PhD. thesis

University of Szeged Faculty of Medicine
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MODERN DIAGNOSTIC AND SURGICAL MANAGEMENT OF THORACIC DISEASES IN OUR PRACTICE

PhD. thesis

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List of full papers related to the subject of the thesis

I. **Ottlakan A, Martucci N, Rocco G.** Is surgery still the best management option for early stage NSCLC? Transl Lung Cancer Res. 2014 Jun; 3 (3): 159-163.

II. **Ottlakán A, Géczi T, Pécsy B, Borda B, Lantos J, Lázár G, Tiszlavicz L, Klivényi P, Furák J.** Myasthenia gravis miatt végzett három különböző típusú csecsemőmirigy-eltávolítás sebészeti és korai neurológiai eredményei. [Three different types of thymectomy for myasthenia gravis: Surgical and early neurological results.] Magy Seb. 2015 Dec; 68: 219-224.

III. **Ottlakan A, Borda B, Lazar G, Tiszlavicz L, Furak J.** Treatment decision based on the biological behavior of pulmonary benign metastasizing leiomyoma. J Thorac Dis. 2016 Aug; 8: 672-676.

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IV. **Aurel Ottlakan, Bernadett Borda, Zita Morvay, Aniko Maraz, Jozsef Furak.**
The Effect of Diagnostic Imaging on Surgical Treatment Planning in Diseases of the Thymus.
Contrast Media Mol Imaging. 2017 Jan; 2017: 9307292.
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V. **Aurel Ottlakan, Jozsef Furak, Gaetano Rocco.** Shared decision making in the treatment of stage I non small cell lung cancer—a choice which should equally involve both sides. Ann Transl Med. 2017 Sep; 5: 359.

VI. **Ottlakán A, Pécsy B, Csada E, Gábor A, Maráz A, Borda B, Lázár Gy, Furák J.** Tüdőlebeny eltávolítását követő kemoterápia tolerabilitását befolyásoló perioperatív tényezők. [Perioperative factors influencing the tolerability of chemotherapy after lung lobe resection.] Orv Hetil. 2018 May; 159: 748-755.
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List of abstracts related to the subject of the thesis

I. **Ottlakán Aurél, Furák József, Géczi Tibor, Pécsy Balázs, Lázár György, Tiszlavicz László**

Multiplex tüdőmetasztázisokat adó benignus leiomyoma egy eset kapcsán

Magyar Sebészet, 67:(3) p. 195. (2014)

II. **Ottlakán Aurél, Furák József, Géczi Tibor, Pécsy Balázs, Borda Bernadett, Lázár György**

Multiplex benignus metaszatizáló leiomyoma (BML) Magyar Sebészet 68:(2) p. 46. (2015) Fiatal Sebészek III. Kongresszusa

III. **Aurel Ottlakan, Bernadett Borda, Gyorgy Lazar, Laszlo Tiszlavicz, Jozsef Furak**

Behavior of Benign Metastasizing Leiomyoma

Medis Timisoara 2016

IV. **Aurel Ottlakan, Laszlo Torday, Laszlo Tiszlavicz, Tamas Zombori, Gyorgy Lazar, Jozsef Furak**

Primary cancer of the diaphragm

Interact Cardiovasc Thorac Surg. 2016 Sept; 23: 70–71. ESTS Napoli, 2016

V. **Ottlakán Aurél, Géczi Tibor, Pécsy Balázs, Németh Tibor, Borda Bernadett, Tóth Illés János, Kovács Viktor, Maráz Anikó, Tiszlavicz László, Lázár György, Furák József**

