Modern diagnostic and surgical management of thoracic diseases in our practice

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Ph.D Thesis

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2018
Szeged

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.

IF: 2,365

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.
IF: 2,934

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.
IF: 0,349

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

ADC: apparent diffusion coefficient; AF: atrial fibrillation; AS-LC: advanced stage lung cancer; AS-NSCLC: advanced stage non-small cell lung cancer; BMI: body mass index; BML: benign metastasizing leiomyoma; CALGB: Cancer and Leukemia Group B; CC: carcinoma; CCI: Charlson comorbidity index; ChS: chemical shift; CI: confidence interval; CT: computed tomography; CVT: classic VATS thymectomy; DWI: diffusion weighted imaging; EBUS: endobronchial ultrasound; EET: ectopic thymic tissue; ES-NSCLC: early stage non small cell lung cancer; ESTS: Europian Society of Thoracic Surgeons; EVT: extended VATS thymectomy; FEV1: forced expiratory volume 1 second; FS: fat suppression; FVC: forced volume vital capacity; HR: hazard ratio; HRQoL: health-related quality of life; IASLC: International Association for the Study of Lung Cancer; ITMIG: International Thymic Malignancy Interest Group; LC: lung cancer; LR: local recurrence; MG: myasthenia gravis; MGFA: Myasthenia Gravis Foundation of America; MGRM: myasthenia gravis related morbidity; miRNA: micro ribonucleic acid; MK-SCS: Masaoka-Koga stage classification system; MRI: magnatic resonance imaging; MUST: Malnutrition Universal Screening Tool; NSCLC: non-small cell lung cancer; OD: odds ratio; OS: overall survival; PAL: prolonged air leak; PET: pozitron emission tomography; PPBC: postoperative platinum based chemotherapy; PS: performance status; RCT: randomized clinical trial; SPVATS- single port video-assisted thoracic surgery; SRM: surgery-related morbidity; STS: Society of Thoracic Surgeons; STST: standard transternal thymectomy; TC: thymic carcinoma; TEMLA: trascervical extended mediastinal lymphadenectomy; TH: thymic hyperplasia; THA: thymoma; VAMLA: video assisted mediastinal lymphadenectomy; VATET: Video-Assisted Thoracosopic Extended Thymectomy; VATS- Video Assisted Thoracic Surgery; uVATS: uniportal 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 (1). 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. The development of uniportal VATS (uVATS) allowed surgeons not only to further minimize the number of incisions and trauma to the patient, but by requiring only a single incision, uVATS also reduced the amount of postoperative analgesia and the occurance of chronic pain compared to conventional VATS. The features of diagnostic methods for lung cancer (LC) have also changed appreciably with time, resulting in a shift towards early diagnosis of LC. This change is thought to be the result of a more frequent and precise trend in imaging techniques- especially low-dose chest computed tomography (CT)- and the introduction of screening programs- even using everyday devices, such as smartphones to alart individuals at high risk for LC - throughout the years, which pattern also seems to be of increasing importance in Hungary (3,4).

Anatomic pulmonary resections are the most common surgical procedures in cases of operable lung cancer, and minimal access lobectomy through the VATS approach is increasingly used worldwide (5). Since the first VATS lobectomy was performed in 1993 (6,7), this technique has evolved in enormous steps. The Cancer and Leukemia Group B (CALGB) 39802 trial established the most accepted definition of the VATS lobectomy technique in 2007: 1. no use of rib-spreading; 2. utility incision with a maximum length of 8 cm to deliver the specimen; 3. individual dissection of the vein, arteries and airway for the lobe; 4. standard lymph node sampling or dissection (8). This definition of minimal access would warrent a procedure causing less trauma to the patient, with improved surgical outcomes, maintaining oncological principles

(9). Perioperative benefits of the VATS approach compared with open thoracotomy include reduced incidences of prolonged air leaks, arrhythmias, pneumonia, pain and decreased inflammatory markers, reduced hospitalization (with increased cost-effectiveness) (10). Long-term outcomes including overall mortality and disease recurrence proved to be similar or even superior for VATS lobectomy compared with thoracotomy (10).

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? With the increasing effort to personalize patient care and tailor treatments for the individualized targeting of LC, does surgery still remain the best treatment option for early stage (ES) tumors, or can SBRT be an alternative choice of treatment? With VATS emerging as a major alternative even for sophisticated thoracic procedures (sleeve lobectomy, chest wall resections, tracheal resection), is the VATS approach able to maintain oncological radicality in cases of advanced malignant diseases?

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. The pattern experienced among different types of thymectomies bears high similarity with the ones mentioned during LC treatment. Starting with the open approach, through sternotomy (STST: standard transternal thymectomy), changes have pointed towards a less invasive method called the Video-Assisted Thoracoscopic Extended Thymectomy (VATET) which was introduced at our Department in 2004. With international trends leading the way towards VATS thymectomy, we soon started to convert our surgical techniques to conventional (or classic) VATS (cVATS). Thymic abnormalities have been widely connected to various autoimmune diseases, especially

myasthenia gravis (MG). The surgical treatment involving MG with thymomas and non-thymomatous conditions alike, have a great affect on patient quality of life through improvement of symptoms. However the debate arises, on which method to turn to when it comes to thymectomy. 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, even with facilitation of cosmetic outcome? In addition, what are the peioperative 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?

During the diagnostic workup of patients, differentiating between thymic conditions such as different types of thymomas (THA) and thymic hyperplasia is of pivotal importance regarding treatment strategy (surgical or non-surgical). Although computed tomography (CT) has remained the gold standard in the diagnosis of lung cancer, in various thymic conditions, differentiating between benign and malignant lesions,-with emphasis on thymic hyperplasia (TH) and thymoma (THA)- and especially esthimating the rate of regression after neoadjuvant therapy, draw great challange for radiologists and surgeons alike. Magnetic resonance imaging (MRI), including fat suppression- and chemical shift modalities, has widend the possibilities of more accurate diagnosis, leading us to precise and individually tailored treatment options, with decreasing rates of overtreatment.

The question arises whether diagnostic imaging of the thymus should 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

Lung cancer is associated with the most cancer-related deaths in both genders worldwide (12). With the development of imaging techniques for diagnosis and surgical methods pointing towards thoracoscopy, many changes have been experienced in the surgical treatment of LC. The pattern of minimal access approach not only applies for the management of LC, but is also widely used in the treatment of various thymic conditions. The improvement of accuracy in imaging

of the thymus (MRI) leading to a better verification and differentiation of conditions (thymic hyperlasia vs thymoma subtypes) result in better patient care and decreased rate of overtreatment. During our clinical study we investigated ongoing questions and debates in line with early- and advanced stage lung cancer and various thymic abnormalities. In the first part of the study we focus on the management of LC, addressing topics such as novel treatment options for ES-LC, perioperative outcomes of AS-LC, current updates of VATS vs thoracotomy in thoracic surgery, individualized treatment planning for patients with ES-LC (shared decision making). The second part of the study deals with minimal access treatment options (STST, VATET, cVATS) for different thymic conditions, with myasthenia gravis (MG) with the discussion of surgical- and early neurological results and the improvements of imaging techniques used in the differentiation of thymic hyperplasia, various subtypes of thymomas, and ectopic thymic tissue.

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 (13). 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 and according to current National Comprehensive Cancer Network (NCCN) guidelines, surgery remains the best therapeutic option (14). Stereotactic body radiation therapy has been used as an alternative treatment therapy for patients with inoperable lung cancer (15) and in those considered to be at high-risk as a result of comorbidities, poor pulmonary function, and/or advanced age. With the recent development and the expansion of therapeutic options, treatment reevaluation of ES-NSCLC is a timely objective in order to succeed in choosing the best alternative therapy for ES-LC patients. When diagnosed at an early stage, surgical resection of NSCLC offers an acceptable prognosis, with 5-year survival rates of 70–90% for small, localized, stage I tumors (16). However most patients (approx. 75%) are diagnosed with LC at an already advanced stage (stage III/IV), resulting in poor prognosis (17). Recently international screening programs (National Lung Screening Trial) have aimed at detecting LC in an early stage (18), by acquiring low dose computed tomography (LDCT), with Hungary- sadly leading the statistics for lung cancer-related deaths- also having its share since 2013, through the Hunchest program.

Surgery has been considered for decades the ideal therapeutic option mainly to ensure optimal local control of lung cancer.

