. Median survival in our patients was 33 months in lymph node-positive cases

and 39.3 months in lymph node-negative cases. These values were 54.8 months vs 59.6 months in the first period and 14.9 months vs 30.5 months in the second period. In sarcomas and CRC, the presence of short disease free interval (DFI), multiple lung metastases, complemented by elevated preoperative carcinoembryonic antigen (CEA) levels and mediastinal lymph node metastasis in CRC, is considered a poor prognostic factor, whereas resection of a previous CRC metastasis in the liver does not affect survival [6,7,21,22]. In CRC with lung metastases, thoracic lymph node involvement ranged from 7.1% to 30.3%, compared with 20.3% in sarcomas and 42.2% in renal cell tumours [7]. Among our patients, mediastinal lymph node involvement was found in 19.3% and 9.7% of patients per group during the study periods.

The number of operations performed for the indication of pulmonary metastasis more than doubled during the two studied periods (n = 57 vs. n = 134). No significant difference in the distribution of primary tumours was found. A review of surgical techniques shows a significant decrease in the number of pulmonectomies (10.5% vs. 1.5%) and an increase in the number of segmentectomies (7% vs. 9.7%).

The disease-free period between the primary tumour process and the operation for lung metastasis decreased from an average of 45.2 months in the first group to 33.82 months. We believe that regular and continuously improving oncological care and improved diagnostic possibilities play a significant role in this, allowing earlier diagnosis and treatment of lung metastases. DFI can range over a wide spectrum depending on the underlying disease. Schmid et al. found a DFI of 14.7 months for bone and soft tissue sarcomas [23], while Pfannschmidt et al. in their comprehensive study of colorectal tumours obtained DFI values between 20 and 37.5 months [7]. In our case series, we found a disease-free period of 17.9 months between surgery of the primary tumour and metastasis in patients undergoing metastasectomy for bone and soft tissue sarcomas, and 33.6 months for colorectal tumours.

The rate of repeated metastasectomy with two or more sessions was 5.6% in the first period and 17.5% in the second period. One of our patients had the highest number of metastasectomies, 4. Petersen et al. found an average disease-free survival of 9 months between surgeries for repeated double- or multi-session same- or opposite-site metastasectomies for melanoma malignum [20]. For our patients, this was an average of 7.3 months and 6 months per group, respectively. There was no significant reduction in survival with multi-session metastasectomy compared with single-session metastasectomy (15 months vs 17 months) [20], and some authors have even suggested that it may increase survival [24].

As in the case of lung metastases, the treatment regimen should always be tailored to the patient's overall ability to bear the burden and the optimal therapeutic option. In addition to

surgical resection, chemotherapy, radiotherapy, immunotherapy, biological therapy, laser therapy, 'ligasure', 'ultracision', thermoablative therapy may be considered [6,7,18,21,25].

Minimally invasive metastasectomy is recommended if the primary tumour is of colorectal or renal cell origin - these usually present as 1-2 larger nodules, as opposed to sarcomas which metastasise more and smaller [26]; if the metastasis is 3 cm or more in diameter, located in the peripheral lung area and there is no metastasis to the opposite lung [24].

The rate of VATS metastasectomy in our practice has increased significantly during the study periods (5.3% vs. 64.9%), which is in line with Hungarian national statistics, according to which in 2008, 15 out of 200 metastasectomies (7.5%) were performed with VATS [27], and in 2013, 107 out of 316 operations (33.9%) were performed with VATS [4]. With advances in diagnostic and localisation techniques, the removal of small lesions by VATS has been possible [28], with results consistent with those of open surgery [29]. Several techniques such as wire or isotope marking [28], dye marking with methylene blue, electromagnetic navigation bronchoscopy (ENB), intraoperative ultrasound [30] can be used to mark intrapulmonary lesions that are not palpable or small. At present, we do not have intraoperative chest CT scan - hybrid surgical facilities for accurate localization of such lesions. High resolution thin slice chest CT scan has a significant role in the increase of metastasectomies performed with thoracoscopic surgical technique. In a study by Kang et al, a 16-channel, multi- detector CT scan with a slice thickness of 1 mm for lung metastasis of non-osteosarcoma found a sensitivity of 96%. The same study showed a sensitivity of 100% in selected groups for lesions larger than 5 mm [31]. Thus, the indication for thoracotomy [7], previously performed only for the palpation localization of small lung metastases [32], is beginning to be eclipsed.

If the lesion seen on the preoperative CT scan is not found during VATS, or if we are unable to perform the resection due to any technical disadvantages of thoracoscopy or other technical reasons, Mutsaerts et al. recommend conversion to thoracotomy; in their patient series they found a conversion rate of around 20% [24].

Following metastasectomy, patients undergo regular oncological follow-up according to a protocol appropriate to the primary tumour. The 5-year survival can vary widely depending on the underlying disease. The best results are seen in germ cell tumours (68%), while the worst are seen in melanoma metastases (21%) [6]. In the latter cases, metastasectomy can increase 5-year survival from 3-5% to 21% [20]. In CRC, 5-year survival after metastasectomy is around 50%, while in untreated cases it is less than 5% [7,22]. In osteosarcoma, 5-year survival ranges from 20-25%, and in soft tissue sarcoma from 13-15% [19]. The 5-year survival independent of the primary tumour site of origin was 41% in both our groups.

The most important message of our study is that we have observed a significant increase in the number of minimally invasive surgeries over the period. In the first period, 5.3% of VATS surgeries were performed, with no uniportal VATS or VATS NITS interventions, whereas in the second period, 64.9% of surgeries were performed with VATS, of which 50.5% were multiportal VATS, 33.4% uniportal VATS, and 16.1% VATS NITS. For metastasectomies performed in the second session, we operated on from posterolateral thoracotomy in the first period and from sternotomy and VATS penetration in the second period. The rate of mechanical wedge resections and segmentectomies also increased in the second period, increasing the number of parenchyma-sparing minimally invasive thoracic surgery (MITS).

In order to reduce the stress on patients, we started to use the NITS technique, which required a revision of previous preoperative and intraoperative methods, both in terms of surgical technique and anaesthesia. During the daily use of the NITS technique, we were confronted with the fact that it could only be used in patients who met very strict criteria and that the laryngeal mask used in these patients did not provide an adequately secured airway. We therefore started to develop a method that preserves the advantages of NITS but protects against its disadvantages. Thus, the spontaneously ventilated intubated anaesthesia, where the patient is intubated with a double lumen tube but breathes spontaneously for a large part of the operation, was introduced and is now part of daily routine use, the practical use of which will be described later.

3. PERIOPERATIVE SYSTEMIC INFLAMMATORY REACTION DURING SURGICAL TREATMENT OF LUNG TUMOURS

Systemic inflammation (SI) is an immune response that can occur when an organism is injured. Regardless of its origin, the normal anatomical unit or the function of a particular organ or organs is impaired. The trigger may be infectious or non-infectious, such as a surgical procedure. Initially, the inflammatory process is always localized, and then the reaction and overreaction in response leads to a systemic inflammatory response reaction (SIRS). In the case of an infectious origin, the systemic inflammatory response reaction may be referred to as sepsis [33,34]. For an accurate diagnosis of a systemic immune response, the Sepsis-3 definition or the sepsis-related organ failure assessment (SOFA) scoring system may be used. In the first, the presence or absence of organ function is the determinant, while in the second, laboratory factors indicative of each organ function are the relevant: respiratory system test - partial pressure for O2 in arterial blood (PaO2), fraction of inspired oxygen (FiO2), presence or absence of mechanical one-lung ventilation (mOLV), coagulation parameters test - platelet count, liver function test - serum bilirubin level, cardiovascular system test - degree of hypotension, central nervous system test – glasgow coma scale (GCS), renal function test - serum creatinine level [35,36,37].