Thymomák miatt végzett műtétek gyakorisága és eredményei Klinikánkon

A Magyar Sebész Társaság sebészeti onkológiai szekciójának 1. Kongresszusa

VI. **Ottlakán Aurél, Géczi Tibor, Pécsy Balázs, Németh Tibor, Molnár Zsolt, Lázár György, Varga Endre, Furák József**

Traumás pneumopericardium sebészeti kezelése két eset kapcsán

Fiatal Sebészek V. Kongresszusa 2017

CONTENTS

ABBREVIATIONS

BMI: body mass index; BML: benign metastasizing leiomyoma; CCI: Charlson comorbidity index; CT: computed tomography; FEV1: forced expiratory volume 1 second; FVC: forced volume vital capacity; GI: gastrointestinal; IASLC: International Association for the Study of Lung Cancer; ITMIG: International Thymic Malignancy Interest Group; KVT: klasszikus VATS thymectomia; LC: lung cancer; MG: myasthenia gravis; MK-SCS: Masaoka-Koga stage classification system; MRI: magnatic resonance imaging; MUST: Malnutrition Universal Screening Tool; NSCLC: non-small cell lung cancer; PPBC: postoperative platinum based chemotherapy; PET: pozitron emission tomography; PS: performance status; SDM: shared decision making; SS: surgical sensitivity; STST: standard transsternal thymectomy; TC: thymus carcinoma; SBRT: stereotactic body radiation therapy; TH: thymus hyperplasia; THA: thymoma; VATET: Video-Assisted Thoracosopic Extended Thymectomy; VATS- Video Assisted Thoracic Surgery;

1 Introduction

The surgical methods of accessing the inner thoracic organs has evolved throughout recent decades. After the introduction of the minimal access surgical approach in the 1980s, it was rapidly acquired for thoracic procedures, leading to the development of the so called Video-Assisted Thoracic Surgery (VATS) approach. The advantages of VATS- including reduced postoperative wound pain, minimized intraoperative blood loss, shorter hospital stay and improved postoperative quality of life- have gradually come in the limelight, with great acceptance from surgeons and patients alike. Features of VATS not only include better cosmesis with smaller incisions, but also decreases systemic inflammatory response caused by general anesthesia and intubation.

During our thesis our purpose was to address questions and debates concerning VATS and define its place in the modern treatment of early stage (ES)- and advanced stage (AS) LC, with special regards to thoracotomy and alternative treatment options such as stereotactic body radiation therapy (SBRT). In the modern era of individualized patient care, our work also emphasizes the need for more patient tailored treatment discussion and the need for shared decision making (SDM) between physicians and

patients. Despite this growing body of evidence favouring the VATS approach, the question of debate remains regarding the role and place of thoracotomies and their value, with the obvious question flashing: is traditional thoracotomy considered obsolate in the emerging era of VATS?

The VATS approach not only applies for the treatment of lung cancer, but also plays a major role in the surgery of the mediastinum, especially in the surgery of the thymus. However numerous questions arise in connection with the minimal access approach. Is the minimal access approach as good as traditional sternotomy and is it capable of reaching R0 resection and complete removal of ectopic thymic tissue (ETT)? When so, is it accompanied by better surgical and neurological results in myasthenia gravis (MG), even with facilitation of cosmetic outcome? In addition, what are the perioperative rates of morbidity and mortality in each method, and how does the chosen surgical technique affect long term quality of life and rates of remission? In terms of thymic imaging, should diagnostic imaging of the thymus stick with conventional CT, or can MRI also be helpful in differentiating between thymic abnormalities? Can MRI be able to more accurately point out ectopic thymic foci and thus lead the scalpel?

2 Objectives

Addressed questions summarized:

1. to review best diagnosis and treatment options for early stage lung cancer
2. study on the effect of perioperative factors influencing postoperative chemotherapy treatment and deciding which factors have the most positive influence in receiving the highest number of complete postoperative chemotherapy cycles (Study 1)
3. defining the role of open thoracic procedures in the current minimal access era through the presentation of multiple tumor resections via mini-thoracotomy (Study 2)
4. to emphasize the need for shared decision making between physicians and patients, in order to choose the best treatment option for early stage lung cancer
5. defining the best surgical treatment options with early neurological results of thymectomies in patients with myasthenia gravis (Study 3)

6. to review current diagnostic and imaging options in various thymic conditions and define the place of MR imaging of thymomas (and subtypes), thymic hyperplasia and ectopic thymic foci

3 Modern diagnostic and treatment options for lung cancer

3.1 Treatment approaches in the treatment of early stage NSCLC

Lung cancer is the leading cause of cancer-related deaths worldwide. Lung cancer is divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), the former of which includes adenocarcinoma and squamous cell carcinoma.