Recurrent tumors may be present at different sites after initial surgery. In this setting, and unlike many of the series based on other modalities of local control of NSCLC, the surgical series are characterized by a precise definition of the concept of local recurrence (LR) (19). In case of LR, tumors may involve adjacent lung parenchyma, the bronchial stump, or the adjacent hilum. Regional failure means

that recurrence is located in the hilum separate from the bronchial stump, mediastinum, chest wall or the ipsilateral pleura (20). When distant failure is present, tumor occurs in the separate lobe of the ipsilateral lung, contralateral thorax, supraclavicular lymph nodes or in distant organs (20). According to ACOSOG Z0030 trial conducted – using the the 7th Edition TNM on lung cancer-, among 578 pT1 and 440 pT2 patients with recurrent ES-NSCLC, the median overall survival (OS) for pT1 tumors was 9.1 years and 6.5 years for pT2, respectively (20). The 5-year disease free survival was 77% for pT1 and 58% for pT2, respectively whereas the 5-year local disease-free survival was 95% for pT1 and 91% for pT2, respectively (20). When the patterns of recurrence were considered, LR was observed in 1% and 3% of T1 and T2 tumors, respectively (20). Moreover, regional and combined local and regional recurrences were seen in 4% and 0.4% for T1, and, 3% and 0.7% for T2 subsets, respectively.

On the other hand SBRT 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 (20). Moreover 2 years after SBRT treatment, a 4.9% and 7.8% local- and regional recurrence rate was noted in retrospective studies (21). A direct comparison among the possible treatment options for ES-NSCLC was published in 2012 (22), among more than 10000 elderly (66 years <) including lobectomy, sublobar resection, SBRT, conventional radiation, and, observation. After 6 months, lobectomy proved to have the best overall- and disease specific survivals, while SBRT showed the best mortality rates (22). The diagnosis of lung cancer has also experienced some changes throughout the years. One among the many diagnostic options is a promising novel technique, namely accurate diagnosis from blood samples. Sozzi et al. have demonstrated, that the combination of low dose CT with miRNA signatures can reduce the rate of false negatives by fivefold, decreasing the rate of unnecessary surgery (23). Blood-based diagnosis would theoretically facilitate targeted treatment of LC, or be an alternative option for inoperabile patients, or those reluctant for surgery and still confirm a histological type. However due to multiclonality within the same tumor mass, leading to increasing resistance in cases of targeted therapy, only adequate sampling of tumors could

lead to precise genomic profiling, thus surgical biopsies still remain our best option at the moment (24).

Correct clinical and pathological staging is pivotal in the adequate staging of LC. The quest for identifying patterns of mediastinal nodal involvement amenable to primary surgery has provided important practical consequences (25). Moreover occult as well as single station N2 NSCLC are now increasingly considered a surgical disease given the encouraging survival rates reported in surgical series (25). The wide introduction of VATS has enabled thoracic surgeons to verify diseases through accurate staging using locoregional anesthesia (26). Procedures carried out via uniportal VATS are used to distinguish between T2 and T3 or N2 and N3 when endobronchial ultrasound (EBUS) and mediastinoscopy fail to be informative or cannot be technically carried out. In the subset of single port surgery, video assisted mediastinal lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA) also represent a feasible option to better select surgical candidates for lung resection (27). 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% (28).

With taking all possible treatment options into account, our main goal still remains finding the best individualized treatment strategy, and trying to obtain the best recurrence free survival for patients with lung cancer. In this context, sublobar resections are under scrutiny for their oncologic efficacy, compared with SBRT as an alternative to lobectomy for ES-LC.

Be as it may, 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 (29).

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. Moreover, PPBC has become a standard recommendation for NSCLC patients with lymph node metastases, tumors larger than 4 cm, or extensive local invasion (30). Patients vary considerably in the ability to tolerate PPBC after recovering from a lung cancer resection. Numerous perioperative factors including patient comorbidities, extent and approach of surgical resection, and the occurrence of postoperative complications can play an important role in the ability to tolerate postoperative systemic therapy in the perioperative period. 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.

The proportion of lobectomies performed through thoracotomy and VATS have changed significantly during the last decade (Figure 1).

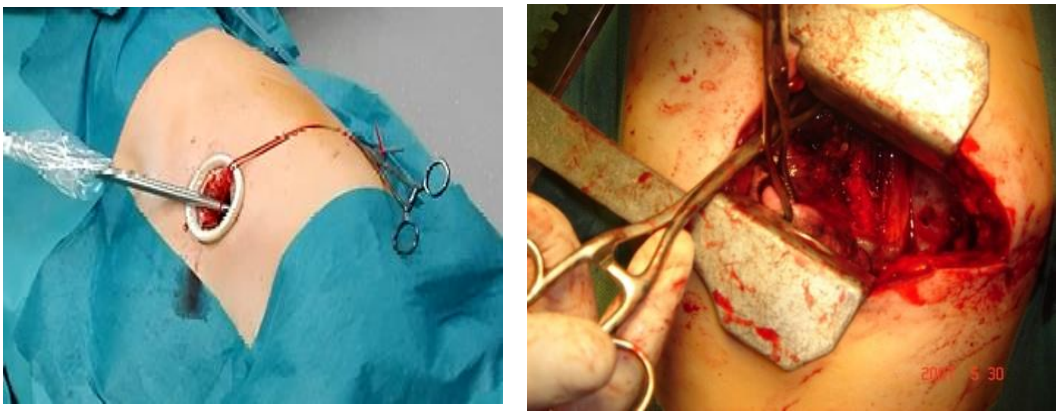

Figure 1: Intraoperative picture during uniportal VATS lobectomy (left) and intraoperative situs during thoracotomy with rib spreading (right)

courtesy of University of Szeged, Dep. of Surg.- Dr. Jozsef Furak

According to the database of The Society of Thoracic Surgeons (representing data of US thoracic centers) the proportion of VATS is the highest in the United States and the lowest in South America (31). The proportion varies highly in European

countries, for example, in 2014, VATS was used in 3.6% of lobectomies in Romania, 17% in Italy and France, and 27% in Belgium [data from the European Society of Thoracic Surgeons (ESTS) database]. In Hungary the proportion of VATS lobectomies peformed due to LC was 41% in 2016 (32). The advantages of VATS procedures in the treatment of ES-LC is well established (20), but is it also effective in the management of advanced stage lung cancer (AS-LC), and does it meet demanded oncological criteria?

Numerous authorative studies demonstrated the effectiveness of VATS lobectomies in terms of oncological radicality and validity of mediastinal intra-operative staging (33). VATS major pulmonary resections still demand advanced surgical skills and experience, due to diffult manoeuvres and delicate dissection of structures, resulting in potentially life threatening bleedings. Results from a study conducted between 2014-2017 from the Italian VATS Group Database (34), comparing VATS lobectomies in case of ES-LC (IA, IB, IIA) and AS-LC (IIB, IIIA, or higher), showed that there was no significant difference in terms of 30-day mortality. Furthermore with comparing early stage (cT1 and cT2) and advanced stage NSCLC managed by uniportal VATS lobectomy, Gonzales-Rivas et al. published a complication rate of 17.2% and 14.0%, respectively (35). These results may lead us to the conclusion, that in carefully selected patients, managed in experienced centers possibly grant the feasibility of VATS lobectomies even in advanced cases of lung cancer. Moreover VATS may even improve survival rates by allowing patients to receive postoperative oncological therapy faster, than those who underwent lobectomy via thoracotomy (36).

The initiation of PPBC definitely improves survival rates for stage IIA and higher LCs (37). According to the statement of the Non-Small Cell Lung Cancer Collaborative Group in cases of surgically resected LCs (NSCLC) cisplatin based postoperative chemotherapy showed a 5% survival improvement (38), which was also confirmed by data of the International Adjuvant Lung Cancer Trial (39).

The porpose of our own study was to analyze the tolerability of PPBC, after surgically resected cases, and highlight the perioperative factors with appreciable impact.

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. In order to reach a homogenous group of patients, we excluded small cell- and non-small cell lung cancer cases and patients with atypical carcinoid and only cases of adenocarcinoma and squamous cell carcinoma were included. Only cases involving anatomical lung resections (lobectomy) were included, cases of pulmonectomies and wedge resections were not 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). During staging of LCs, 7th TNM staging system of the IASLC (International Association for the Study of Lung Cancer) was used.

Our guidelines involving the initiation of PPBC followed international protocols (4-8 weeks after surgery) (40) as well as the number of administered cycles of agents (41). A PPBC protocol was deemed complete if the patient received all 4 cycles of chemotherapy. Regarding PPBC 6 types of chemotherapeutic agents (CDDP: cisplatin; CBP: karboplatin; NVB: navelbin; TAX: paclitaxel; VP: vindezin; Gemzar: gemcitabin) were acquired as mono- or combined therapy. Postoperative protocols were devided into the complete group (CG- patients receiving complete course of 4 cycles of PPBC) and the non-complete group (NCG- patients receiving less than 4 cycles of PPBC, due to the occurance of medication refractory complications). The rate of CG/NCG, as well as the reasons of termination were analyzed. The reasons of PPBC termination were catagorized into an objective (gastrointestinal-, cardiac- hematological-, nephrolocical complications, noval distant metastasis, surgical wound infection, soft tissue damage) and a subjective (regarding personal patient decision and psychological

state) group. In the same setting besides PPBC, 20 patients (27.77%) received postoperative radiotherapy.