During the initial phase of systemic inflammation and then the inflammatory response, within the first few hours after the onset of the ictus, natural/innate immunity is activated, which includes activation of neutrophil granulocytes, macrophages, natural killer cells. This early defence mechanism is followed by the activation of the adaptive immune system. Two main parts of the adaptive immune system are known, one cellular (many types of T cells, B cells) and the other humoral (cytokines and molecules affecting immune function). Both parts of the body's defence line then work together in a coordinated manner to combat the systemic inflammatory trigger.

Systemic inflammation occurs during surgical and thoracic interventions, triggering proinflammatory and anti-inflammatory response processes [38,39]. Two important factors associated with SI in interventions for lung resection are postoperative morbidity and tumour cell spread [33,38,39]. Currently accepted thoracic surgical interventions for lung resection can be divided into two main groups. The first group includes open thoracoscopic surgery using one type of thoracotomy, while the second group includes minimally invasive thoracic surgery, such as VATS or robotic-assisted thoracoscopic surgery (RATS). MITS type procedures induce a smaller inflammatory response than open thoracic surgery [40] and the postoperative period

is easier for patients because of lower morbidity, shorter chest drainage time and shorter postoperative hospital stay [41,42].

In addition to surgical trauma, the type of anaesthesia has a significant impact on the development of systemic inflammation. Double lumen isolated tube intubation and mechanical ventilation are generally accepted in thoracic anaesthesia. The negative impact of mechanical one-lung ventilation on systemic inflammation can be reduced if the patient is spontaneously breathing – spontaneous one-lung ventilation (sOLV) [43]. MITS, most notably with the widespread adoption of VATS, has developed the technique of spontaneous ventilation, further reducing the systemic response [44], thus making already minimally invasive interventions simpler and shorter [45]. The most important pathophysiological change during spontaneous ventilation is the reduction of both the immune response and the inflammatory response to the intervention [46,47,48].

3.1. Pathophysiology of systemic inflammation

During systemic inflammation, the innate immune system and immune response is activated first, such as neutrophil granulocytes, macrophages, natural killer cells (NK) and dendritic cells, which are able to phagocytose tissue damaged during surgical trauma or mOLV and perform antigen presentation. These innate immune cells are also able to recognize pathogen-associated molecular patterns (PAMPS) and damage-associated molecular patterns (DAMPS) in the early postoperative period, such as tissue damage signals from surgical incision and dissection, which are recognized by TLRs (Toll-like receptors). These receptors are located on the surface of macrophages and dendritic cells. DAMPS are also able to bind to NOD (nucleotide-binding oligomerization domain-containing protein) receptors located intracellularly. Binding of DAMPS to TLR or NOD receptors activates proinflammatory cytokine production. Subsequently, pro-inflammatory cytokines TNFα, IL-6, IL-8, IL-1β, and anti-inflammatory cytokines IL-4, IL-10, IL-13, IL-1Ra, TGF-β would be released. This process occurs relatively rapidly. IL-6, IL-8, and IL-10 levels are already elevated by the time of skin closure after lung resection, contributing to postoperative complications [49,50]. These cytokines play a key role in cell-to-cell communication, in the generated immune response, and in the immune regulation. Normal levels of cytokines have a positive effect on the defence mechanism, but when their levels exceed normal levels, they have a negative side effect on immune regulation, inflammation, organ function and tumour cell proliferation [50,51]. Proinflammatory cytokine production triggers the systemic inflammatory immune response. SIRS benefits the body by reducing tissue injury, removing remnants of dead cells and initiating

healing processes [50]. NK cells are activated by high mobility group box protein 1 which is also released from the damaged tissue. For a specific immune response, a connection between antigen-presenting cells (APCs: macrophages, dendritic cells) and T-lymphocytes must be established. During SIRS, there is a massive immature neutrophil release from the bone marrow into the circulation, which causes an elevated white blood cell count after surgery and reduces lymphocyte numbers in the postoperative days by apoptosis [50,52]. After the encounter of antigens, cytokines and CD4+ lymphocytes, lymphocyte differentiation is initiated. Native CD4+ Th0 cells can develop in several directions, these cells are precursors of future Th1 and Th2 cells. Antigen-presenting cells, such as monocytes, macrophages, and dendritic cells, present antigens to CD4+ Th0 cells. It depends on the antigen whether Th0 cells differentiate into Th1 or Th2 cells by cytokines (IL-12, IL-4). Th1 cells produce proinflammatory cytokines such as interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumour necrosis factor-beta (TNF-β), which play an important role in the destruction of intracellular pathogens and tumour cells. Th2 cells produce anti-inflammatory cytokines such as IL-4, IL-5, IL-10, and IL-13, which play an important role in antibody production and protection against extracellular parasites. The antigen-presenting cell is part of the natural immune system, whereas T cells belong to the acquired immune system [51,53]. After activation of the acquired immune system, the number of leukocytes in the circulation increases, but at the same time the number of CD4+ and CD8+ lymphocytes decreases, which causes a shift in the Th1/Th2 ratio towards Th2, which will result in immune suppression. Both differentiation pathways are regulated and influenced by cytokines [50,54]. Adequate levels of cytokines are required for normal, physiological function of the immune system. Inflammation can remain localised if the cellular response and cytokines can be controlled, if not then the process progresses, and systemic inflammation develops. If the SIRS is prolonged, excessive proinflammatory cytokine production has a negative impact on the normal function of the body, leading to loss of organ function such as acute lung injury (ALI), possibly termination, or multiple organ failure (MOF), or in more severe cases, multiple organ failure syndrome (MODS). In advanced systemic inflammatory response, negative processes induced by cytokines may damage the cell membrane, lead to disseminated intravascular coagulation (DIC), capillary dysfunction through ischemia-reperfusion, all of which increase the rate of postoperative complications [50,55]. The association between proinflammatory cytokine levels and postoperative systemic inflammation has been proven [38,50,54]. To counteract the severity and time course of SIRS, the compensatory anti-inflammatory immune response (CARS) is activated. A significantly reduced Th1/Th2 ratio was observed from postoperative day 2 to postoperative day 14. The reduced Th1 response and

the intensified Th2 response are important factors in the development of postoperative complications [50]. The role of CARS is to maintain immune homeostasis through the production of anti-inflammatory cytokines (IL-4, IL-10). The previously accepted view was that the initial phase of SIRS is followed by CARS, but nowadays the predominant view is that SIRS and CARS develop in parallel [50,51]. Contrary to its original purpose, CARS may have an immunosuppressive effect, whereby it may also promote the development of sepsis and other secondary infections in late MODS [50]. Changes in leukocytes, NK cells [48], lymphocytes, and cytokines have been analysed in several studies [54,56], which have shown that these changes are smaller after NITS than in relaxed surgical cases [47]. The reduced inflammatory and immune changes after NITS suggest that immunosuppression is also smaller after NITS compared to relaxed cases [56,57].