Recommended treatment for ES-NSCLC has historically been lobectomy with mediastinal lymph node dissection. Stereotactic body radiation therapy has been used as an alternative treatment therapy for patients with inoperable lung cancer and in patients considered to be at high-risk as a result of comorbidities, poor pulmonary function, and/or advanced age.

Stereotactic body radiation therapy remains a promising modality for local control of NSCLC which is demonstrated by the 91% and 87% 3-year local and loco-regional recurrence free survival rates observed in RTOG 0236 study. Moreover 2 years after SBRT treatment, a 4.9% and 7.8% local- and regional recurrence rate was noted in retrospective studies.

The purpose of precise surgical lymphnode sampling is to ensure accurate patient selection and avoid possible overtreatment by surgery. Without histological confirmation, only clinical stages can be compared, which is especially relevant if one is aware, that regional failures after SBRT may be as high as 15% and mediastinal failures as high as 7.5%. One shared statement by the Society of Thoracic Surgeons' transmits a compact and wholsome recommendation for ES-LC treatment, namely, that "the least parenchymal resection compatible with current diagnostic and oncologic principles performed through the least invasive surgical approach" should be carried out.

3.2 The importance of VATS procedures in the treatment of advanced stage lung cancer- consideration of perioperative factors

While surgical resection remains the mainstay of treatment in advanced LC cases, the introduction of postoperative platinum based chemotherapy (PPBC) proved to be pivotal in improving overall survival. Our porpose was to evaluate the most important perioperative factors influencing the tolerability of postoperative chemotherapy and highlight the possibility of higher treatment uptake according to our results.

3.2.1 Patients and method

Our study involves a 6 year period (01.01.2011-31.12.2016) during which data of 72 patients who underwent surgical lung resection of pathologically confirmed stage IB or higher LC (except for stage IV) and received oncological treatment afterwards, were analyzed. The following parameters were analyzed: rate of open- and VATS lobectomies, duration of surgery, postoperative fever, need for blood transfusion, rate of redo surgery, rate of prolonged air leaks (PAL), histology, pathological stage, genders, body mass index (BMI), Malnutrition Universal Screening Tool (MUST), Charlson comorbidity index (CCI), forced expiratory volume 1 second (FEV1), malignancies in patient history, rate of atrial fibrillations (AF) and performance status (PS).

3.2.2 Results

During data analysis of the 72 patients (CG (complete group): n= 53 [73.61%]; NCG (non complete group): n= 19 [26.38%]) mean patient age was slightly higher in CG (64.11 years), however there were no significant differnces in terms of gender distribution, FEV1, BMI, MUST, previous malignancies in patient history, AF and PS. There was no significant difference noted in terms of postoperative fever, need for blood transfusion, PAL, redo surgeries, histological distribution (adenocc vs squamous cell cc) or pathological stages. During unary logistic regression analysis, there was a remarkable, although non-significant difference among the types of surgery, regarding the number of complete- and non-complete

cycles (CG: n= 26; 83.87% vs NCG: n= 5; 16.12%), favouring the VATS approach. Multivariate analysis was carried out in case of five high priority parameters (VATS/open approach, upper/middle vs lower lobe resection, diabetes, PAL, postoperative fever) which showed significantly positive affect on the number of PPBC cycle received, favouring VATS (p=0.0495). In terms of received PPBC cycles upper/middle lobectomies and the lack of diabetes showed highly positive, although non-significant differences (p=0.0678 and p=0.0971, respectively). There were no significant results obtained in cases of postoperative fever and PAL (p=0.248 and p=0.328, respectively). Termination of PPBC occured in 19 cases (26.38%), mainly due to gastrointestinal (GI) complications (31.57%) (Table 1).