3.2.2 Results

During data analysis of the 72 patients (CG: n= 53 [73.61%]; NCG: 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 (Diagram 1, Table 1). 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 (Diagram 2, Table 1). 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) (Table 2). 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) (Table 2). Termination of PPBC occured in 19 cases (26.38%), mainly due to gastrointestinal (GI) complications (31.57%). Details are to be found in Table 3.

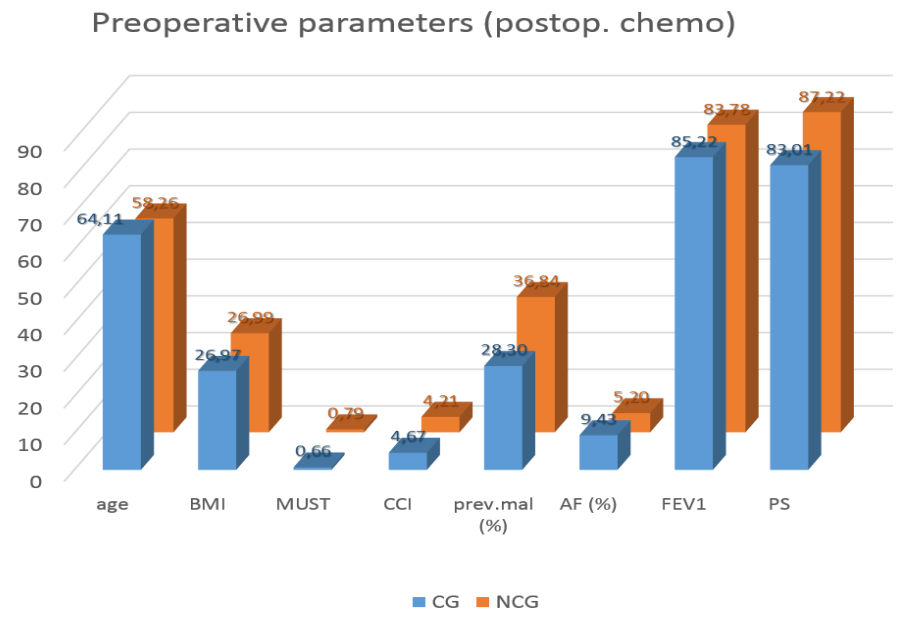

Diagram 1: preoperative parameters

CG: complete group; NCG: non complete group

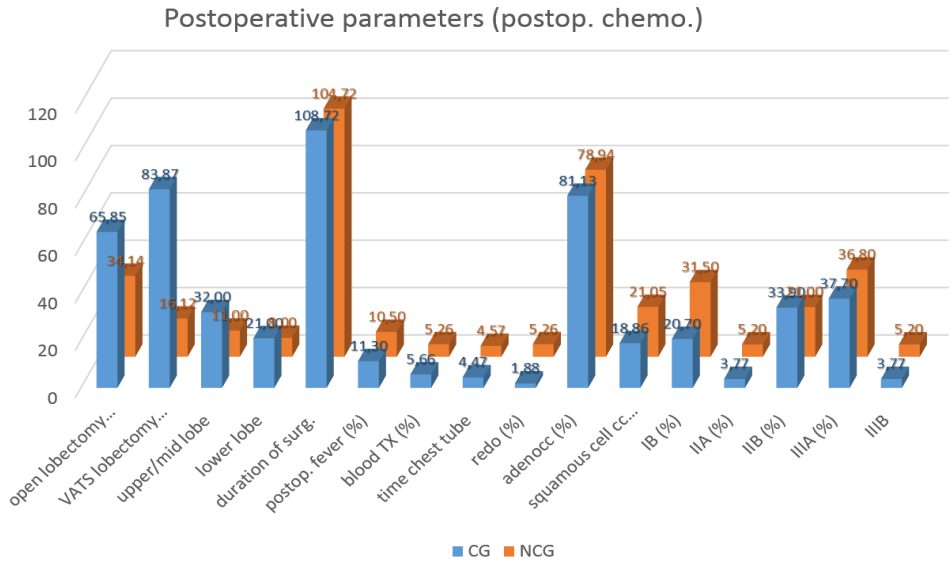

Diagram 2: postoperative parameters

CG: complete group; NCG: non complete group

	Complete group (n=53)	**Non-complete group (n=19)**	***p***	**OR**
Preoperative parameters				
Age (years)	64.11	58.26	*0.678*	0.854
BMI (mean)	26.97	26.99	*0.752*	0.765
MUST (mean)	0.66	0.789	*0.834*	0.435
CCI (mean)	4.67	4.21	*0.567*	0.756
Previous malignancies in history	15/53= 28.301%	7/19= 36.84%	*0.874*	0.745
AF	5/53= 9.43%	1/19= 5.2 %	*0.532*	0.967
FEV1	85.22%	83.78%	*0.856*	0.358
PS	83.01	87.22	*0.539*	0.456
Postoperative parameters				
Open lobectomy (n=41)	27(65.85%)	14(34.14%)		
VATS lobectomy (n=31)	26(83.87%)	5(16.12%)	*0.092*	0.356
Upper lobe/mid-lobe	32	11		
Lower lobe	21	8	*0.173*	0.724
Duration of surgery (min)	108.72	104.72	*0.326*	0.528
Postoperative fever	6 (11.3%)	2 (10.5%)	*0.632*	0.739
Need for blood transfusion	3 (5.66%)	1 (5.26%)	*0.734*	0.835
Time of chest tube (days)	4.47	4.57	*0.892*	0.673
Redo surgery	1 (1.88%)	1 (5.26%)	*0.950*	0.845
Adenocc	43 (81.13%)	15 (78.94%)	*0.534*	0.834
Squamous cell cc	10 (18.86%)	4 (21.05%)	*0.934*	0.623
IB	11/53= 20.7%	6/19=31.5%	*0.367*	0.34
IIA	2/53= 3.77%	1/19=5.2%	*0.457*	0.834
IIB	18/53= 33.9%	4/19= 21.0%	*0.645*	0.567
IIIA	20/53= 37.7%	7/19= 36.8%	*0.563*	0.967
IIIB	2/53= 3.77%	1/19= 5.2%	*0.379*	0.367

Table 1: Pre- and postoperative parameters in the complete and non-complete groups
OR: Odds Ratio

	*CG	**NCG	*p*
VATS	26 (49.05%)	5 (26.31%)	***0.0495***
Open	27 (50.94%)	14 (73.68%)	
Upper/Mid-lobe	32 (60.37%)	11 (57.89%)	*0.0678*
Lower lobe	21 (39.62%)	8 (42.10%)	
Diabetes +	7 (13.20%)	1 (5.26%)	*0.0971*
Diabetes -	46 (86.79%)	18 (94.73%)	
PAL +	12 (22.64%)	6 (31.57%)	*0.328*
PAL -	41 (77.35%)	13 (68.42%)	
Postoperative fever +	7 (13.20%)	2 (10.52%)	*0.248*
Postoperative fever -	46 (86.79%)	17 (89.47%)	

Table 2: The effect of high priority perioperative factors on received PPBC cycles in CG and NCG (multivariate analysis). *CG: complete group; **NCG: non-complete group

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 3: Reasons for PPBC termination. §PPBC: Postoperative platinum based chemotherapy