3.2. Systemic inflammation and tumour immunity

In tumour surgery, an important issue is intraoperative tumour cell dispersion and the control of circulating tumour cells [58]. We know from animal studies that circulating tumour cells are significantly increased after tumour biopsy but disappear after resection of the tumour tissue. Circulating tumour cells can be detected up to 6 weeks after resection, so it is important that the immune system functions normally in the postoperative period, helping to clear circulating tumour cells [59]. The number of lymphocytes and NK cells, and their effectiveness against tumour cells, also decreases [60]. Clinical studies have shown that VATS is preferable to thoracotomy because it preserves cellular immune function better after surgery, with less reduction in circulating CD3+, CD4+, CD8+ T cells after surgery, which reduces the imbalance of immune regulation, preserves immunosurveillance, and reduces the chance of tumour growth and recurrence [60,61]. However, lobectomy and major lung resections performed during open thoracotomy and intubated VATS do not significantly reduce T-cell counts [40,62]. In non-intubated VATS surgery for non-small cell lung cancer (NSCLC), it was observed that not using a tube caused a smaller decrease in NK cell and lymphocyte counts than if it had been used [47,57]. The reason for the decrease in lymphocyte count is not fully understood. It is conceivable that lymphocytes are redistributed to the surgical site, apoptosis occurs, T cells are regulated by decreased numbers of T helper cells and increased numbers of cytotoxic T cells [63,64,65]. T cells are absolutely necessary and play a crucial role in immune regulation and tumour suppression. An imbalance of CD8+ cytotoxic and CD4+ helper/regulatory T cells within tumour-infiltrating lymphocytes (TILs) is a prognostic factor after surgical treatment of NSCLC [66]. T-lymphocytes regulate the anti-tumour response and facilitate tumour-specific

antigen depletion by binding to major histocompatibility complex (MHC-I). Upon activation of antigen-presenting cells, CD8+ T cells are given permission to destroy tumour cells and can greatly enhance the production of proinflammatory cytokines, thereby achieving immune-mediated tumour cell destruction. Nevertheless, tumour cells try to evade the immune response of the body by various mechanisms, such as the expression of inhibitory receptors and cytokines. The role of cytokines in tumour regulation and their molecular background is well established [67,68], most notably IL-6, which has a central role and has been extensively analysed in various clinical studies [44,54,57,69]. IL-6 has an important role in tumour cell communication. IL-6 also promotes tumour progression and dissemination of metastases and has an important systemic effect by which it misdirects metabolism, leading to mental problems in tumour patients [70]. There is more or less an equilibrium between Th1 immunity and Th2 immunity, but the presence of tumour cells and surgical interventions break this balance. Th2 immunity is increased while Th1 immunity is decreased, which will result in tumour progression. If Th1 immunity becomes predominant, immune stimulation will act in the direction of tumour regression [53]. The predominant role of cytokines is also seen in their ability to activate carcinogenesis and promote tumour growth, and to protect tumour cells from therapy-induced genome damage and programmed cell death [71]. During chronic inflammation or tumour growth, T lymphocytes are constantly exposed to high antigenic load, which leads to the appearance of inhibitory receptors on their surface, which limits further activation of inflammatory cells. Programmed-Death 1 (PD-1) is an inhibitory receptor that is also an immunological checkpoint, its ligand Programmed Death Ligand 1 (PDL-1) is absolutely necessary for proper immune tolerance, whereby T lymphocytes can regulate the PD-1 receptor and therefore lose their ability to increase proliferation and activation [72,73]. Tumour cells are able to produce PDL-1 and promote binding to the PD-1 receptor, thereby reducing T cell-mediated tumour cell death and avoiding cell death [74]. Recently, PDL-1 inhibitors have become the focus of treatment in a number of cancers (Hodgkin lymphoma, melanoma, advanced NSCLC). Compared with standard chemotherapy, PD-1 inhibitory IgG4 monoclonal antibodies are more effective because they have been associated with longer tumour progression-free survival (PFS) and overall survival (OS) [75,76]. Studies of 'immune checkpoint inhibitor' (ICI) treatment in patients with stage IV NSCLC have shown that elevated levels of inflammatory cytokines such as IL-6, neutrophil granulocyte/lymphocyte ratio, present prior to immunotherapy, negatively affect treatment response, with significantly shorter PFS [77]. The potential negative impact of systemic inflammation on ICI treatment is under investigation [78].

3.3. Systemic inflammation and surgical intervention

Postoperative morbidity after VATS lobectomy is significantly lower than after open lobectomy. In VATS, there are fewer cases of atrial fibrillation, renal failure, shorter hospital stays, shorter time to chest drain use, and less frequent development of postoperative pneumonia [41,42]. Although these studies do not mention the reasons for the observed differences in the number of postoperative pneumonia cases and the reasons for the improved immune response when using MITS surgical technique. The postoperative proinflammatory response is greater after open surgery than if VATS surgery had been performed, which is associated with a natural immune response [69]. IL-6 levels are significantly higher after open surgery compared to VATS surgery [46], SI/SIRS rates are significantly correlated with elevated IL-6 levels [38]. In oesophageal surgery, IL-6 and IL-8 levels are associated with the usage of thoracotomy, length of surgery, and amount of blood lost [37]. Among MITS techniques, robot-assisted thoracoscopic surgery is steadily increasing among surgeries for lung tumours. Perioperative outcomes are similar for both RATS and VATS [79], but in many cases operative times are longer with RATS than with VATS. There was no significant difference in the amount of acute phase proteins and immune response when comparing the two surgical techniques, suggesting that the degree of surgical trauma is similar between the two minimally invasive procedures [80]. Comparing different minimally invasive thoracic surgery techniques, Tacconi found no difference in systemic inflammatory response regardless of whether uniportal, multiportal, or hybrid VATS lobectomy was performed. They found that biomarkers of systemic inflammation returned to preoperative levels in 5 days [81].

3.4. Relationship between mOLV and sOLV

In thoracic anaesthesia for lung resections, the currently recommended procedure is mechanical ventilation through one lung in a relaxed patient. Knowledge of partial anatomy is very important, so it is easier to prepare for possible anatomical variations. The nomenclature of one-lung ventilation dates back to the pre-NITS era, which currently distinguishes 2 subgroups: mechanical one-lung ventilation (mOLV), previously called one-lung ventilation, and spontaneous one-lung ventilation (sOLV). There are several pathophysiological differences between the two procedures. In mOLV, in order to maintain oxygen levels or at least to reach near physiological levels, it is necessary to increase the ratio of oxygen in the inspired air or to use positive end-expiratory pressure (PEEP) or positive pressure ventilation (PSV). Nevertheless, hypoxia develops in 30-90% of patients ventilated with mOLV. The setting of the different parameters on the ventilator depends on the experience of the anaesthetist and

his/her expertise in thoracic anaesthesia. The smallest unit of the lung, the alveolus, may be damaged if the above parameters are not physiological or tolerated by the lung parenchyma. Mostly the so-called alveolo-capillary membrane, including the endothelial glycocalyx, is damaged. These changes are the basis of acute lung injury due to mechanical ventilation [82]. In order to avoid or at least reduce the number of complications, the use of protective ventilation is recommended, which involves keeping the tidal volume between 4-5ml/kg, the PEEP used between 5-10 cmH2o, an alveolus recruitment technique and the use of inhalation anaesthetics [83]. In cases where the cardiopulmonary status of the patient is normal, the use of protective ventilation is easily feasible, but in patients with obstructive lung disease, incipient pulmonary hypertension, it may be difficult. In mOLV, even a small difference in lung volume can cause hypoxia, hemodynamic imbalance, increased pulmonary vascular resistance, decreased cardiac output. To restore oxygenation, higher pressures and volumes are required to ventilate, which can already damage the alveolus [84]. Clinically, mOLV can be compared to ventilation in post-pulmonectomy patients. In a clinical study, it has been shown that an increase of 1ml/kg in tidal volume increases the chance of pathophysiological changes in the lung by a factor of approximately four [85]. It can be concluded that the respirator settings used for mOLV, which are mainly applied to patients with low respiratory function and impaired lung parenchyma, would need to be changed. High tidal volume can cause end-expiratory over-expansion in the lungs (volutrauma), which increases the risk of postoperative pulmonary complications [86]. Atelectrauma can be encountered in cases where ventilation was performed at low volume, unfortunately volutrauma can also develop during correction of atelectrauma. By using NITS we can protect our patients from these pathophysiological abnormalities.