Causes of termination for §PPBC	**n=19**
GI complications	6 (31.57%)
Cardiac complications	1 (5.26%)
Hematological complications	2 (10.52%)
Noval distant metastasis	2 (10.52%)
Worsening of renal function	1 (5.26%)
Surgical wound infection	1 (5.26%)
Soft tissue damage	1 (5.26%)
Subjective complaints of patient	5 (26.31%)

Table 1: Reasons for PPBC termination.
§PPBC: Postoperative platinum based chemotherapy

3.2.3 Discussion

Deciding whether VATS or thoracotomy is the better approach in terms of receiving more cycles of postoperative chemotherapy is still an ongoing debate. During our investigation we compared both methods in terms of the two groups receiving chemotherapy cycles (CG/NCG), and found that patients having underwent VATS lobectomy managed to receive higher numbers of PPBC (4 cycles) (CG: 81.25% vs NCG: 15.62%), although significance was only shown during multivariate analysis

(p= 0.0495). During oncological treatment 20-80% of patients suffer from malnutrition, resulting in liability to infections, decreased wound healing and skin turgor. The present study showed no significant difference in terms of BMI and MUST results among CG and NCG. The Charlson comorbidity index (CCI) was used on measuring comorbidities. According to multicentric studies on age and CCI, the latter maintained better value of prediction, especially in case of advanced stage NSCLC. In terms of CCI there was no significant difference between the two groups in our study, thus based on our own results it can be stated that the value of CCI did not considerably influence the number of received PPBC cycles. Five high priority parameters (VATS/open approach, upper/middle vs lower lobe resection, diabetes, PAL, postoperative fever) were included in multivariate analysis. Better tolerability of postoperative oncological treatment also means higher efficacy of treatment (chemotherapeutic agents), which can result in better OS rates, thus the number of received complete cycles play a paramount role in patient care. The current study showed that in case of VATS lobectomies the number of completed PPBC cycles was significantly higher, which was confirmed by multivariate analysis.

3.3 The role of open thoracic procedures in the modern era of VATS

With the increasing popularity of VATS procedures, the minimal access approach has radically changed the facade of thoracic surgery.

A disease called benign metastasizing leiomyoma (BML) is a rare condition occurring in women several years after a hysterectomy or uterin myomectomy. It features multiple distant metastases in the lung, retroperitoneum, lymph nodes, bones, muscular tissues or the nervous system, with the lung beeing the most frequent site. Our unusual study case involves a 36 year old non-smoking, asymptomatic female patient, who presented with multiple solid nodules in both lungs during routine chest X-ray and later computed tomography (CT). Hysterectomy was carried out 7 years earlier due to myoma of the uterus. During her workup (core biopsies and later histological examination after surgery) all lesions were verified as benign, containing smooth muscle characteristics, confirming their uterin origin. From the initial diagnosis of BML, continuous oncological treatment was administered (VIP protocol: etoposide, ifosfamide, cisplatin), with no significant effect, thus a decision was made by our tumor board in favour of surgery.

During a series of 7 procedures, mini-thoracotomy was carried out, involving parenchyma-sparing cautery resection (enucleation) and wedge resection. During the first two procedures, we removed 31 lesions from the right-, and 36 lesions from the left lung, after which oncological treatment was once again administered. Mean surgical sensitivity during the seven procedures was 95% (40–150%). During procedures in which over ten nodules were present on chest CT or removed surgically, mSS was 97.7%. During the first period (elapsed days: 162), the mean change in nodule size was 23.165%, whereas during the second period (elapsed days: 493) the mean value decreased to 10.5%. The 100-day normalized growth ratio was 14% versus 2.1% during the two periods. According to our results, the speed of nodule enlargement was significantly slower with elapsed time (p=0.023). Seven months after the last procedure, spirometry results of the patient were as follows: FVC (forced volume vital capacity) 77%; FEV1 64%; FEV1/FVC 0.83. Mean hospital stay was 5.14 days (range, 4–6 days). Fluorescent in situ hybridization confirmed the presence of a 19q 22q terminal deletion, which is pathognomonic for BML. During this unusual case, 87 nodules have been removed either by cautery resection (n=83; 95%) or wedge resection (n=4; 5%), during seven procedures. After the surgeries, the patient remained asymptomatic, continued with her job, and had a near-normal FEV1 (64%). There were no lobectomies performed, her physical status and excellent postoperative results were achieved only by the use of parenchyma-sparing metastasectomies. Eventhough the patient also received oncological treatment, based on our results, its effect was not significant, while surgical removal of the 87 lesions proved to be successful, resulting in acceptable life quality of the patient.

