Evaluation of early and late postoperative results of non-intubated thoracoscopic surgery

Attila Farkas M.D.

Ph.D. Thesis

Szeged

2024.

University of Szeged
Albert Szent-Györgyi Medical School
Doctoral School of Clinical Medical Sciences

Evaluation of early and late postoperative results of non-intubated thoracoscopic surgery.

Ph.D. Thesis

Attila Farkas M.D.

Thesis leader:
József Furák M.D., Ph.D. med. habil.

Ph.D. Program:
Clinical and Experimental Research for Reconstructive an Organ-sparing Surgery
Program Director: Prof. György Lázár M.D., Ph.D., D.Sc.

Szeged

2024.

LIST OF CONTENTS

List of abbreviations

ASA – American Society of Anaesthesiologists

BIS – Bispectral Index

BMI – Body Mass Index

CRP – C-Reactive Protein

CT – Computed Tomography

FEV1 – Forced Expiratory Volume in 1s

GCS – Glasgow Coma Scale

IL-1 – Interleukin-1

IL-4 – Interleukin-4

IL-6 – Interleukin-6

IL-10 – Interleukin-10

iVATS – intubated VATS

NGF – Nerve growth factor

NITS – Non-Intubated Thoracoscopic Surgery

NK – Natural Killer

NSCLC – Non-Small Cell Lung Cancer

OS – Overall Survival

PaO2 – Partial Pressure for O2 in arterial blood

PaCO2 – Partial Pressure for CO2 in arterial blood

PET/CT – Positron Emission Tomography/ Computed Tomography

PAL – Prolonged air leak

TCI – Target-controlled intravenous

TGF-ß1 – Transforming growth factor-ß1

TNF – tumor necrosis factor

VAS – Visual Analog Scale Score

VATS – Video-Assisted Thoracoscopic Surgery

List of original papers

List of papers relating to the subject of the thesis

1. **Farkas A,** Csókási T, Fabó Cs, Szabó Zs, Lantos J, Pécsy B, Lázár Gy, Rárosi F, Kecskés L, Furák J. Chronic postoperative pain after non-intubated uniportal VATS lobectomy. Front. Surg., 13 November 2023 Sec. Thoracic Surgery Volume 10 - 2023 doi: 10.3389/fsurg.2023.1282937. **IF:1,8 Quartile: Q2**
2. **Farkas A,** Andrási K, Szűcs E, Rárosi F, Kecskés L, Furák J. Comparison of non-intubated, spontaneously breathing and intubated, mechanically ventilated videothoracoscopic lobectomy. Orv Hetil., 2024 Mar 10;165(10):393-399. doi: 10.1556/650.2024.33008. **IF:0,6 Quartile: Q4**

Cumulative impact factor of the publications on which this thesis is based: **2,4**

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

1. Gieszer, B, Török, K, Radeczky, P**, Farkas A**, Ghimessy Á, Mészáros L, Bogyó L, Filkorn, R, Benedek, A, Kocsis, Á, Döme B, Lang Gy, Rényi-Vámos F, Agócs L. Primer idiopathiás chylopericardium. Med.thorac. 2016 2 pp. 100-102., 3 p. **Quartile: Q4**
2. Ghanim B, Hess S, Bertoglio P, Celik A, Bas A, Obernhofer F, Melfi F, Mussi A, Klepetko W, Pirker C, Berger W, Harmati I, **Farkas A**, Ankersmit J, Döme B, Filinger J, Aigner C, Hegedűs B, Rényi-Vámos F, Lang Gy. Intrathoracic solitary fibrous tumor - an international multicenter study on clinical outcome and novel circulating biomarkers. Sci Rep. 2017 Oct 2;7. (1):12557 **IF: 4,12 , Quartile: Q1**
3. Ghimessy Á, Lohinai Z, Gieszer B, Farkas A, Radeczky P, Török K, Mészáros L, Levente B, Mónika Gy, Filinger J, Tóth E, Ganofszky E, Vadász P, Moser B, Kocsis Á, Agócs L, Rényi-Vámos F, Lang Gy, Döme B. Epithelial tumours of the thymus: experience with a national database on prognostic factors and treatment. Mediastinum 2017 Sept;1:AB032. **Quartile: Q4**
4. **Farkas A.**, Kocsis Á., Andi J, Sinkovics I, Agócs L, Mészáros L, Török K, Gieszer B., Bogyó L, Radecky P, Ghimessy Á, Lang Gy, Rényi-Vámos F. Minimally invasive resection of nonpalpable pulmonary nodules after wire- and isotope-guided localization. Orv Hetil. 2018 Aug;159(34):1399-1404. **IF:0,32 Quartile: Q4**
5. Gieszer B., Radeczky P., Ghimessy Á., **Farkas A**, Csende K, Bogyó L, Fazekas L, Kovács N, Madurka I, Kocsis Á, Agócs L, Török K, Bartók T, Dancs T, Schönauer N,