3.5. Pathological changes in mOLV

High-pressure and high-volume ventilation are the main risk factors for alveolar damage in mechanical, single-lung ventilation. Lung elasticity is determined by the amount of elastic and collagen fibres. More than normal elongation may result in rupture injury of the alveolar wall, the alveolo-capillary membrane or the endothelial glycocalyx. Injury to the lung parenchyma results in cytokine release, inflammatory cell (neutrophils, macrophages, lymphocytes) influx and oedema in the ventilated lung [87]. From an experimental study, we know that in mechanical ventilation, the above changes are already observed in the first 90 min [88]. As part of the mOLV-induced biotrauma, immune cells would be activated and the inflammatory cascade is triggered, cytokines are produced. In addition, hyperperfusion develops at the affected site in mOLV. If hyperperfusion is combined with hyperinflation,

alveolar damage occurs, with interstitial oedema and microhaemorrhages [82,87]. During NITS, the disadvantages caused by mOLV, such as volutrauma, atelectrauma, biotrauma, can be further reduced.

3.6. Physiological changes with mOLV

Ventilation and perfusion are the most important functions of the lung, and given their close relationship, they are measured together as ventilation/perfusion ratio (V/Q). V/Q ratio shifts can occur at different stages of both mOLV and sOLV, but they can be influenced by several factors such as patient position, chest exploration, manipulation of the operated lung. Specific respiratory abnormalities during mOLV have been discussed previously. Pressure in the pulmonary artery, vein and alveolus play a central role in perfusion. Where lung volume is increased, alveolar capillaries are compressed, and thus pulmonary vascular resistance is increased. Hypoxic pulmonary vasoconstriction (HPV) is an oxygen-sensitive mechanism of the lung that reduces perfusion of a hypoxic lung area, thus creating a better ventilated area. The consequence of these factors is a V/Q shift. We know from experimental studies that a V/Q imbalance with hyperperfusion and alveolar injury on the ventilated side also develops in mOLV [88]. The beneficial effect of spontaneous ventilation on the V/Q ratio in patients with acute respiratory distress syndrome (ARDS) has been well studied. Spontaneous ventilation increases the ventilation/perfusion ratio, enhances cardiac function and results in better oxygenation [89]. A similar effect can be observed with sOLV. In mOLV ventilated lung abnormalities are reduced or eliminated when using the NITS technique with sOLV, but other potential drawbacks such as hypoxia or hypercapnia should be considered. Hypercapnia is one of the leading reasons for conversion to mOLV in NITS. In NITS, transient permissive hypercapnia ($pCO2<55$ mm Hg) is an accepted and well-known fact, which can be controlled by lung re-expansion and intermittent non-invasive ventilation (NIV), which may be converted if this is not successful [43].

3.7. Cardiac and haemodynamic effects of mOLV

As we have seen so far, pressure changes in the chest play a crucial role in the regulation of cardiopulmonary function. During mOLV, the pressure within the chest increases and the lung volume increases, which has a negative effect on atrial preload and thus on cardiac output. This usually only affects the right ventricle, and in normal myocardial function the left ventricle is not affected [84]. Using the NITS technique, preload may increase, similar to surgery in relaxed patients. The difference between sOLV and mOLV is clearly seen when the chest is

just opened and the negative intrapleural pressure is disappeared. During the onset of positive intrapleural pressure, when the lung collapses, changes such as hypoxic pulmonary vasoconstriction, increased pulmonary vascular resistance, and decreased venous return are seen. These changes stress the right ventricle and cause a transient reduction in right ventricular ejection fraction. During mechanical ventilation, when patients are ventilated with positive pressure and positive end-expiratory pressure, hypoxic pulmonary vasoconstriction and pulmonary vascular resistance can be reduced. There is little scope for the use of PEEP during NITS, but if the surgical procedure can be suspended for a short period of time, allowing the use of PEEP, both hypoxic pulmonary vasoconstriction and pulmonary vascular resistance can be reduced. Restoration of cardiac function often requires the administration of vasoconstrictive drugs. For these reasons, transient cardiac instability is very often encountered during the phase of NITS when the chest has just been opened. In our experience, after 5-8 min, when the increased hypoxic pulmonary vasoconstriction and pulmonary vascular resistance caused by the change in chest pressure have resolved, there is no difference between mOLV and sOLV in either cardiac or haemodynamic function. It should be noted that in NITS surgery, the type of this transient haemodynamic instability may show differences in patients undergoing thoracic epidural anaesthesia and in patients where paravertebral/intercostal anaesthesia and vagus nerve block have been used [90-94].

3.8. Systemic inflammation and spontaneous ventilation

For manipulation in the chest cavity and for resections involving the lungs, mOLV is the recommended anaesthetic technique, with the ventilated lung providing the gas exchange that was previously provided through both lungs, with known negative effects. mOLV uses higher tidal volumes and higher O2 concentrations, higher PEEP values, possibly using positive pressure ventilation, to maintain physiological oxygen and carbon dioxide levels during anaesthesia. Despite the protective ventilation technique, damage is often caused to patients' lungs previously damaged by a numerous diseases (fibrosis, emphysema, obstructive pulmonary disease, pulmonary arterial hypertension). Ventilation causes damage to the alveoli, overstretching their walls and resulting in volutrauma/barotrauma and atelectrauma [82,83,86]. These changes serve as a basis for the accumulation of inflammatory cells (neutrophil granulocytes, macrophages and lymphocytes), the release of cytokines (TNF-α, IL-6, IL-8, IL-1β), cause oedema in the dependant lung (biotrauma), ultimately leading to a systemic inflammatory response [87,88]. The unwanted effects of mOLV mentioned so far can be reduced by the use of sOLV. In both intubated and non-intubated sOLV thoracic surgery

[95,96], Spontaneous ventilation (SV) can prevent or at least reduce mOLV-induced volutrauma, atelectrauma and biotrauma. It has been investigated and reported in several publications that better immune responses and less immunosuppression can be seen with SV. When SV is used, there is a smaller change in NK cell count and lymphocyte count, and they return to baseline levels sooner than when surgery is performed in a relaxed patient [48]. These studies have revealed that SV has a smaller measure of immunosuppression [47] and have shown that SV has a long-term effect on survival. Patients operated on for pleural effusions of malignant origin and anaesthetised with SV were found to have longer survival than patients who were relaxed and mechanically ventilated. SV has an effect not only on immune cells but also on cytokine release. Studies of lung metastasectomy have compared the effects of the non-intubated technique and the relaxed technique. Non-intubated anaesthesia had less impact on immune function and systemic inflammatory response, with less IL-6 release [57]. The lower systemic inflammatory response observed in SV thoracic surgery in the perioperative period has clinical manifestations such as lower postoperative morbidity and shorter hospital stay. In a study of large lung resections, cytokine release was investigated in patients undergoing non-intubated SV thoracic surgery and found that IL-6 and TNF-α levels were significantly lower in patients undergoing SV surgery than in relaxed patients [44]. Changes in the levels of stress hormones, as factors involved in systemic inflammation, were also less marked in SV surgical cases compared to relaxed cases [97]. With sOLV, the levels of these released cytokines are lower than with mOLV, so they have less negative impact on the body's anti-tumour defences and are associated with better long-term outcomes after NITS. sOLV has significantly better OS and disease free survival (DFS) after surgery for lung tumours than the same surgery with mOLV. In spontaneously ventilating patients, the type of anaesthesia is an independent factor of OS and DFS [98]. mOLV versus sOLV has not been found to have a significant difference in recurrence or survival in other studies [99]. Meanwhile, awake patients undergoing breast tumour surgery also had shorter operative times and hospital length of stay than patients with extrathoracic tumours [100,101]. Case presentations have shown that thoracic part has been successfully performed in patients with oesophageal tumours who were spontaneously ventilating [102].

3.9. Relationship between locoregional anaesthesia and SVI

In spontaneous ventilation with intubation (SVI), the most commonly used locoregional anaesthetic technique is thoracic epidural cannula anaesthesia and paravertebral/intercostal anaesthesia combined with vagus nerve block. Thoracic epidural anaesthesia has several beneficial pathophysiological effects, such as improving left ventricular function in the presence of coronary artery disease, reducing morbidity and mortality associated with cardiac causes, fewer postoperative pulmonary complications and better management of patient pain [91, 93]. Unfortunately, epidural anaesthesia cannot be used in all cases, and its use is contraindicated in cases of spinal cord injury, epidural haemorrhage or haematoma, and inflammatory processes [103]. Studies have shown that paravertebral/intercostal block combined with vagus nerve block is preferable and better than thoracic epidural anaesthesia. In thoracic epidural anaesthesia (TEA), hypotension, pulmonary or urological complications, nausea or vomiting are more frequently encountered; however, these studies have not found any association between the type of locoregional anaesthesia and cardiac function or pulmonary circulation [94,104]. The sympatholytic effect of locoregional anaesthesia should be mentioned. Any of these methods of anaesthetic intervention reduces the stress factor caused by the surgical procedure, as well as IL-6, IL-8, and TNF-α levels [91,105], and troponin T and C-reactive protein (CRP) levels [106,107]. Epidural anaesthesia with mOLV and open oesophagectomy also reduces proinflammatory cytokine levels [108]. In principle, this effect should be even more pronounced with the use of sOLV. Intercostal nerve block can also significantly reduce the stress response by decreasing IL-6 and TNFα (tumour necrosis factor α) levels [105]. It is worth mentioning the meta-analysis studies that demonstrated that there is no significant difference between different types of anaesthesia in terms of the postoperative inflammatory response [109].

3.10. Effect of relaxation on immune function

The indirect effects of mOLV and relaxation on the immune response have been detailed, but the effects of muscle relaxants on macrophages, where they induce direct cytokine release, have not been discussed. An experimental study has compared the presence of acetylcholine (ACh), the α7ACh receptor on blood mononuclear cells and the cholinergic anti-inflammatory pathway [110,111]. ACh has been found to significantly reduce the release of proinflammatory cytokines in human macrophage cultures. in mOLV, drugs used to induce relaxation block neuromuscular junction by binding to ACh receptors. Theoretically, these muscle relaxants also inhibit ACh binding at the surface of macrophages, although to our

knowledge, which relaxant drugs bind to ACh receptors on the surface of macrophages has not yet been investigated. It is likely that the α7ACh receptor is found both on the postsynaptic muscle membrane and on the surface of macrophages. As a consequence, relaxation has a dual effect on the immune system, both in inducing cytokine release via mOLV and affecting cytokine release from macrophages. Both mechanisms can be avoided by using a NITS technique rather than mOLV.

3.11. Treatment of systemic inflammation

Several studies mention that one possible treatment for the inflammatory response is to reduce the levels of various cytokines, but the best treatment is probably to prevent it or minimise the factors that contribute to its development. The treatment of the pathophysiological presentation of systemic inflammation may be to remove or at least reduce cytokines from the circulation. A few approaches (filtration, dialysis, adsorption) have been tried to reduce cytokine levels, but no significant results have been achieved [112]. The most promising approach is the CytoSorb haemoadsorption procedure, which has a positive effect on advanced inflammatory responses such as sepsis and pneumonia [113]. In lung resections, the ability of cytokine elimination to prevent the development of systemic inflammation in the early postoperative period has not yet been investigated. In cardiac surgery, no difference between intraoperative and early postoperative cytokine levels and clinical outcomes has been found when investigating the Cytosorb absorption technique [114].

3.12. Discussion

The outcome of systemic inflammation after surgery depends on the proinflammatory and anti-inflammatory responses to the underlying pathological factors, which influence the clinical picture. Every patient undergoing lung surgery expects a rapid recovery and long-term survival, and our surgical management must be adapted to this expectation. All thoracic surgery results in systemic inflammation, and the best outcome is achieved with the least damaging surgical technique. The more minimally invasive the thoracic surgery, the more normal immune function is preserved. The changes in cellular defences and cytokine levels induced by postoperative systemic inflammation last for 3-12 days, although our impact is not limited to the early postoperative period but is also reflected in 30-day mortality [47,54,57]. The reduced number and function of lymphocytes and NK cells may also result in the loss of cellular defences. In clinical practice, this can manifest as post-operative pneumonia, wound infection, or other inflammatory processes. The rates of postoperative pneumonia were 5% and 10%,

respectively, yet the rates of wound infection were 0.4% and 1% after VATS and open lobectomy, respectively [42]. Because of the low induction of proinflammatory response, the use of SV may further reduce the incidence of several postoperative morbidities [96]. Using SV surgical approaches, the incidence of postoperative morbidity is 5%, compared with 23% in relaxed surgical cases [57]. After SV VATS lung resections, the time to postoperative confusion (fasting), use of chest drain, and postoperative hospitalization were shorter than in relaxed VATS cases [115,116]. The long-term oncological impact of SI in the case of tumour resection depends on the type of resection procedure. In one meta-analysis, relaxed VATS was shown to be superior in long-term survival outcomes in lung tumour resections, presumably due to the lower cytokine release associated with VATS compared to open surgery [117]. Another publication compared long-term survival between two groups of patients operated on with VATS and open surgery, but found no significant difference in survival [118]. Similar results in long-term survival were seen in patients operated on with SV VATS technique. Immune function decreases less after SV surgery, with several reports on its benefit on long-term survival. One of the most influential publications describes immune system changes after SV surgery and its impact, and found that survival was improved after surgery for malignant pleural effusions [47], respectively. that significantly better survival and disease-free survival were observed after lung tumour resections for SV surgery compared to patients who were relaxed [98]. In contrast, other authors have not found SV surgery-related benefits when examining survival or recurrence rates after SV surgery [99]. There are some encouraging results in short-term oncological treatment for SV surgery. Patients tolerated adjuvant oncological treatment better after non-intubated VATS lobectomies than after relaxed VATS lobectomies. There was less toxicity of oncological treatment and more patients (92%) could receive the adjuvant chemotherapy protocol compared to 72% in relaxed surgery [119]. Less toxic and higher rates of completion of adjuvant oncological treatment lead to better oncological outcomes. Similar trends are seen in patients undergoing ICI treatment. Although the present studies have only examined the effectiveness of ICI treatment in non-operated patients, the results are still clear, the greater the systemic inflammation at the start of immunotherapy, the less favourable the outcome. For this reason, postoperative systemic inflammation should be at its lowest before planned ICI treatment. Lymphocytes are critical in the anti-tumour response, which explains why whether a patient undergoes intubated or non-intubated VATS surgery is important in determining prognosis in patients with advanced NSCLC undergoing immunotherapy [77,78].

In conclusion, the thoracic surgeon can contribute to the reduction of postoperative SI by reducing the tissue-damaging effects of surgery for lung tumours, which is in line with

oncological principles. The more minimally invasive the intervention, the less immunosuppression the patient will experience. The positive impact of VATS surgery on SI is reflected in improved postoperative outcomes. To further reduce the adverse effects of surgery, SV is an excellent option. Nevertheless, SV is not a widely used intervention. The message is clearly that locoregional anaesthesia has a significant SI-reducing role whether used during relaxed VATS or open surgery.

4. VIDEO-ASSISTED THYMECTOMIES IN SPONTANEOUSLY VENTILATING, INTUBATED PATIENTS

Diseases located in the mediastinum can be removed from many procedures. In the past, open, median, total sternotomy and thymectomy from this were widely used [120-123]. With the continuous technical development, several modalities of VATS surgical techniques have come to the fore, including single-port, multi-port, lateral or subxyphoid incision, and robotic-assisted thoracoscopic surgery [124]. Currently, radical thymectomy is the accepted surgical option with VATS or RATS [125-128]. Significant surgical technological advances have led from 1866, the first awake patient thoracoscopy, to the "tubeless" thoracic surgery described in 2017 [129]. Of course, these technical advances would not have been possible without a significant evolution of anaesthesia. In patients who had previously undergone routine double-lumen tube airway securing and unilateral mechanical ventilation, postoperative myasthenic crisis occurred in about 34% of cases [130-132]. The use of muscle relaxants during surgery increases the risk of postoperative myasthenic crisis, and physiological changes during mechanical ventilation also have a tendency to increase the incidence of myasthenic crisis due to abnormalities in the inflammatory response [133,134]. Due to these factors, regional anaesthetic solutions have gradually come to the fore, and other techniques have been introduced to reduce the development of myasthenic crisis, such as short-acting muscle relaxants, neuromuscular block monitoring, e.g., train-on-four (TOF) [135,136]. In 2004, Tsunezuka et al. performed extended thymectomy in a fully awake patient using thoracic epidural anaesthesia from median transsternal exploration [137]. In 2008, Matsumoto et al. performed thymectomy in a fully awake patient from subxyphoid exploration using a sternal elevator [138]. Further developments in general anaesthesia have made it possible to perform non-intubated thoracoscopic surgery. However, there is potentially no safe airway during NITS surgery, and therefore a solution was needed to allow patients undergoing thymectomy to benefit from the NITS surgical solution. By combining these advantages, a solution has been developed whereby the patient is intubated but breathes spontaneously for a significant part of the operation, thereby providing an airway, minimising the amount of muscle relaxants and limiting the adverse effects of mechanical ventilation to a small part of the operation [96,139].

In our review, we report the early clinical experience, results and benefits of SVI VATS thymectomy.

4.1. Patient and method

In our clinical study, we present the results of patients who underwent SVI VATS thymectomy at the Department of Surgery of the University of Szeged between 9 October 2020 and 31 December 2022. During this period, we performed SVI VATS thymectomy in 15 patients, evaluating general data, perioperative data and their outcomes. The mean follow-up was 13.5 months (4 months - 29 months).

4.1.1. Patient selection

Many patients would not have undergone surgery because of the conditions used in non-intubated spontaneous breathing surgery (NITS) for chest surgery, as explained in detail earlier. In contrast, the indication for SVI had only one parameter to keep in mind, that the patient's BMI should not be more than 28 kg/m2. In some cases, where the type of obesity did not influence the type of thoracic surgery intervention, patients with a BMI above 30 kg/m2 were included in the SVI VATS thymectomy study group.

4.1.2. Surgical considerations

At the beginning of surgery, patients are given a short-acting muscle relaxant (mivacurium) and then intubated with a double-lumen isolated tube. During the short-acting muscle relaxant, the skin is anaesthetised with lidocaine hydrochloride and incisions are made on the right side: 10mm incision in the submammary fold in the anterior axillary line, 5mm incision between the sternal edge and the submammary port, 3cm incision in the mid-axillary line in the 3rd rib intercostal space. Identify the right vagus nerve and infiltrate the surrounding area with 5ml of 0.5% bupivacaine hydrochloride to inhibit the cough reflex (Figures 1-3). Inject a further 5ml of 0.5% bupivacaine hydrochloride into the subpleural space adjacent to the intercostal nerve 2-5 (Figure 4). Once the short-acting muscle relaxant has broken down, the patient breathes spontaneously without coughing. In some patients, a positive end-expiratory pressure of 4-6 Hgmm (PEEP) is used to maintain normal oxygenation. Thymectomies for myasthenia gravis involve removal of the entire thymus with all 4 horns, the adipose tissue around the thymus, the right pericardium - diaphragm angle, the superior vena cava - aortic angle and the adipose tissue in the aortopulmonary window. The phrenic nerve is identified and spared on both sides, the brachiocephalic sinistral vein is evacuated and the thymus vein running into it is supplied. Because of the many variations in the anatomy of the thymus and the thymic collateral horns, the area under the brachiocephalic vein is carefully explored and then a thymectomy is performed, dissecting down to the left phrenic nerve and

pulling off the cervical horns of the thymus. If the left chest cavity opens, anaesthesia uses a pressure-assisted mode (PSV), in which exhalation and inhalation are controlled by the patient. At the end of the operation, the tissue to be removed is placed in an Endobag and removed through the incision in the mid-armpit. At the end of the operation, a 28Ch drain is inserted into the retrosternal space in the surgical site, in place of the previous 10 mm port. A 3cm axillary incision is then closed in layers.

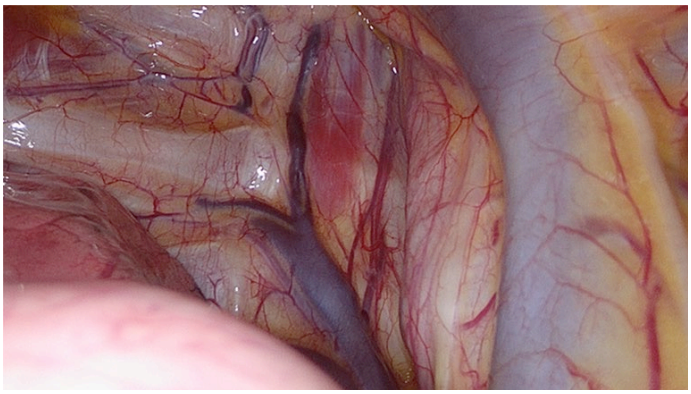

Figure 1. Finding the vagus nerve.

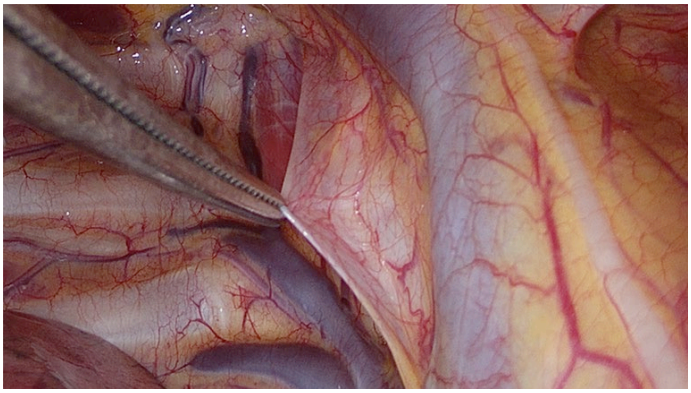

Figure 2. Elevating the pleura above the vagus nerve.

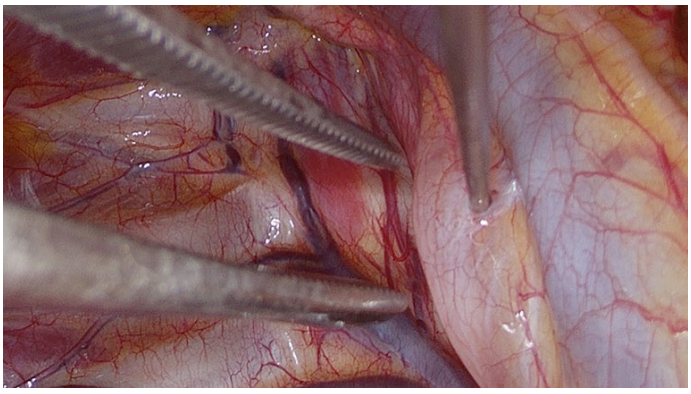

Figure 3. Administration of bupivacaine hydrochloride into the space adjacent to the vagus nerve under the mediastinal pleura.

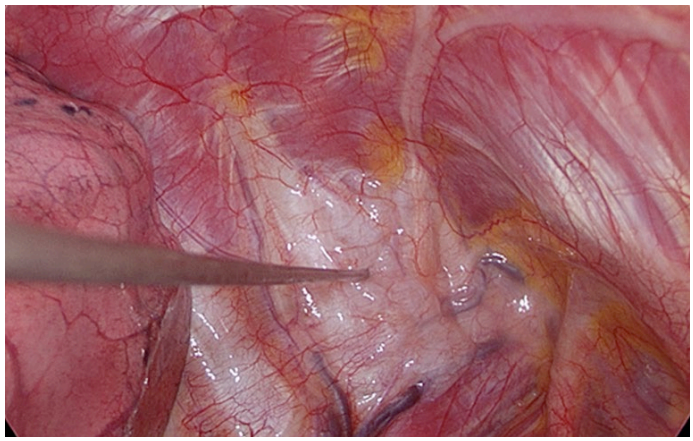

Figure 4. Formation of a paravertebral nerve block.

4.1.3. Anaesthetic considerations

Prior to surgery, patients are premedicated with midazolam and fentanyl, induction is started with propofol, and then they receive additional propofol during total intravenous anaesthesia (TIVA), while sleep depth is monitored by Bispectral Index monitoring. After induction, they receive short-acting mivacuronium chloride, during which they are intubated with an isolated double-lumen tube. Patients are then gas-exchanged using mechanical ventilation. As soon as the short-acting non-depolarising muscle relaxant is degraded, spontaneous breathing returns. Since vagal block has been established by this time, no cough reflex occurs. O2 saturation and pCO2 are monitored and FiO2 and PEEP are adjusted to be within normal ranges, PSV may be used if necessary. After surgery, our patients spend at least 2 hours in the postoperative observation room, and when the visual analog scale (VAS) value is less than 3, they are discharged to the thoracic surgery ward. In those cases where it was necessary to achieve a blood oxygen saturation of 94%, O2 was administered by face mask at a flow of 2-4 L/min. No other oxygenation improving treatment was required.

4.2. Results

In our retrospective study, we reviewed data from 15 patients who underwent SVI VATS thymectomy. Eleven patients were diagnosed with myasthenia gravis (myasthenia group), while 4 patients had a non-myasthenia indication (non-myasthenia group). Of the latter, 3 patients had a preoperative diagnosis of thymoma, while one patient had a post-COVID chest CT scan confirming thymus persistent without evidence of myasthenia.

The ASA value was 2.067 on average, 3 patients belonged to ASA group III. Clinical patient data are summarized in Table 1. There were no conversions either for surgical reasons

or for anaesthesia reasons, so we could perform SVI VATS thymectomy in all patients, no sternotomy or thoracotomy was required, and no continuous mechanical ventilation was needed.

During the first part of the operation, while the fast-acting muscle relaxant is in effect and intubation is done, patients are mechanically ventilated by machine, at a rate of 22.44% of the total operating time. Thus, patients are spontaneously ventilated 77.56% of the operating time. Perioperative results are summarized in Table 2.

The postoperative period was uneventful, with no significant pulmonary complications clinically or radiologically. One patient developed a postoperative pneumothorax after drain removal, underwent repeated chest drainage, but was emitted 5 days later and had no other complications.

We had to return 2 patients to the Neurology Clinic. One of them had worsening myasthenic symptoms (increased muscle weakness in the upper limbs, eye movement disturbances), while the other patient had progressive general weakness for which he received additional steroid and pyridostigmine bromidum treatment. The first patient was discharged from the Neurology Clinic after 5 days and the second patient after 7 days. No patient developed a myasthenic crisis. Exacerbation of myasthenic symptoms was observed in 9% (n=1) of patients. Anaesthesia-related neuromuscular block did not develop in any patient.

Patient characteristics	Data
Females/males	10/5
Age (year)	38.9 [19–74]
BMI (kg/m^2)	24.6 [15.9–33.7]
Osserman classification of MG (n=11)	
I	3
IIa	4
IIb	3
III	0
IV	1
Preoperative treatment of MG (n=11)	
No pharmaceutical treatment	1
PB alone	7
PB + CS + AZA	1
PB + CS + AZA + IVIG	1
AC + RIX	1
TPE	0

Table 1. Clinical patient data. Distribution of gender, age, BMI, Osserman MG classification and preoperative treatment. PB: pyridostigmine bromide, CS: corticosteroid, AZA: azathioprine, IVIG: intravenous immunoglobulin, AC: ambenonium chloride, RIX: rituximab, TPE: therapeutic plasma exchange - plasmapheresis.

Perioperative characteristics	Results
Operative time (min)	75 [60–120]
Chest tube duration (days)	1 [1–5]
Hospital stays (days)	4 [4–7]
Abnormality in the radiological results of the chest X-ray	
Fluid (no required intervention)	5/15
Pneumothorax (no required intervention)	2/15
Pneumothorax (required intervention)	1/15
Atelectasis (no required intervention)	3/15
Infiltration	0/15
Minimal arterial oxygen tension (mmHg)	82.4 [56.1–247.2]
Maximal arterial carbon-dioxide tension (mmHg)	59.2 [44.8–67.8]
Histology (n=15)	
Persistent thymus	9
Follicular hyperplasia	4
Micronodular thymoma	1
Lobulated fatty tissue + lymphoid infiltration	1

Table 2. Perioperative results. Operative time, chest drainage time, hospital length of stay, postoperative chest X-ray abnormalities, minimum paO2, maximum paCO2, histological findings.