3.4 Shared decision making in the process of early stage lung cancer treatment, lobectomy vs stereotactic body radiation therapy

With novel options such as SBRT coming into the limelight besides surgery in the treatment of early stage NSCLC, changes in the discussion patterns of treatment options between physicians and patients have also surfaced. Until recently, surgery has been regarded as the standard choice of treatment in ES-NSCLC. Lobectomy with mediastinal lymph node dissection or sampling provides 50% of 5-year OS in these cases. During the previous decade SBRT has been introduced with 1 to 10

fractions of high-dose radiation delivery (>100 Gy) to the patient in a relatively short time. Compared to conventional radiation OS proved to be better with SBRT. Recently SBRT has been considered a fair alternative to surgery in the treatment of stage I NSCLC, especially for elderly patients and those with severe comorbidities being weak candidates for surgery. According to a recent study on clinicians dealing with ES-NSCLC, 26% of surgeons, 20% of pulmonologists and 12% of radiation oncologists claimed the regular use of SDM during routine patient care. These numbers clearly indicate the infant state of SDM among health care professionals and draw attention to the fact that only a relatively moderate number of PCPs are willing to change this in the future. Overall it can be noted that SDM should probably be better promoted among both patients and physicians due to the fact that it makes doctor-patient relationships much more reliable based on a more detailed information which, in turn, results in improved patient compliance. The detailed discussion of not only SBRT vs lobectomy, but also various thoracic surgery procedures should involve SDM, especially when it comes to deciding whether a minimal access (VATS)-, or an open approach should benefit the patient.

4 Modern diagnostic and treatment options of thymic conditions

The incidence of thymic pathologies occurring among MG patients is roughly 75%: with thymic hyperplasia (TH) occurring in 60–77% and thymoma (THA) in 15–30% of cases. In cases of MG, thymectomy is necessary when the disease is accompanied by THA, however when TH alone is present, thymectomy can be recommended, but is not mandatory. In a meta-analysis conducted in 2018 by Cataneo et al. including randomized clinical trials (RCTs), non-randomized controlled studies and observational studies, comparing medical management with surgical treatment in the treatment of generalized MG in patients without THA, showed that thymectomy was effective in the treatment of nonthymomatous MG with remission rates greater than non-surgical treatment. However superiority of either treatment is still a question of debate.

4.1 Surgical management of thymic conditions with myasthenia gravis

The types of thymectomies can be cathegorized as follows:

1. Transcervical thymectomy
   a. simple
   b. extended
2. Videothoracoscopic thymectomy
   a. simple (classic)
   b. extended („VATET”- Video-Assisted Thoracoscopic Extended Thymectomy)
3. Transsternal thymectomy
   a. simple
   b. extended
4. Transcervical and transsternal thymectomy

4.2 Surgical treatment and early neurological results in myasthenia gravis

Between 1995 and 2011, 105 MG patients underwent thymectomy at our department, although complete follow-up was only available in 71 cases. Outcomes of 23 patients undergoing standard transsternal thymectomy (STST) (between September 1995 and September 2004), 22 patients with VATET (September 2004–August 2009), and 26 with CVT (classic VATS thymectomy) (between September 2009 and December 2011) were compared.

4.2.1 Frequency of thymectomies

During a 17 year period a total of 105 patients were operated for MG. While only 71 patients had complete follow-up with full enrolment in the study, we included all 105 patients in the calculation of the frequency of each type of surgery. All other results are reported only with regard to the 71 patients who underwent the complete 1-year postoperative follow-up. During the first 10 years of the study period, 39 patients (3.9/year) underwent STST. During the 5 years after the introduction of VATET, 34 (6.8/year) patients underwent this type of

procedure, and during the 2.5 years after we adopted CVT, 32 patients (10/year) were operated with this method.