Tóth K, Szabó J, Noémi E, Bohács A, Czebe K, Csiszér E, Mihály S, Kovács L, Müller V, Elek J, Rényi-Vámos F, Lang Gy. The start of the Hungarian lung transplantation program and the first results. Orv Hetil 2018.Nov; 159(46): 1859-1868. **IF:0,564, Quartile: Q4**

6. Ghimessy Á, **Farkas A**, Gieszer B, Radeczky P, Csende K, Mészáros L, Török K, Fazekas L, Agócs L, Kocsis Á, Bartók T, Dancs T, Tóth K, Schönauer N, Madurka I, Elek J, Döme B, Rényi-Vámos F, Lang Gy, Taghavi S, Hötzenecker K, Klepetko W, Bogyó L . Donation After Cardiac Death, a Possibility to Expand the Donor Pool: Review and the Hungarian Experience. Transplant Proc. 2019 May;51(4):1276-1280. **IF:0,85, Quartile: Q3**
7. Gieszer B, Radeczky P, **Farkas A,** Csende K, Mészáros L, Török K, Fazekas L, Bogyó L, Agócs L, Varga J, Bartók T, Dancs T, Tóth K, Schönauer N, Madurka I, Elek J, Döme B, Rényi-Vámos F, Lang Gy, Jaksch P, Ghimessy Á. Lung Transplant Patients on Kilimanjaro. Transplant Proc. 2019 May;51(4):1258-1262. **IF:0,85, Quartile: Q3**
8. Radeczky, P, Ghimessy Á, **Farkas, A**, Csende K, Mészáros L, Török K, Fazekas L, Agócs L, Kocsis Á, Bartók T, Dancs T, Tóth K, Schönauer N, Bogyó L, Bohács A, Madurka I, Elek J, Döme B, Rényi-Vámos F, Lang Gy, Gieszer B. Antibody-Mediated Rejection in a Multiple Lung Transplant Patient: A Case Report Transplant. Proc. 2019 May 51 : 4 pp. 1296-1298. , 3 p. **IF:0,85, Quartile: Q3**
9. Fazekas L, Ghimessy Á, Gieszer B, Radeczky P, Mészáros L, Török K, Bogyó L, Hartyánszky I, Pólos M, Daróczi L, Agócs L, Kocsis Á, Bartók T, Dancs T, Tóth K, Schönauer N, Madurka I, Elek J, Döme B, Rényi-Vámos F, Lang Gy, **Farkas A**. Lung Transplantation in Hungary From Cardiac Surgeons' Perspective. Transplant Proc. 2019 May;51(4):1263-1267. **IF:0,85, Quartile: Q3**
10. Milada Z, Pirker R, Petruzelka L, Zbozínkova Z, Jovanovic D, Rajer M, Bogos K, Purkalne G, Ceriman V, Chaudhary S, Richter I, Kufa J, Jakubikova L, Zemaitis M, Cernovska M, Koubkova L, Vilasova Z, Dieckmann K, **Farkas A**, Spasic J, Fröhlich K,Tiefenbacher A, Hollósi V, Kultan J, Kolarová I, Votruba J. