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

Ph.D. Thesis

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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**
2. **Németh T,** Pécsy B, Géczi T, Sas K, Szpisjak L, Rieth A, Kiss V, Szőnyegi F, Tiszlavicz L, Zombori T, Lázár G, Furák J. Successful multidisciplinary management of tetraplegia with a thoracic operation. Unicentric, mediastinal Castleman disease [Tetraplegia sikeres multidiszciplináris kezelése mellkassebészeti műtéttel. Unicentrikus mediastinalis Castleman-betegség esete]. Orv Hetil. 2020 Jan;161(1):33-38. Hungarian. doi: 10.1556/650.2020.31560. PMID: 31884815. **IF: 0.54**
3. Fabó Cs, Oszlányi A, Barta ZV, **Németh T**, Lantos J, Vaida SN, Szabó Zs. Anesthesiology of the spontaneous ventilation in thoracic surgery: a narrative review. AME Surg J. 2 Paper: 14 , 7 p. (2022)
4. Furák J, Barta ZV, Lantos J, Ottlakán A, **Németh T,** Pécsy B, Tánczos T, Szabó Zs, Paróczai D. Better intraoperative cardiopulmonary stability and similar postoperative results of spontaneous ventilation combined with intubation than non-intubated thoracic surgery. Gen Thorac Cardiovasc Surg. 70 : 6 pp. 559-565. , 7 p. (2022) **IF:1,2**
5. Lantos J, **Németh T**, Barta Zs, Szabó Zs, Paróczai D, Varga E, Hartmann P. Pathophysiological Advantages of Spontaneous Ventilation. Front Surg 9 Paper: 822560 , 7 p. (2022) **IF:1,8**
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7. Ábrahám Sz, **Németh T**, Benkő R, Matuz M, Váczi D, Tóth I, Ottlakán A, Andrási L, Tajti J, Kovács V et al. Evaluation of the conversion rate as it relates to preoperative risk factors and surgeon experience: a retrospective study of 4013 patients undergoing

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10. Furak J, Rieth A, Ottlakan A, **Nemeth T,** Torday L, Tiszlavicz L, Lazar Gy. Adenocarcinoma arising from a foregut cyst of the diaphragm: importance of multimodality treatment: a case report. BMC Surg. 20 : 1 Paper: 332 , 7 p. (2020) **IF:2,102**
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INTRODUCTION

Scientific and technical advances have led to the development of newer, less demanding types of operation in many areas of surgery compared to previous types. Even with the most careful and tissue-friendly operation techniques, in our thoracic surgery procedures, tissue damage occurs, which activates the body's natural immune response, upsetting its homeostasis and triggering a reaction called inflammatory response. The severity of the inflammatory response depends on a few factors, some of which depend on the parameters of the actual surgical intervention and others are a consequence of the anaesthetic intervention.

Setting of objectives

(1) In our study, we sought to find out what surgical and anaesthetic changes and technical advances in the surgical management of resectable pulmonary metastases have taken place over 12 years, comparing two five-year periods, and what positive outcomes this has brought for patients.

(2) We investigated the processes involved in the development and maintenance of the perioperative inflammatory response during minimally invasive lung resections and how these are influenced by thoracic surgery and anaesthetic factors. We reviewed the physiological and pathophysiological differences between mechanical ventilation involving one lung and spontaneous unilateral breathing. We examined the possibilities to prevent or influence the already developed inflammatory response and evaluated these effects in relation to postoperative outcomes.

(3) In a pilot study of minimally invasive thymus removal using the video-assisted thoracoscopic technique, we investigated whether the anaesthetic aspects of spontaneously breathing double-lumen tube intubation could be performed as safely as isolated tube intubation and mechanical ventilation.

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

In the case of metastatic tumours in the lung, if they meet the criteria for resectability, intact resection can result in complete tumour-free survival of patients, improving long-term survival. In 2013, 316 resections were performed in Hungary for lung metastases, 107 of which were performed using video-assisted thoracoscopic surgery (VATS) (Korányi Bulletin 2014). According to 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 (ESTS Silver Book 2015). For unilateral involvement, VATS approach can be chosen in addition to anterior, axillary and posterolateral thoracotomy, while for bilateral metastases, either sternotomy and 'clamshell' exploration (Pfannschmidt et al. 2007), but also subxyphoid and transcervical exploration may be effective. While Morton et al. in 1973 localised on palpation and performed pulmonary metastasectomies from bilateral thoracotomies, subsequent developments have led to Murakawa et al. in 2014 finding better survival for VATS metastasectomies for colorectal (CRC) tumours than for open surgery.

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 second 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 surgeries were for the removal of the first metastasis, while 14.9% (n = 20) were for repeat metastasectomy. Patients were intubated with a 2-lumen isolated tube to perform the surgeries. For non-intubated spontaneously breathing (NITS) surgery, patients are not intubated and relaxed. Patients are positioned in a lateral position on the operating table. The resections performed from the posterolateral thoracotomy are segmentectomy, lobectomy, pulmonectomy and atypical resection. At the end of the operation, after leaving 1 or 2 chest drains and 1 subpleural analgesic cannula behind, the thoracotomy wound is closed in layers. Statistical analysis was performed using SPSS v. 15 with Kaplan-Meier method (IBM®, Armonk, NY, USA).

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 metastases (36.8% vs. 38.8%), followed by kidney (14% vs. 9%) and then skin - melanoma malignum (14% vs. 7.5%). 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 metastasectomy. For 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. Metastasectomy was performed in 3% (n = 4) from both sides in one session, including 2 patients from sternotomy and 2 patients from single-session bilateral VATS approach. Solitary lung metastases were detected in 58.2% (n = 78) and multiple metastases in 41.8% (n = 56). When reviewing the distribution of surgeries performed, we found that atypical mechanical wedge resection was the most frequently performed procedure (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%). Looking at the surgical technique, we can see that between 2006 and 2010, 5.3% (n = 3) of surgeries were performed with VATS technique, no uniportal VATS or VATS NITS surgery, whereas between 2014 and 2018, 64.9% (n = 87) of surgeries were performed with VATS, 21.7% (n = 29) with uniportal VATS, while 10.4% (n = 14) with VATS NITS metastasectomy. The mean disease-free period between primary tumour and lung metastasis removal in the first period was 45.2 months (0-168 months) and 55.4 months (0-168 months) for solitary metastasis, 30,9 months (0-144 months) for multiple metastases, while the average duration of the second period was 33.8 months (0-180 months), 39.3 months (0-174 months) for solitary metastases 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 demonstrated (p = 0.282).

Discussion

The first lung metastasis was removed by Weinlechner in 1882. In colorectal cancer, approximately 20% of patients have metastatic tumours, including liver or lung metastases, at the time of diagnosis (Qui et al. 2015), with a combined incidence of 5-10% (Pfannschmidt et al. 2007). In osteosarcoma, 81% of patients have lung metastases at the time of diagnosis (Treasure et al. 2012). In patients with cutaneous melanoma, 80% have metastatic tumours and 40% have only solitary pulmonary metastasis (Petersen et al. 2007). The number of surgeries with indication of pulmonary metastasis more than doubled during the two study periods (n = 57 vs. n = 134). No significant difference in the distribution of primary tumours was found. Our surgeries were complemented by mediastinal and hilar lymph node sampling or block dissection. Median survival in our patients was 33 months in lymph node-positive cases and 39.3 months in lymph node-negative cases. The disease-free period between the primary tumour process and the surgery for lung metastasis decreased from a mean of 45.2 months in the first group to 33.82 months. After metastasectomy, patients underwent regular oncological follow-up according to the protocol for 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%) (Treasure et al. 2014).

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 localised, 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 also be referred to as sepsis (Zotova et al. 2016, Bone et al. 1992). For an accurate diagnosis of systemic immune response, the Sepsis-3 definition or the SOFA scoring system may be used (Marik et al. 2017, Fernando et al. 2018, Vincent et al. 1996). During the initial phase of systemic inflammation and then the inflammatory response, natural/innate immunity is activated within the first few hours of injury, 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 that influence immune function). Both parts of the body's defence line then work together in a coordinated manner to combat the systemic inflammatory trigger. During thoracic surgery, systemic inflammation occurs, triggering proinflammatory and anti-inflammatory response processes (Takenaka et al. 2006, Sakamoto et al. 1994). Minimally invasive thoracoscopic surgery (MITS) elicits a smaller inflammatory response than open thoracic surgery (Leaver et al. 2000) and the postoperative period is easier for patients because of lower morbidity, shorter chest drainage time and shorter postoperative hospital stay (Scott et al. 2010, Villiamizar et al. 2009). The negative impact on systemic inflammation can be reduced by spontaneous ventilation of the patient (sOLV) (Kiss et al. 2015). MITS, most notably the widespread use of VATS, has developed the technique of spontaneous ventilation, further reducing the systemic response (Jeon et al. 2021). The most important pathophysiological change during spontaneous ventilation is the reduction of both the immune response and the inflammatory response to the intervention (Nagahiro et al. 2001, Mineo et al. 2018, Vanni et al. 2010).

Pathophysiology of systemic inflammation

In systemic inflammation, the innate immune system and immune response is activated first, such as neutrophil granulocytes, macrophages, natural killer cells and dendritic cells, which are able to phagocytose and present antigens to damaged tissue during surgical trauma or mechanical ventilation (mOLV). 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. Binding of DAMPS to the TLR or NOD receptor activates proinflammatory cytokine production. Subsequently, proinflammatory cytokines TNFα, IL-6, IL-8, IL-1β, and anti-inflammatory cytokines such as 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 (Kaufmann et al. 2018, Dabrowska et al. 2014).

These cytokines play a key role in intercellular communication, the established immune response, and immune regulation. Normal levels of cytokines have a positive effect on the defence mechanism, however, when their levels exceed normal levels, they have a negative side effect on immune regulation, inflammation, organ function, tumour cell proliferation. Proinflammatory cytokine production triggers the systemic inflammatory immune response (SIRS). The SIRS benefits the body by reducing tissue injury, removing remnants of dead cells and triggering healing processes (Dabrowska et al. 2014, Marik et al. 2012). For a specific immune response to occur, a connection between antigen-presenting cells (APCs, macrophages, dendritic cells) and T lymphocytes must be established. 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 (APCs), 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 with the help of 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), these cytokines 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. After the 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, causing a shift in the Th1/Th2 ratio towards Th2, which will result in immunosuppression. Adequate levels of cytokines are necessary for normal physiological functioning of the immune system. Inflammation may remain localised if the cellular response and cytokines can be kept under control, if not then the process will progress and systemic inflammation will develop. If SIRS is prolonged, excessive proinflammatory cytokine production has a negative impact on normal body function, leading to loss of organ function: '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 DIC, capillary dysfunction through ischemia-reperfusion, which all together increase the rate of postoperative complications (Dabrowska et al. 2014, Jaffer et al. 2010). The association between proinflammatory cytokine levels and postoperative systemic inflammation has been demonstrated (Takenaka et al. 2006, Breuning et al. 2011). To compensate for the severity and time course of SIRS, the compensatory anti-inflammatory immune response

(CARS) is activated. The reduced inflammatory and immune changes after NITS suggest that immunosuppression is also less after NITS compared to relaxed cases (Yu et al. 2019, Mineo et al. 2017).

Systemic inflammation and tumour immunity

In tumour surgery, an important issue is intraoperative tumour cell dispersion and the control of circulating tumour cells (Alieva et al. 2017). Circulating tumour cells can be detected up to 6 weeks after resection, so it is important to have a normal immune system in the postoperative period to help clear circulating tumour cells (Juratli et al. 2015). The role of cytokines in tumour regulation and their molecular background is well mapped (Dunlop et al. 2000, Negus et al. 1996). If Th1 immunity is compromised, tumour progression will result. If Th1 immunity becomes predominant, immune stimulation will act in the direction of tumour regression (Chang et al. 2017). The predominant role of cytokines is also seen in their ability to activate carcinogenesis and promote tumour growth, as well as to protect tumour cells from therapy-induced genome damage and programmed cell death (Briukhovetska et al. 2021).

Systemic inflammation and surgical intervention

The post-operative proinflammatory response is greater after open surgery than if VATS surgery had been performed, which is associated with a natural immune response (Jones et al. 2014). Perioperative outcomes are similar for both robotic-assisted thoracoscopic surgery (RATS) and VATS (Guo et al. 2019), but in many cases operative times are longer with RATS than with VATS. Tacconi found no difference in systemic inflammatory response regardless of whether uniportal, multiportal, or hybrid VATS lobectomy was performed (Tacconi et al. 2021).

Relationship between mOLV and sOLV

In thoracic anaesthesia for lung resections, the currently recommended procedure is mOLV, which can cause alveolar damage. To reduce the number of complications in these cases, the use of protective ventilation is recommended. Clinically, mOLV is comparable to ventilation in post-pulmonectomy patients. Expiratory end-expiratory hyperinflation (volutrauma) can develop in the lungs (Kozian et al. 2010). Atelectasis (atelectrauma) may be encountered in cases where ventilation has been performed at low volumes. The use of spontaneous ventilation (SV) can protect our patients from these pathophysiological abnormalities.

Pathological changes in mOLV

High-pressure and high-volume ventilation are the main risk factors for alveolar damage in mechanical, single-lung ventilation. As part of the mOLV-induced biotrauma, immune cells would be activated and the inflammatory cascade would be triggered, producing cytokines. In addition, hyperperfusion develops on the affected side in the case of mOLV. If hyperperfusion is combined with hyperinflation, alveolar damage occurs, with interstitial oedema and microhemorrhage (Lohser et al. 2011, 2015). During NITS, the disadvantages caused by mOLV such as volutrauma, atelectrauma, biotrauma can be further reduced.

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 a lot of factors such as patient position, chest cavity exploration, manipulation of the operated lung. Hypoxic pulmonary vasoconstriction (HPV) is an oxygen-sensitive mechanism of the lung that reduces the perfusion of a hypoxic lung area, thus creating a better ventilated area. The consequence of these factors is a V/Q shift. Spontaneous ventilation raises the ventilation/perfusion ratio, enhances cardiac function and results in better oxygenation (Putensen et al. 1999).

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 intra-thoracic pressure is elevated and lung volume increases, which has a negative effect on atrial preload and thus on cardiac output. The difference between sOLV and mOLV becomes apparent when the chest is just opened and the negative intrapleural pressure is removed, at which time there is hypoxic pulmonary vasoconstriction, increased pulmonary vascular resistance and decreased venous return. These can be reduced, for example, by using PEEP. Our experience has shown that after 5-8 min, when the abnormalities due to changes in chest pressure have ceased, there is no difference between mOLV and sOLV in either cardiac or haemodynamic function (Tacconi et al. 2010).

Systemic inflammation and spontaneous ventilation

mOLV often causes damage to patients' lungs despite the use of protective ventilation techniques. Ventilation causes damage to the alveoli, their walls are overstretched, resulting in volutrauma/barotrauma and atelectrauma (Lohser et al. 2011, Kozian et al. 2010, 2011). These changes serve as the 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 dependent lung (biotrauma), ultimately leading to a systemic inflammatory response (Lohser et al. 2015, Kozian et al. 2008). These can be reduced by the use of spontaneous ventilation with intubation technique (sOLV). It has been investigated and reported in a number of sites that improved immune responses and less immunosuppression can be seen with SV. Changes in the levels of stress hormones, which are also involved in systemic inflammation, are also less marked in SV surgical cases compared to relaxed cases (Tacconi et al. 2010). sOLV after lung tumour surgery has significantly better OS and DFS than if the same surgery had been performed with mOLV. In patients with spontaneous ventilation, the type of anaesthesia is an independent factor of OS and DFS (Zheng et al. 2021).

Relationship between locoregional anaesthesia and SVI

In SVI, the most commonly used locoregional anaesthetic technique is thoracic epidural cannula anaesthesia and paravertebral/intercostal anaesthesia combined with vagus nerve blocks. 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 patients' pain (Mineo et al. 2007, Kao et al. 2012). The sympatholytic effect of locoregional anaesthesia should be mentioned. Any of these anaesthetic interventions reduces the stress factor caused by the surgical procedure, as well as the levels of IL-6, IL-8, and TNF-α (Zhan et al. 2017), and also reduces troponin T and C-reactive protein (CRP) levels (Loick et al. 1999, Palomero et al. 2008).

Effect of relaxation on immune function

In an experimental study, the presence of acetylcholine (ACh), the α7ACh receptor on blood mononuclear cells, and the cholinergic anti-inflammatory pathway were compared (Borovikova et al. 2000, Benfante et al. 2021). It was found that ACh significantly reduces the release of proinflammatory cytokines in human macrophage cultures. 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.

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 most promising procedure is the CytoSorb haemoadsorption procedure, which has a positive effect on advanced inflammatory responses such as sepsis and pneumonia (Akil et al. 2021).