4.2.2 Results

4.2.2.1 Surgical results

There were no perioperative deaths. The lengths of surgery, drainage, and hospital stay differed significantly depending on the type of surgery. The longest operative times were observed during VATET (mean: 211 min) mostly due to our single-team approach, and the shortest ones were achieved during the STST (mean: 112 min), closely followed by CVT (mean: 116 min) ($p = 0.001$). Drainage time depended on the extent of surgery and the number of drains. In case of VATET, 2 drains were placed, while after the STST or CVT, generally only 1 drain was inserted, which was removed when the fluid output was less than 200 ml. The shortest period of postoperative drainage was observed after CVT (mean: 1.65 days) and the longest after VATET (mean: 2.23 days). Hospital stay, essentially depending on the drainage period and postoperative pain, was the shortest after CVT (mean: 4.0 days), which was less than half as much as after STST (mean: 8.9 days) ($p = 0.001$).

4.2.2.2 Morbidity

Approximately 1:4 patients in the STST group and 1:3 in the VATET group, had complications compared with 1:13 in the CVT group. The overall rates of morbidity were 26.1%, 31.8%, and 7.7% after STST, VATET and CVT, respectively ($p = 0.097$). The overall MG-related morbidity rate was 15.5% (11 out of 71 patients), with 21.7%, 18.2%, and 7.7% after STST, VATET, and CVT procedures, respectively ($p = 0.365$). MG-related morbidity was divided into MG-related respiratory insufficiency or worsening of non-respiratory MG-related muscle symptoms. MG-related respiratory insufficiency

requiring intubation and assisted ventilation developed in every group (14% of all patients), and was the most frequent after STST (5 out of 23 patients; 21.7%), less frequent after VATET (3 of 22 patients; 13.7%), and least frequent after CVT (2 of 26 patients; 7.7%) (p = 0.071). MG-related worsening of symptoms without the need of intubation occurred only after VATET (1 of 22 patients, 4.5%). Plasmapheresis due to worsening MG status was performed in 3 patients, two patients who required assisted ventilation after a transsternal thymectomy and one patient without the need for intubation after VATET. The overall surgery-related complication rate was 5.6%. It was 4.3% after sternotomy (fever with pneumonia) and 13.7% after VATET (1 pneumothorax, which was drained; 1 chylothorax, which was cured with the original chest drain; and 1 intraoperative bleeding from the brachiocephalic vein, which was sutured through the collar incision). There were no surgery-related complications after CVT among the patients evaluated in this study (p = 0.118).

4.2.2.3 Neurological results

Concerning the preoperative Osserman state, treatment, or duration of the disease prior to surgery, there was no significant difference among the 3 groups. When dividing patients into early stage MG (Osserman I and IIA) and advanced stage MG (Osserman IIB, III, and IV), a shift became apparent. The distribution of early stage MG was 52.2%, 81.8%, and 76.9% after STST, VATET, and CVT, respectively (p = 0.062), which was not significant, although it did represent the changing tendencies among the types of thymectomies. Improvement rates at the end of the 1-year follow-up were 91.3%, 94.7%, and 87.5% after STST, VATET, and CVT, respectively (p= 0.712). Due to short follow-up period, a complete stable remission rate could not be accurately stated, though many patients had

reached a symptom- or medication-free status at 1 year, which was deemed as complete remission. According to these results, our complete remission rates were 13%, 10.5%, and 11.5%, respectively (p = 0.917).