4.3. Discussion

In myasthenia gravis, the accepted standard minimally invasive procedure is VATS thymectomy, despite the fact that exacerbations of myasthenic symptoms are often seen with long-acting muscle relaxants. Liu et al. found a 5.88-fold higher incidence of postoperative myasthenic crisis when surgery was performed from thoracotomy versus VATS [139,140]. In addition to the use of thoracic epidural anaesthesia [137], the use of the NITS technique is not associated with the administration of muscle relaxants [141,142]. The use of the NITS technique is limited by several previously published criteria [125-127,143]. If the surgery is performed in a spontaneously breathing, intubated patient, only the limitation due to BMI should be considered (BMI < 30 kg/m2). In NITS surgery, there is no reassuring airway protection, which may increase the chances of the need for intratracheal intubation later in the operation [130]. However, this is both rarely necessary in everyday practice and technically easy to perform, as the patient lies in a near-perfect intraoperative position on the operating table for intubation. During SVI, conversion to an intubated, relaxed state is even easier, because it essentially involves intravenous administration of a muscle relaxant.

Spontaneous ventilation can also be used in cases where both pleural spaces are open [130]. If oxygenation is impaired, during NITS, oxygenation can be corrected by PEEP into the laryngeal mask, but in these cases both lungs will be inflated, making surgical manipulation difficult. Whereas during SVI VATS, no such problem exists because gas exchange on the non-operated side can be assisted by PEEP or PSV through the tube. During SVI VATS thymectomies, vagal block is created even during the short-acting muscle relaxant, however, Jiang et al. concluded that during NITS VATS thymectomy this is not necessary, but cough reflex can be reduced by a level of 6ml 2% lidocaine hydrochloride delivered to the lung surface [131]. Considering our postoperative results, we found no significant difference between the SVI VATS technique we used, and the NITS technique found in the literature.

The time to chest drainage was 1 day in our study compared to 1.9 and 3.5 days in NITS, while the average hospital stay was 4 days in our patients compared to 2.66 and 4.7 days in NITS [125-127]. During our SVI VATS thymectomies, the proportion of short-acting muscle relaxants per total operative time during the first part of the operation, when patients are intubated and mechanically ventilated, is 22.44%. During the remaining part of the operation, which is 77.56% of total operative time, patients are spontaneously ventilated and do not receive muscle relaxants. We believe that this factor, together with the fact that long-acting muscle relaxants are not used, leads to the prevention of postoperative unwanted neuromuscular blockade, and thus to the worsening of myasthenic symptoms, including the development of myasthenic crisis.

5. SUMMARY

Metastasectomies

Pulmonary metastasectomy may be the most optimal therapeutic option for patients with solitary or multiple metastases, after individual assessment. Considering the nature of the primary tumour, the number of metastases, other effective treatment options and the patient's surgical tolerance, it can be seen that a parenchymal-sparing - even multiple - lung resection, performed with minimally invasive approaches, if possible, can result in long-term disease-free survival of the patient. Both the proportion of minimally invasive interventions and parenchyma-sparing solutions have become more prevalent over the study periods. In the second period, already 16.1% of VATS surgeries were performed with a newly introduced anaesthetic solution - NITS - technique, which is more beneficial for patients, showing that it is a safe and better tolerated method for patients when used with appropriate criteria. By evading the limitations of NITS, we have moved forward to introduce and make the spontaneously ventilated intubated anaesthetic solution part of the daily routine.

Systemic inflammatory reaction

During our resections for lung tumours, we contribute to reducing the postoperative inflammatory response by minimizing tissue injury, such as less proinflammatory cytokine release or less decreased lymphocyte function, through our minimally invasive thoracic surgery procedures and the use of spontaneous ventilation. These positive effects are also reflected in our early post-operative outcomes and in the efficacy of post-operative oncological treatments. Although surgeries using spontaneous ventilation are not yet widespread, locoregional anaesthesia is simple to perform, low cost and offers an excellent opportunity to further reduce SI either in open surgery or VATS.

Thymectomy

Despite several limitations of our retrospective study, which was limited to patients undergoing thoracic surgery at a single centre, we have succeeded in presenting a new and safe technical solution for patients in the form of the SVI VATS thymectomy procedure. It can also be used in myasthenia gravis, and we believe that these patients may benefit even more than the standard SVI, as only a short-acting muscle relaxant is administered and only approximately in the first quarter of the operation. Thus, in addition to the negative effect of mechanical ventilation on the systemic inflammatory response, the chance of developing myasthenic symptoms caused by prolonged neuromuscular block due to long-acting muscle relaxants may be reduced.

6. OUR RESULTS

1. We have been the first to demonstrate the applicability of international trends in pulmonary metastasectomy in Hungary. Due to closer oncological control and increasingly accurate imaging diagnostics, pulmonary metastasis in patients was detected earlier, thus reducing the time between surgery for the primary tumour and pulmonary metastasis. After our parenchyma-sparing lung resections, median survival improved by 20 months, with 5-year survival unchanged. After less invasive thoracic surgery, further reducing other patient stress factors, we introduced and were the first in the country to use NITS technique for metastasectomies.

2. Spontaneously breathing patients have lower rates of trauma from mechanical injury to the alveoli and less systemic inflammation, which reduces the degree of biotrauma. This results in a better postoperative immune response, such as less tumour cell proliferation, fewer postoperative complications, and more effective oncological treatments. In spontaneously breathing patients, more physiological cardiac and pulmonary values are seen. By intubating during SVI, we eliminate the unsecured airway - the major disadvantage of NITS method, and we also improve the patient's gas exchange.

3. We pioneered and successfully introduced the SVI technique for thymus removal in our department. In our VATS thymectomies for myasthenia gravis, the SVI anaesthetic solution resulted in patients not receiving long-acting muscle relaxants, with spontaneous breathing during more than ¾ of the surgery. No significant pulmonary complications developed. There was no myasthenic crisis and no anaesthesia-related neuromuscular block. Due to SVI, a stable airway was provided throughout and no conversion to relaxed anaesthesia was performed. Postoperative chest drainage time was reduced to 1 day.

7. NEW FINDINGS

We confirmed the feasibility of VATS in the surgical treatment of lung metastases.

We confirmed that the NITS technique is a successful method for the removal of lung metastases.

The oncological follow-up and diagnostic procedures have also been significantly improved over the 12-year duration of the study, resulting in earlier detection and surgery of pulmonary metastases.

Parenchyma-sparing surgery for MITS pulmonary metastasectomies did not worsen 5-year survival of patients.

We are the first in the world to demonstrate the applicability of the SVI technique for thymus removal.

SVI VATS thymectomy is as safe as mOLV VATS thymectomy in all aspects.

The time of chest drainage after SVI VATS thymectomy is shorter than after NITS VATS thymectomy.

In myasthenia gravis, VATS thymectomy is preferable if SVI rather than mOLV, given the use of fewer and shorter-acting muscle relaxants.

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