Discussion

It can be said that the thoracic surgeon can contribute to the reduction of post-operative SI by reducing the tissue damaging effects of surgery for lung tumours, which also agrees 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 damaging effects of surgical trauma, SV is an excellent option. Nevertheless, SV is not a widely used intervention. Locoregional anaesthesia has a significant SI reducing role whether used during relaxed VATS or open surgery.

VIDEO-ASSISTED THYMECTOMIES IN SPONTANEOUSLY VENTILATING, INTUBATED PATIENTS

Currently, the accepted surgical option for radical thymus removal is VATS or RATS (Liu et al. 2019, 2020, 2021, O'Sullivan et al. 2019). Muscle relaxants used during surgery increase the risk of postoperative myasthenic crisis, and physiological changes during mOLV due to abnormalities in the inflammatory response also have a tendency to increase the incidence of myasthenic crisis (Collins et al. 2020, Blichfeldt et al. 2012). Due to these factors, regional anaesthesia has gradually been brought to the fore and other techniques have been introduced to reduce the development of myasthenic crisis, such as short-acting muscle relaxants and neuromuscular block monitoring, e.g. TOF (Brull et al. 2013, Neuman et al.

2022). In our review, we report early clinical experience, outcomes and benefits of SVI VATS thymectomies.

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).

Patient selection

The criteria used in NITS would have prevented many patients from undergoing surgery, whereas the SVI indication had only one parameter to consider, that the patient's BMI should not be more than 28 kg/m2.

Results

In our retrospective study, we reviewed data from 15 patients who underwent SVI VATS thymectomy. 11 patients had a diagnosis of myasthenia gravis with an ASA value of 2.067. Clinical patient data are summarized in Table 1. There were no conversions either for surgical reasons or for anaesthesia reasons, so we were able to perform SVI VATS thymectomy in all patients, no sternotomy or thoracotomy was required, nor was continuous mechanical ventilation necessary. During the first part of the surgery, while the fast-acting muscle relaxant is in effect and intubation is done, the patients are mechanically ventilated by machine, at a rate of 22.44% of the total operating time. Thus, the patients are spontaneously ventilated 77.56% of the operating time. Perioperative results are summarized in Table 2. Postoperative period was uneventful, no significant pulmonary complications were observed clinically or radiologically. No patient developed a myasthenic crisis. In 9% (n=1) of patients, worsening of myasthenic symptoms was observed. 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.

Discussion

The accepted standard minimally invasive intervention for myasthenia gravis 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 by thoracotomy versus VATS (Furák et al. 2021, Geng et al. 2020). In addition to the use of thoracic epidural anaesthesia (Tsunezuka et al. 2004), the use of the NITS technique is not associated with muscle relaxant administration (Rieth et al. 2022, AlGhamdi et al. 2020). There is no reassuring airway safety during NITS surgery, which may increase the chance of needing intratracheal intubation later in the surgery (Pompeo et al. 2018). Considering our postoperative results, we did not find any 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 reported in NITS, while the average hospital stay in our patients was 4 days compared to 2.66 and 4.7 days in NITS (Liu et al. 2019,2020,2021). During our SVI VATS thymectomies, the proportion of short-acting muscle relaxants per total operative time during the first part of surgery, when patients are intubated and mechanically ventilated, is 22.44%. During the remaining part of surgery, which is 77.56% of total operative time, patients are spontaneously ventilated and do not receive muscle relaxants.

OUR RESULTS

1. We were the first to demonstrate the domestic applicability of international trends in pulmonary metastasectomy. Due to closer oncological control and increasingly accurate imaging diagnostics, pulmonary metastasis in patients was detected earlier, resulting in less time between surgery for primary tumour and pulmonary metastasis. After our parenchymal-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. Spontaneous breathing patients have lower rates of trauma from mechanical injury to the alveoli, less systemic inflammation, and thus lower rates of biotrauma. This results in a better postoperative immune response, such as less tumour cell proliferation, fewer postoperative complications and more effective oncological treatments. Spontaneously breathing patients show more physiological cardiac and pulmonary values. By intubating during SVI, we eliminate the major disadvantage of the unsecured airway - NITS method and also improve the patient's gas exchange.

3. We were the first in the world to use and then successfully introduced the SVI technique for removal of the pancreas 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 operation. 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**.**

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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