4.2.3 Discussion

There was no perioperative mortality and postoperative morbidity occured in 11 %. The first type as a direct result of surgical manipulation (surgery-related morbidity- SRM), the second type as the result of the reactivation of MG due to surgical manipulation (MG-related morbidity- MGRM). Our rate of SRM was lower (5.6%) than the rate of post-operative MG-related neurological disorders (15.5%). Surgery-related morbidity most frequently developed after VATET (13.7%) followed by sternotomy (4.3%), and there were no SRMs documented among CVT patients. In our study, the rate of MG-related respiratory insufficiency requiring intubation and assisted ventilation (14%) and the worsening of MG-related non-respiratory muscle symptoms (1.5%) were strongly influenced (p = 0.071) by the type of surgery. The more extensive the surgery, the more frequently the patients developed respiratory insufficiency, i.e. 21.7% after STST, 13.7% after VATET, and 7.7% after CVT. We found that both MG- and surgery-related morbidity rates were lowest in cases of CVT, though in order for this approach to be widely applyed, it must first prove to be as effective as the other methods used in the surgical treatment of MG. Our results demonstrate that improvement rates with symptom- and medication-free status at the end of the 1-year follow-up were similar after each type of thymectomy (91.3%, 94.7%, and 87.5% improvement with 13%, 10.5%, and 11.5% complete remission after STST, VATET, and CVT, respectively). Based on our results we can conclude that CVT has become a well-accepted procedure among patients and neurologists alike. It maintains the best cosmesis, the shortest hospital stay, and the lowest rates of postoperative morbidity. At 1-year follow up all three types of thymectomies have had similar

beneficial effects on MG symptoms, with the lowest rate of MG-symptom worsening and the least need for mechanical ventilation, after CVT. Thus, we recommend the routin use of CVT in cases of MG without apparent thymoma. VATET, having the highest occurrence of surgery-related morbidity but the best improvement rate, is performed in cases when thymectomy is combined with thyreoidectomy or in the presence of previous thyreoidectomy or any other cervical surgeries. The number of STSTs for MG has been reduced, and it is currently reserved for MG patients with thymomas larger than 4 cm and for cases with a large volume of mediastinal fat.

4.3 Thymoma, thymic hyperplasia, ectopic thymic tissue. Diagnosis and imaging.

Accurate diagnosis is of great importance in the treatment management of thymic pathologies. Regarding thymectomy, there are three important topics which are significant in terms of thoracic surgery: [1] differentiating between TH and THA, [2] deciding whether a possible thymoma invades surrounding tissues, and [3] declaring the presence of ectopic thymic tissue (ETT) around the thymus. In cases where the diagnosis of THA is obvious and an absolute indication for thymectomy is obtained, the most important factor for the surgeon is the radio-clinicopathological data concerning the THA. In connection, the following questions arise. [1] Is the THA resectable, [2] does it infiltrate surrounding tissues so that neoadjuvant therapy should come first, [3] what is the rate of regression after neoadjuvant treatment, and [4] should the resection be extended? These questions can be answered after an extended and more meticulous imaging process with the adaptation of the newly proposed TNM classification. The MK-SCS (Masaoka-Koga stage classification system) has recently been developed by the International Thymic Malignancy Interest Group (ITMIG)/IASLC (International Association for the Study of Lung Cancer) as the proposed eighth edition of staging for thymic epithelial tumors, resulting in new updates, with an important aspect in terms of imaging as well. One of the newly proposed eliminations is the essential focus, on which a tumor is encapsulated or, by expanding beyond the border of the capsule, infiltrates the thymus and neighbouring fat. This important

modification is based on the fact that all THAs are considered malignant, irrelevant of the presence or lack of a capsule and should be treated surgically. Preoperative imaging should point out the exact borders and presence or lack of invasion of THA concerning the above-mentioned tissues or organs. In resectable cases primary thymectomy is indicated, while in case of an unresectable tumor, neoadjuvant treatment should be applied. In terms of lymphnode involvement, the N1 level affects the anterior nodes, while the N2 level is limited to the deep intrathoracic or cervical nodes. The preoperative imaging of ETT is not routinely carried out in current clinical practice, a number of MRI and PET-CT reports state that in numerous cases ETT can be detected on the neck or in the mediastinum. Principles of surgical treatment of MG include complete removal of the thymus with perithymic fat and possible ETT. In MG cases usually two questions arise in terms of surgical treatment. [1] Does the patient have THA? [2] Is there any amount of ETT or “abnormal fat” around the thymus or in the mediastinum?