3.2.3 Discussion

The current primary treatment option for lung cancer is still surgery, however postoperative oncological therapy is also pivotal in banishing the disease. Increased survival rates after PPBC have been reported in a large meta-analysis (Lung Adjuvant Cisplatin Evaluation- LACE) (37), which described a 5.4% overall benefit (overall HR of death: 0,89- 95% CI; p= 0.005) at 5 years for 4584 AS-NSCLC patients receiving PPBC after undergoing successful surgery, compared to those not receiving PPBC after surgery (mortality hazard ratio [HR]: 0.89; confidence interval [CI]: 95%, 0.82-0.96; p=0,005). Survival rates were significant in cases of stage II and IIIA (HR: 0.93) (37). Numerous parameters may influence the ability of starting a patient on PPBC (see Table 1), however the type of surgery is surely an important one. Deciding whether VATS or thoracotomy is the better approach in terms of receiving more cycles of postoperative chemotherapy is still an ongoing debate (42,43). During our investigation we compared both methods in terms of the two groups receiving chemotherapy cycles (CG/NCG), and we 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). Teh et al. emphasized the improved tolerability of PPBC cycles after VATS procedures, even with stage III patients (44). Another important factor influencing postoperative treatment tolerabiliy is patient nourishment status. During oncological treatment 20-80% of patients suffer from malnutrition (45), resulting in liability to infections, decreased wound healing and skin turgor (46). There are different methods in measuring patient malnutrition (body weight loss, serum albumin levels, BMI), however there is wide accordance on the fact, that malnutrition in the case of oncologically treated patients leads to decrease in long term survival rates (47). Malnutrition also plays a major role in the ability of completing PPBC cycles, although the present study did not show significant difference in terms of BMI and MUST results among CG and NCG (Table 1). The Charlson comorbidity index (CCI) was used on measuring comorbidities. There is still ongoing debate on the affect of comorbidities in case of malignant diseases, Grosso et al. for instance found that in cases of stage I-III colorectal cancer patients, age did not significantly affect the incidence of intraoperative complications (48). According to multicentric studies on

age and CCI, the latter maintained better value of prediction, especially in case of advanced stage NSCLC (49). 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. Besides the analysis of numerous perioperative factors, five high priority parameters (VATS/open approach, upper/middle vs lower lobe resection, diabetes, PAL, postoperative fever) were included in multivariate analysis. One of them was the rate of prolonged airleaks, which are seen in the literature in approx. 50% of patients undergoing pulmonary resections (50). Be as it may, PAL did not significantly influence PPBC uptake in our case (Table 2). 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. According to a meta-analysis by Gao et al., comparing gemcitabin (GEM)+ platinum, or vinorelbin (NVB)+ platinum, the most common side effects were as follows (GEM/NVB), severe (grade 3) anaemia: 14.7%/12.38%; grade 3 neutropenia: 31.37%/49.91%; grade 3 throbocytopenia: 29.06%/4.04%; vomiting: 17.28%/18.76%; nephrotoxicity: 4.73%/10.99%, constipation: 2.74%/5.07% (51). In our own study PPBC was most frequently terminated due to GI side effects (excessive vomiting) (31.57%) and in accordance with subjective patient complaints (26.31%). During the study period, no case of severe anaemia or thrombocytopenia occurred. All occurring side effects and thier proportion can be found in Table 3.

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. Retrospective studies, such as owers usually have the limitations of low patient accrual, however the current analysis adds great value to the day to day practice in thoracic surgery. Our study showed that the number of patients undergoing VATS lobectomy with receiving complete (4 cycles) PPBC was significantly higher and that upper/mid-lobe resections and the lack of diabetes were among the perioperative factors which had considerably advantageous affect on the number of complete PPBC cycles. Among the patients included in this study, 74% successfully received complete PPBC cycles, in which the acquired thoracoscopic (VATS) procedures played a pivotal role.

However, with this rapid emerge of VATS, has open lobectomy on its own lost its value? With highly sophisticated procedures (sleeve lobectomy, tracheal resection, etc.) performed through the minimal access approach, does that mean that thoracotomy has grown obsolete in the armamentary of thoracic surgery? During the evaluation of different thoracic diseases and possible surgical approaches VATS is not always the first choice of option. In cases of simultaneously present, different sized multiple intraparenchymal lesions, or after repeated thoracotomies, surgery may comprise challanges -such as infected wounds, thoracic adhesions, difficult to approach chest wall- which may necessitate the use of thoracotomy.

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. However, taking into account whether a patient is suitable for a VATS procedure, depends on many factors, especially on the decision of the operating surgeon.

Factors such as tumor location and size, previous surgery or infection (TB), body structure and frame of the patient, and last but not least, surgeon VATS experience have an impact on whether a patient undergoes VATS or open resection. In case a patient has multiple benign solid tumors in the lung, reoccurring throughout many years, surely an unique surgical approach would have to be applyed in order to successfully treat the condition.

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 various locations, such as the lung, retroperitoneum, lymph nodes, bones, muscular tissues or the nervous system, with the lung beeing the most frequent site. Lesions are also positive for estrogen- and progesteron receptors, revealing the origin of the disease (52). Medical treatment of BML offers hormonal therapy (gonadotropin-releasing hormone analogues, selective ER modulators, or progesterone and aromatase inhibitors) with or without oophorectomy, although it has been mostly suggested in non-resectable cases (52).

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 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 (Figure 3), after which oncological treatment was once again administered.

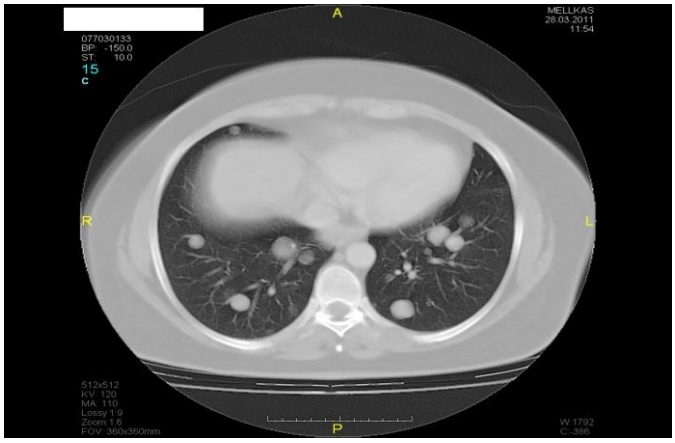

Figure 2: Contrast enhanced chest CT with BML lesions in both lobes

courtesy of University of Szeged, Dep. of Surg.- Dr. Jozsef Furak

Figure 3: Benign metastasizing leiomyoma (BML)-lesions removed from the left side (n= 36)

courtesy of University of Szeged, Dep. of Surg.- Dr. Jozsef Furak

Surgical sensitivity (SS) and mean SS were measured in connection with each removed lesion (Table 4). SS was defined as the rate of surgically removed and CT-diagnosed metastases in each individual surgery, and mSS was the mean of the SS results for the seven procedures. The number of recurrent lesions were counted, their size measured, and growth dynamics observed in a given time period owing to scheduled operations and controlled CTs verifying the results of oncological treatment.

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. One of the challenges of repeat metastasectomies is finding smaller lesions in the lung parenchyma. SS results show that repeat metastasectomies are feasible and effective in cases of BML. Regarding the growth dynamics of recurrent lesions, we found that tumors grew faster initially, and the number of recurrent lesions decreased with elapsed time (P=0.023). 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.

This case of BML, involving repeated mini-thoracotomies sheds a light on the obvious fact, that traditional open thoracic surgery is not obsolate, indeed, in some cases it is inevitable. The comparison of VATS and open surgery is a continuous ongoing subject of analysis (53). With its novel approach and expanded appliance, VATS offers many well known advantages in patient management (shorter time of chest tubes, better cosmesis, decreased trauma during surgery). On the other hand, in cases where previous thoracic procedures were carried out, or after inflammation in the chest (with probable adhesions) and in cases of multiple re-thoracotomies the choice of surgical method should be an important subject of discussion. Through our unusual case we've sought to evaluate the value of repeated thoracotomies in a scenario where the minimal access approach would not have been satisfactory. To more precisely evaluate the role of thoracotomies in treatments needing multiple chest wall openings, further studies are needed. Our own case sheds light on the time-proven part played by the open approach on the stage of thoracic surgery.

Procedures	**t** (months from the first surgery)	**m1** (number of metastases revealed by CT)	**m2** (number of metastases removed surgically)	***Surgical sensitivity** (SS)	**Type of resection**	**Side**	**Days of hospital stay**
I.	0	36	31	86.1%	**E	R	6
II.	3	37	36	97.2%	E	L	6
III.	15	5	2	40%	E	L	5
IV.	24	10	11	110% mean: 97.7%	E+§W	R	6
V.	26	2	2	100%	E+W	L	5
VI.	35	2	2	100%	W	L	4
VII.	41	2	3	150%	E	R	4

Table 4: *Surgical sensitivity (SS): rate of surgically removed and CT diagnosed metastases regarding the same surgery.

** Enucleation (cautery resection); §Wedge resection; R: right; L: left

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 (54). Compared to conventional radiation OS proved to be better with SBRT (55). Recently SBRT has been considered a fair alternative to surgery in the treatment of stage I NSCLC (21). Results of phase 2 prospective studies showed that the OS of patients treated with SBRT was similar to those treated surgically with operable stage I NSCLC (22). Moreover disease-specific survival rates for SBRT were also at least comparable with those of surgery (22). In addition SBRT may also be an equal alternative for elderly patients and those with severe comorbidities being weak candidates for surgery. However it should be noted, that according to the eighth edition of TNM classification for lung cancer, differences in tumor diameter among T1 subcategories (T1a-c) are considered crucial factors which may have great influence on the outcomes of stage I NSCLC, thus affecting individualized treatment planning (56). Another topic of debate with SBRT is possible disease recurrence at untreated sites (same lung lobe, hilum, mediastinum). Furthermore, while surgically treated patients usually undergo nodal sampling during each procedure (which contributes to precise staging), those treated by SBRT undergo CT, PET-CT or endobronchial ultrasonography which due to possible false-negative/false positive results—may cause stage migration (57). Most recent studies dealing with the comparison of the two methods conclude that surgery (lobectomy) remains the gold standard of treatment in patients with early stage disease (58). Bahig et al. emphasized the “moving target of equipoise”, underlining the fact that health-related quality of life (HRQoL), cost-effectiveness and treatment-related mortality risk may also be additional factors in comparing surgery and SBRT (59). In case of marginally operable patients SBRT-, whereas in clearly operable patients lobectomy proved to be the most cost-effective option of treatment (60). In several randomized controlled trials (RCTs) HRQoL after surgery was associated with decreased physical

function after 6 months, even though the mentioned trials were closed early due to poor patient accrual (61). Based on the above data one could be entitled to presume that the two treatment options are equally effective. In fact SBRT offers a less aggressive treatment on an outpatient basis. Surgery on the other hand, maintains more accurate staging with histological analysis of removed lymphnodes contributing to the successful control of the disease. Shared decision making is a process during which the clinician and the patient work closely together in order to reach a common goal, by considering the benefits and drawbacks of each treatment option (62). The SDM process involves and encourages patients to form an individual opinion on their condition and actively take part in treatment decision making. In a survey conducted among 126 physicians (thoracic surgeons, pulmonologists and radiation oncologists), participants had to express their opinion on surgery vs SBRT, during which both clinician and patient characteristisc were measured (63). The study reports that 54.8% of clinicians thought that SBRT and surgery were equal treatment options and 54% chose to involve patients by applying SDM. In order to measure clinician (un)certainty on treatment recommendations a scale from 1–7 (7 being most uncertain) was used which showed an average score of 2.48 with a relative uncertainty (score 3 or higher) in 41.9% of primary care physicians (PCP). The speciality of the physician undoubtedly played a major role in SDM resulting in the preference of either treatment option. According to the results, thoracic surgeons usually preferred surgery (to SBRT), thus the two choices were in line when the patient also preferred surgery. On the other hand radiation oncologists and pulmonologists preferred SBRT (to surgery), hence the two opinions were more in keeping when the patient also preferred SBRT (62). 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 and a somewhat similar percentage thought that patients should be involved in the treatment decision process (64). 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. The results point out that SDM is still a relatively

unknown and sporadically applied method in routine patient care with some level of negligence from the clinicians' side.

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 and may improve overall survival.

4 Modern diagnostic and treatment options of thymic conditions

4.1 Myasthenia gravis

In terms of the surgical management of MG, the proper knowledge of thymic development and physiology is essential (65). The incidence of thymic pathologies occurring among MG patients is roughly 75% (66): with thymic hyperplasia (TH) occurring in 60–77% and thymoma (THA) in 15–30% of cases (67). 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 (68).

The management of MG includes complex medical and surgical treatment. In terms of immunosuppresant therapy, azathioprine is one of the best tolerated treatments in MG patients, with adjustments for thio-purine-methyl-tranferase levels, allowing the reduction or withdrawal of corticosteroids (69,70). Treatment options for MG, be that medical or surgical should always be tailored to the current state of the patient and MG symptoms. 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 (71, 72). However superiority of either treatment is still a question of debate.

4.2 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) (Figure 4 e-f)
   b. extended („VATET”- Video-Assisted Thoracoscopic Extended Thymectomy) (Figure 4 c-d)

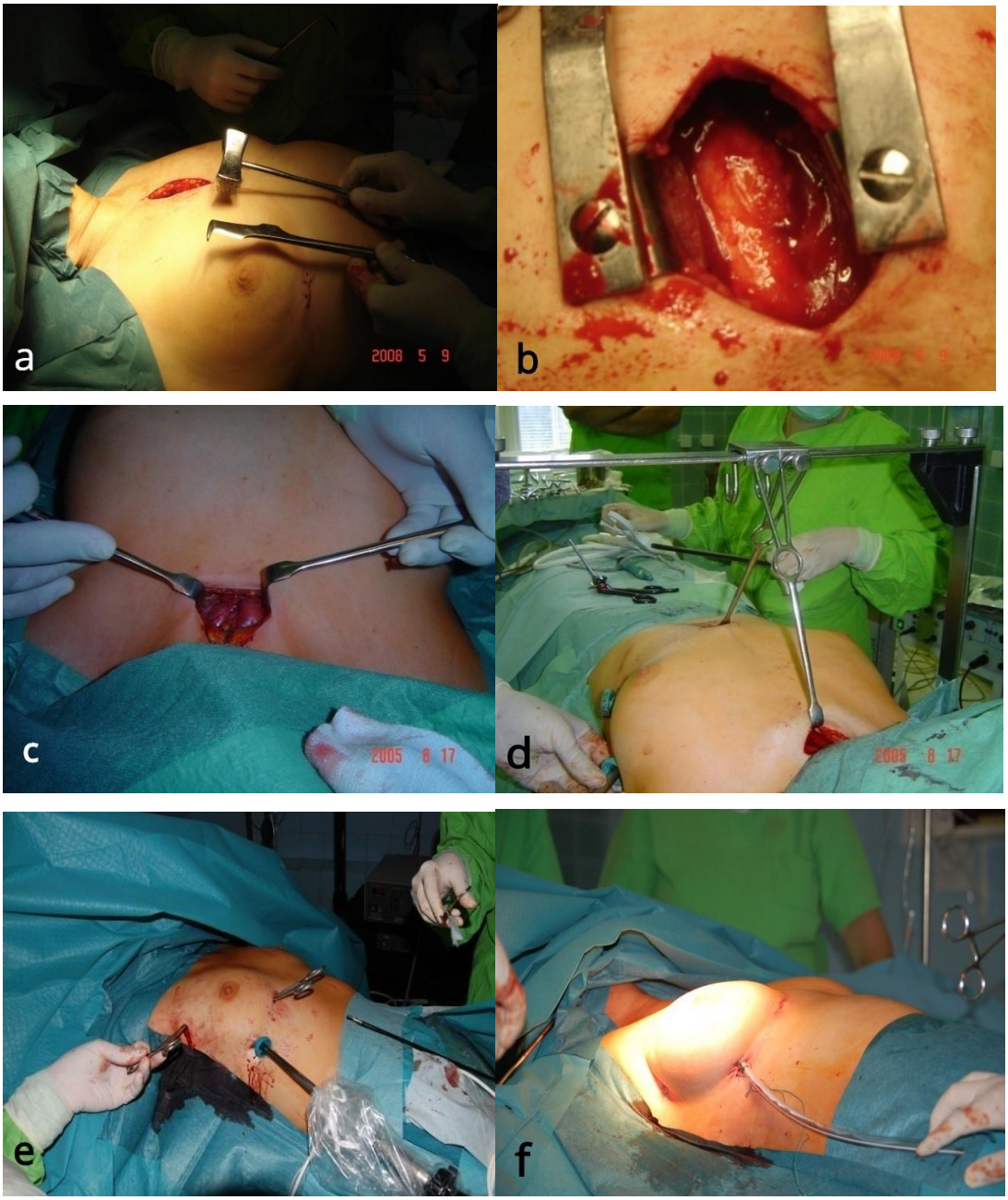

Figure 4: Standard transsternel thymectomy (a,b); VATET (c,d); cVATS thymectomy (e,f).

courtesy of University of Szeged, Dep. of Surg.- Dr. Jozsef Furak

3. Transsternal thymectomy
    a. simple (Figure 4 a-b)
    b. extended
4. Transcervical and transsternal thymectomy

In terms of surgical technique we refer to our earlier publications and the describtion by Zielinski which is the mainstay of our VATET method (73,74,75).

4.2.1 Surgical technique for thymectomies

Taking the advantages of VATS into consideration, videothoracoscopic procedures have also came recently into the limelight. During our clinical practice we have been performing minimal access thymectomy since 2004, introducing both VATS approaches. We began using the „extended" method, after which, in 2009 we switched to the „simple" or „classic" VATS (CVT) thymectomy. Between 2004 and 2010, 42 patients (35 female and 7 male) underwent VATS thymectomy for MG. Extended VATS thymectomy (EVT) was carried out in 22 cases (2004-2009) and CVT (from the right side of the thoracic cavity) in 20 cases (2009-2010). No mortalities were encountered. The mean time of surgeries was 211 minutes (135-300 min) in the EVT group and 128 minutes (90-285 min) in cases of CVT (p= 0.001). Postoperative complications were observed in 7 cases for EVT (3 prolonged need for mechanical ventilation, 2 plasmapheresis, 2 pneumothorax) and 2 cases for CVT (2 prolonged need for mechanical ventilation). Postoperative time of chest tubes were 2.2 days for EVT and 1.9 days for CVT (p= 0.039). We did not find significant difference in hospital stay (EVT vs CVT: 5.6 vs 4.7 days), or the one year improvement of MG symptoms (EVT vs CVT: 83% vs 87%). According to our own results, better cosmetic outcome, shorter time of surgery and lower rate of complications were observed in the CVT group, though symptom improvement of MG showed similar patterns in both groups.

4.3 Surgical treatment and early neurological results in myasthenia gravis

During our study the three main surgical approaches for thymectomy (transsternal thymectomy, VATET and VATS thymectomy) and early neurological changes after surgery have been analyzed among 71 patients with MG. According to international data, until 2015, non of the surgical procedures for thymectomy were declared significantly superior to the other (76). Although retrospective studies supporting one or the other technique have been published, and while in terms of patient outcomes, reviews comparing these methods have stated that VATS has the same effect as the open approach (77), the problem still remains, namely that most studies lack common definitions of disease severity and response to therapy (76).

4.3.1 Patients and methods -Diagnosis, treatment, and follow- up for MG

Diagnosis of MG was based on clinical symptoms, electromyography tests, and, in some cases, serum anti-acetylcholine receptor antibody tests. Chest CT was performed in every case. In terms of clinical assessment of disease severity, a modified Osserman classification consisting of 4 grades was applied. Grade I indicates focal disease (restricted to the ocular muscle); grade II, generalized disease, either mild (IIa) or moderate (IIb); grade III, acute severe generalized disease with respiratory failure; and grade IV, severe generalized disease with respiratory failure (progression within 2 years), (Osserman stages and treatment of MG in patients undergoing different types of thymectomies are shown in Table 5 and Diagram 3). Follow-up period was 12 months. Neurological state was evaluated at 1, 3, 6, and 12 months, and medication adjustments were determined by neurologists, who discussed relevant data with thoracic surgeons in person, via email or phone. In accordance with the recommendations of the Myasthenia Gravis Foundation of America (MGFA) (78), clinical symptoms were considered ‘improved’ when they showed substantial decrease compared to pre-treatment clinical manifestations or when patients achieved a sustained substantial reduction in their MG medication requirements. Due to short follow-up time, we could not define ‘complete stable remission’ by the MGFA standards.

	***STST** n= 23	****VATET** n= 22	**§CVT** n= 26	***p***
Female	19	22	21	0.598
Male	4	2	5	
Mean age	34.7 (16–70)	27.5 (14–52)	32.5 (16–84)	0.283
Mean time to thymectomy (months)	19.4 (1–204)	23.1 (1–230)	23.9 (2–120)	0.924
Osserman I	8.7%	22.7%	23.1%	0.349
Osserman II A	43.5%	59.1%	53.8%	0.563
Osserman II B	26.1%	9.1%	11.5%	0.226
Osserman III	17.4%	4.5%	7.7%	0.316
Osserman IV	4.3%	4.5%	3.8%	0.992
Pyridostigmine	100%	100%	92.3%	0.168
Steroid/Azathioprine	21.7%	36.4%	46.2%	0.201
Plasma exchange	26.1%	9.1%	11.5%	0.226

Table 5: Patient data including severity of myasthenia gravis and types of preoperative treatment

*STST: Standard Transsternal Thymectomy; **VATET: Video-Assisted Thoracoscopic Extended Thymectomy; §CVT: Classic VATS Thymectomy

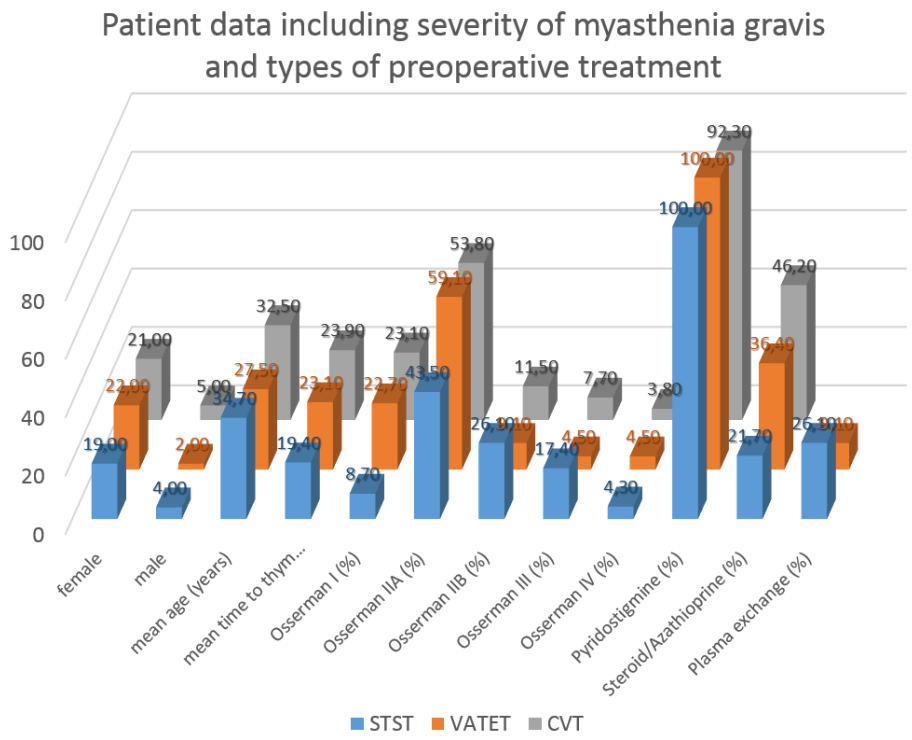

Diagram 3: Patient data including severity of MG and types of preoperative treatment

STST: Standard Transsternal Thymectomy; VATET: Video-Assisted Thoracoscopic Extended Thymectomy; CVT: Classic VATS Thymectomy

Therefore, in case a patient achieved a symptom- or medication-free state within 1 year after surgery, we defined it as ‘complete remission’. Standard preoperative patient medication was not changed, only adjusted to current patient needs. 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 (between September 2009 and December 2011) were compared.

4.3.2 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.

4.3.3 Results

4.3.3.1 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) ($p = 0.001$) (Table 6, Diagram 4). 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) ($p = 0.001$) (for data see Table 6 and Diagram 4).

4.3.3.2 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) (Table 7).

4.3.3.3 Pathology

The most frequent pathological disorders in connection with MG were thymus hyperplasia and persistent thymus (Table 2). Thymic cyst and thymitis were found as well. Thymoma was a more frequent indication for STST (21.7%). Since we have gained more experience with the minimal access approaches, we have removed 2 small thymomas (less than 4 cm) with the CVT method. Unfortunately, in only a few cases was ectopic thymic tissue described in perithymic fat (0%–4.5%) (Table 6 Diagram 4).

4.3.3.4 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 (Table 6). 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 ($p= 0.712$) (Table 6). 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 ($p = 0.917$) (Table 6, Diagram 4).

	*STST n= 23	**VATET n= 22	§CVT n= 26	*p*
Length of surgery (min.)	112	211	116	0.001
Length of drainage (days)	2.04	2.23	1.65	0.001
Hospital stay (days)	8.9	5.6	4.0	0.001
Morbidity	26.1 %	31.8%	7.7%	0.097
Thymus hyperplasia	47.8%	54.5%	46.2%	0.833
Thymus persistens	30.4%	40.9%	38.5%	0.744
Thymoma	21.7%	0%	7.7%	0.045
Thymitis	0%	0%	7.7%	0.168
Thymic cyst	0%	4.5%	0%	0.323
Ectopic thymus	4.3% (epipericardial)	4.5% (cervical)	0%	0.564
Improvement rate	91.3%	94.7%	87.5%	0.712
Complete remission	13%	10.5%	11.5%	0.917

Table 6. Operative, neurological, and histological results

*STST: Standard Transsternal Thymectomy; **VATET: Video-Assisted Thoracoscopic Extended Thymectomy; §CVT: Classic VATS Thymectomy

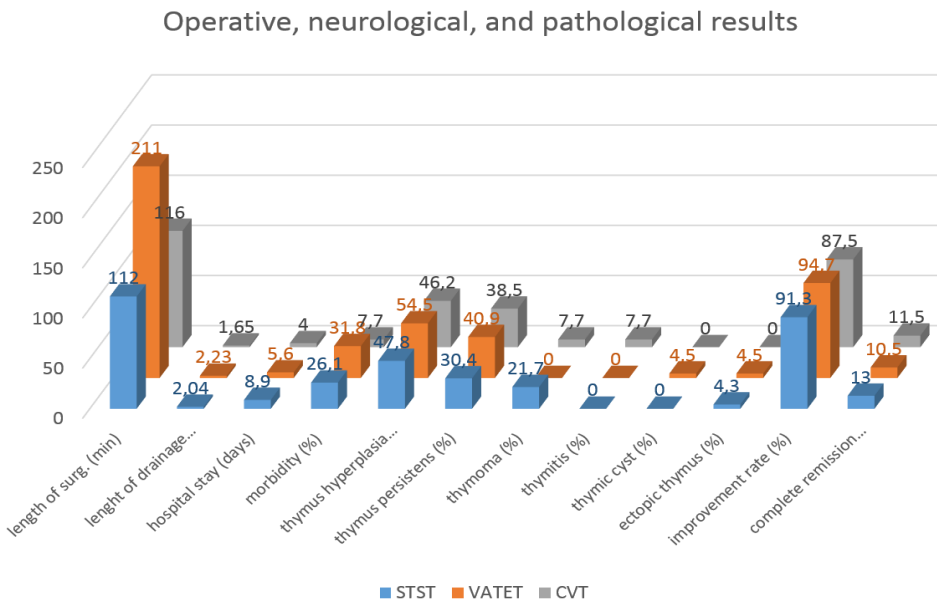

Diagram 4: operative-, neurological-, and pathological results

STST: Standard Transsternal Thymectomy; VATET: Video-Assisted Thoracoscopic Extended Thymectomy; CVT: Classic VATS Thymectomy

4.3.4 Discussion

Surveys for efficiency of minimal access thymectomy were already taking place at the time of its introduction. In 2005, a publication by chinese authors analyzed the data of 38 patients undergoing CVT (79). There was no perioperative mortality and postoperative morbidity occured in 11 %. During a 5 year follow-up, complete remission was observed in 22.2%, improvement of symptoms in 91.6% while 10 years after surgery a 75% complete remission rate was found, according to which a high rate of complete remission rate with low postoperative morbidity for CVT was concluded. With increasing experience in the minimal access approach, results were also compared with open thymectomies. In a 2009 study published in the USA, results of 47 STST were compared with 48 CVT (80), which showed the following in cases of STST vs CVT, respectively: operative time was 119 vs 128 ($p= 0.22$), postoperative ventilation 16.2% vs 4.2% ($p= 0.07$), hospital stay was 4.6±4.2 days vs 1.9±2.6 days ($p< 0.001$) and complete remission rate was 34.9% vs 15.8% (80). Study results show that the VATS approach is indeed applicable, with less burden to the patient and steady improvement in neurological state. We also compared the two methods, which led to an increase in the number of surgeries. While between 2004 and 2009, during a 22 months interval, six extended thymectomies were performed per year on average at our Department, 27 patients underwent surgery using CVT (without exposing the neck) which we started applying in the summer of 2009. This increased surgical number can be explained by the higher acceptance among patients due to better cosmetic results (81). Classic VATS thymectomy without exposure of the neck not only meant better appearance for the patient, but also similar improvement of neurological state during both methods. It was very impressive to see how the prevalence of thymectomies changed and VATS thymectomies

became more frequent during our study period (2004-2010). In one year, we performed 4 STST, 7 VATET, and 10 CVT on average. As a currently observed pattern, patients seek more information and greater participation in their own medical decision-making process, thus they are generally expected to choose procedures that are deemed easier, less painful, and the most effective. Tomulescu mentioned that the thoracoscopic approach has high acceptance from both patients and neurologists due to its better cosmetic results with the same neurological outcomes. In his practice, introduction of VATS led to reduction of preoperative disease duration (18.8 vs. 42.2 months), and a higher rate of complete stable remission after early VATS thymectomy (82). Although the duration of preoperative disease course was not reduced in our practise (23.9 vs. 14.9 months), still we dealt with a greater proportion of early stage (Osserman I, IIA) MG patients by using VATET (81.8%) and CVT (76.9%) compared to STST (52.2%), which also indicates that VATS thymectomy- mainly CVT- has become highly accepted among patients and neurologist alike. Duration of surgery in STST cases (112 min) was similar to that of CVT (116 min) although significantly shorter than that of VATET (211 min). Meyer et al. reported similar operative durations of 128 min in case of CVT and 119 min in STST cases (83), while the two simultaneous VATET teams by Zielinski managed in only 159 min (73). With the exclusion of the collar incision and dissection, we spared a cervical scar, together with approx. 40 min of operating time, although sacrificing the removal of possible ETT in 4.5% of cases. The appearance of ETT in the region of the neck was reported in 10.0% of the patients by Zielinski (73). According to our study, the length of hospital stay was reduced from 8.9 days in case of STST, to 4 days with CVT. These results are concordant with those reported in the review of Zihad (84) and in the comparative study of Meyer (STST vs VATS: 4.6 vs 1.9 days) (80). Regarding surgery associated morbidity, just over 1:4 patients in the STST group (26.1%), about 1:3 patients in the VATET group (31.8%), and only 1:13 in the CVT group (7.7%)

had complications. There are two types of postoperative morbidities usually associated with MG.

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. Our results slightly differ from other international data. Zielinski's study (77) reported a 10% SRM after VATET and in a study by Huang, complication rate was 8.8% after STST (85), and 8.4% after CVT in Tomulescu's study (82). All studies showed that the highest rates of SRM were associated with VATET. 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. In Huang's study (85) the rate of MG-related respiratory failure after STST was 7.1%, 5% after VATET by Zielinski (73), 1% after CVT in the study by Tomulescu (82), and 0% after bilateral CVT in the study by Lee (85). In Meyer's single centre comparison study (80), the need for postoperative ventilation after STST was 16.2% and 4.2% after VATS (80). Although these results somewhat differ from our own experience, the tendency is the same, meaning: the less invasive the thymectomy, the less frequent the postoperative respiratory insufficiency. 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). Comparing these results to other reports, the improvement and complete remission rates at 1-year follow-up after STST were 63% and 20%, respectively according to Huang's study (85), and 82.6% and 17.4%, respectively according to Mantegazza (87) after VATET. 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.

Along with the above discussed types of thymectomies, the diagnosis of thymomas (THA) and subtypes carry mass effect on the surgical outcome and survival rate of patients. While choosing the appropriate method of thymectomy is pivotal, a precise differentiation among THA subtypes and thymic carcinoma (TC) is just as important. Recently the WHO classification for thymic malignancies has clearly stated, that TC is a separate entity from other THAs, with a 5-year survival of 67% after complete resection and 30% in the case of a subtotal resection (88). The importance of distinguishing through imaging prior to surgery is thus essential in treatment planning, with CT being the standard modality and MRI emerging as an option facilitating diagnosis. Separating benign from malignant conditions, deciding

whether the surgical or the medical approach is more beneficial is an equally undisputed matter. With the ability of mimicing THAs, a condition called thymic hyperplasia (TH) may also be difficult to accurately verify during preoperative imaging. In reaching a more precise radiological diagnosis, MRI, with recently added modalities (diffusion weighted- and fat-comprassion imaging) may considerably aid treatment planning, with avoiding overtreatment and improving overall survival. In case of MG patients, thymectomy comprises two major goals, for one, completely removing the gland itself and two, resecting ectopic thymic tissue (ETT) in typical locations. In order to achieve improved surgical and neurological results with high remission rates, ETT must be diagnosed prior to resection and attempt to totally remove ectopic foci must be sought. Imaging techniques, with emphasis on MRI could facilitate the preoperative detection of ETT, thus improving surgical- and neurological outcomes.

4.4 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. Thymomas are the most frequent neoplasms occuring in the anterior mediastinum, accounting for

47% of tumors (89). THAs are associated with various autoimmune diseases, especially MG (90). Approximately 30–50% of THA patients develop MG and 15% of MG patients are diagnosed with THA (91). Numerous histological classifications have been used for THAs over the years, but the most widely applyed is the one introduced by the World Health Organization (WHO) (83). According to the WHO, THAs are cathegorized into 5 subtypes (A, AB, B1, B2, B3) and C as for thymic carcinoma, although it is important to emphasize that TC is a separate entity. With respect to histopathological and clinical features, another staging system has also been commonly used, which was introduced by Masaoka et al. in 1981 and later developed by Koga et al, and is called the Masaoka-Koga stage classification system (MK-SCS) (92). The MK-SCS emphasizes the presence or lack of a capsule in the case of THAs, and classifies stages of invasive- and noninvasive kind. The MK-SCS has recently been developed by the International Thymic Malignancy Interest Group (ITMIG)/IASLC 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 (93). 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. In the study conducted by Zhu et al. which focuses on surgical outcomes, the rate of neoadjuvant treatment was 6% in case of THAs (B2-B3-TC) with a 15% rate of incomplete resection (94). The study by Hayes et al. described that in 87% of incomplete resections, peritumoral fat was missed on preoperative CT, compared to 66% rate in operable cases (95). In terms of the new TNM system, T1 has been divided into two subtypes, namely, T1a (without mediastinal pleural involvement) and T1b (involvement of the mediastinal pleura). In T2 cases the pericardium is involved, while in T3, the lung, brachio-cephalic vein, superior vena cava, chest wall, phrenic nerve, and hilar pulmonary vessels are invaded. The aorta, great branches of the pulmonary artery, myocardium, trachea, or esophagus are involved in T4 tumors (93). 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 (the hyoid bone and diaphragm craniocaudally, the medial edge of the carotid sheaths and mediastinal pleura laterally, the sternum anteriorly, the pericardium and great vessels posteriorly, with the the phrenic nerves posterolaterally), while the N2 level is limited to the deep intrathoracic or cervical nodes (lateral border of the sternocleidomastoid muscle and the vertebral column (anteriorly), and includes the following node stations: jugular, supraclavicular, aortopulmonary window, hilar, paratracheal, subcarinal, esophageal, internal mammary, and supradiaphragmatic) (93,96). Lymph node metastases most frequently occur in the anterior mediastinum and can be proved in 2% of THAs, 27% of TCs, and 28% of neuroendocrine thymic tumors (NETT) (96).

Thymic (lymphoid) hyperplasia refers to a condition, in which thymic tissue is present with lymphoid germinal centers in the medulla (97). It is frequently observed in autoimmune diseases such as MG (up to 65%). It is important to note, that TH without MG is not an indication for surgery, only regular follow-up is mandatory thus diagnostic imaging plays a very important role in differentiating between TH and THAs and deciding whether surgery or conservative therapy should be the method of choice. Although chest CT is considered to be the routinely used modality in the imaging of thymic lesions, in the differentiation between TH and THA, in cases where preoperative diagnosis is ambiguous, MR imaging should be performed (98). In recent years MRI has integrated two important sequences into its armamentary, namely, fat suppression (FS) and chemical shift (ChS) imaging. With the help of these two modalities, differentiating between TH and THAs are much more accurate, indeed in the analysis of Priola et al., the qualitative and quantitative values of CT and CS-MRI in differentiating between THA and TH among 83 patients with MG, resulted in an accurate diagnosis in 86.7% and 96.4% of cases for CT and MRI, respectively (99). Imaging among different subtypes of THAs also carries high value and is essential in treatment planning. MRI can be helpful in differentiating among THA subtypes and can predict the aggressivity of the disease. The presence of a septum within the tumor is highly suggestive of a THA. On MR imaging, the tumors

showing smooth contour, almost complete capsule, septum within the tumor, and homogenous enhancement are more likely to be low-risk, than high-risk THAs or TCs. Sadohara's study states that MRI is more accurate in detecting a capsule, septum, or a haemorrhage than CT (100). It has been declared that diffusion weighted imaging (DWI) with the measurement of the apparent diffusion coefficient (ADC) can not only be helpful in distinguishing between benign and malignant thymic lesions (101), but is also useful in the follow-up of regression of THAs after neoadjuvant therapy (101).

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 (65) (Figure 5). In terms of MG thymectomies, it would be extremely advantageous if some information could be routinely obtained on imaging about the localization of ETT. 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? In case ectopic foci remain in the mediastinum or on the neck, the postoperative improvement of MG is significantly worse (Figure 5).

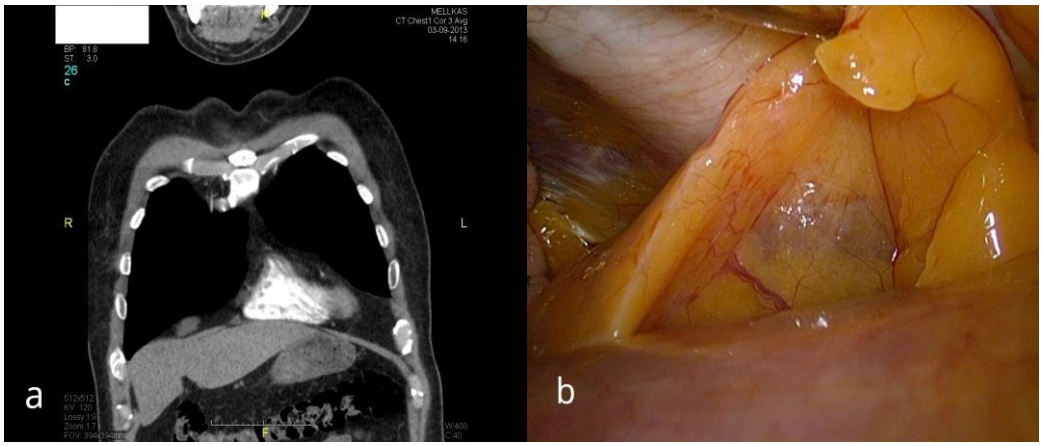

Figure 5: ETT in the right pericardio-phrenic fat, a: chest CT, b: intraoperative picture

EET: ectopic thymic tissue; CT: computed tomography.

courtesy of University of Szeged, Dep. of Surg.- Dr. Jozsef Furak

4.4.1 Discussion

In terms of surgical or nonsurgical treatment planning, precise staging is one of the most important factors. Preoperative imaging should mention T, N, and M status of THAs with special attention to perithymic invasion. 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 an 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. Computed tomography 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. With the adding of chemical shift sequence, MRI maintains a higher accuracy in distinguishing THAs from TH which is essential in the algorithm of treatment planning and deciding whether surgery is needed. 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. Distinguishing among various thymoma subtypes on imaging is fundamental for further treatment planning (preoperative chemo- and radiotherapy or primary surgical resection) and achieving total remission. 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. Preoperative imaging with the inclusion of MR imaging could be extremely helpful in discovering possible ectopic thymic foci.

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. With the rapid spread of VATS, is thoracotomy to be considered obsolate? 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. With the changing trends in patient-physician relationships, a pattern of more detailed and patient centered decision making is taking place in day to day practice. 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. 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 thyroidectomy or for patients who have had previous thyroidectomy 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 those with a large volume of mediastinal fat. Our study was the first to document postoperative surgical- and early neurological outcomes in case of thymectomies performed, through three different types of approach for MG, in the same institute.

6. Besides CT remaining the cornerstone of thymic imaging, MRI has emerged as a useful- and in some cases more accurate modality. With the help of chemical shift sequence, 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. With the adding of diffusion weighted imaging, 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. Preoperative imaging with the inclusion of MRI could be extremely helpful in discovering possible ectopic thymic foci and distinguishing among thymic conditions. The proposal and introduction of a unified lymph node map (anterior- and deep region) not only helps clinical- but can also improve and simplify radiological- and pathological staging with the gathering of relevant information of thymic abnormalities and contributing to future staging- and classification systems.

6 Acknowledgements

First and foremost, I wish to express my gratitude to Prof. Dr. György Lázár and Dr. József Furák for their constant support and encouragement along the scientific process and the handeling of this manuscript. I would like to thank all members of my family for their huge emotional support, with special regards to my Father (Dr. Aurél Ottlakán Sr.), leading me all the way through in good- and hard times as well. I’m also greatful to Prof. Dr. Gaetano Rocco, who during my stay in Naples gave me a head start in scientific publications and made me feel completely part of his staff. I would like to thank Dr.

Carmine LaManna and Dr. Nicola Martucci who made me part of their Families and taught me the way of napolitan living. I would especially like to thank Prof. Dr. Béla Teleky head of surgery in Vienna General Hospital for all his support and mentoring during the preparation of this manuscript and throughout my stay in Vienna. I would also like to thank all my colleagues for their support in my everyday work at the University of Szeged, Department of Surgery, and for the good times we had together, which I will always cherish. During the development of this manuscript I have received financial support for my stay in Vienna, in form of a scholarship from the Tempus Public Foundation (Magyar Állami Eötvös Ösztöndíj).

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