4.3.1 Discussion

Performing a complete resection of not only the gland itself but also surrounding tissues containing thymic cells and lymph nodes is of utmost importance. Incomplete resection is associated with a high-recurrence rate and poor prognosis. Precise diagnosis and differentiation between each thymic condition through imaging is essential for ideal surgical treatment planning and avoiding overtreatment. While CT remains the cornerstone of thymic imaging, MRI evolves as a useful problem-solving modality for evaluation of various thymic conditions and may remarkably support CT in everyday clinical practice, especially in cases accompanied by MG in combination with different types of THAs or TC. CT combined with PET imaging can be effectively used in the diagnosis of advanced THAs or TC, with control of regression after neoadjuvant treatment, thus facilitating the rate of surgical success. MRI is superior to CT in distinguishing normal and hyperplastic thymus from THAs. In terms of neoplastic conditions, MRI proved to be an accurate modality in differentiating high and low-risk thymomas and can be helpful in separating THA from TC. Treating patients with MG is one of the mainstays of thymic surgery. Total removal of the thymus and

the resection of ETT in typical locations (perithymic fat, aortopulmonary window, cervical region, right and left pericardiophrenic fat, and aortocaval groove) are of paramount importance in banishing MG.

5 Summary and key results

1. With the introduction of low dose radiation therapy, SBRT did indeed prove to be a useful method in the treatment of ES LC, although limited to elderly, or multimorbid patients unfit-, or reluctant to surgery. In case of patients with good respiratory parameters and overall state, surgery still remains the best treatment option for early stage lung cancer.
2. With the thorough investigation of perioperative parameters, our retrospective study of 72 patients receiving postoperative chemotherapy after lobectomy, confirmed that patients undergoing VATS lobectomy were able to receive significantly higher number of postoperative chemotherapy cycles compared to the ones undergoing thoracotomy.
3. According to our study conducted in a special case of benign metastasizing leiomyoma, during which 87 solid tumors have been removed from both lungs, through multiple thoracotomies, we confirmed that thoracotomy indeed remains a reliable option in thoracic surgery. In cases of previous thoracic procedures, or after inflammation in the chest (with probable adhesions) and in cases of multiple re-thoracotomies, the open approach should be recommended. In terms of BML, we managed to describe the dinamics of reoccurring metastases.
4. Shared decision making can lead to better patient communication, a more detailed interpretation of evidence based information and improved decision making among different types of thoracic surgery procedures, eventually resulting in improved overall survival.
5. VATS thymectomy for MG has become a well-accepted procedure among patients and neurologists alike. Among the three types of thymectomies- namely standard transternal thymectomy (STST), VATET, and classic VATS thymectomy (CVT)- included in our study, CVT maintains the best cosmesis, the shortest hospital stay, and the lowest rates of postoperative morbidity (MG-related- and surgery related morbidity alike). All 3 types of thymectomies have had similar beneficial effects on MG symptoms at 1-year follow up, and we experienced the lowest rate of

postoperative MG-symptom worsening, especially in terms of the need for mechanical ventilation, after CVT.

6. Preoperative imaging is pivotal in the diagnosis of thymic conditions. Besides CT remaining the cornerstone of thymic imaging, MRI has emerged as a useful- and in some cases more accurate modality. MRI is superior to CT in distinguishing normal thymus and thymic hyperplasia from thymomas. MRI also proved to facilitate the differentiation of high and low risk thymomas, hence being helpful in separating thymomas from thymic carcinoma. MRI is not only capable of distinguishing between benign and malignant thymic lesions, but is also useful in the follow-up of regression of THAs after neoadjuvant therapy. Thymectomy is a mainstay treatment of MG, thus total removal of the thymus, including ectopic thymic foci in typical locations is of utmost importance in gaining remission. Preoperative imaging with the inclusion of MRI could be extremely helpful in discovering possible ectopic thymic foci and distinguishing among thymic conditions.

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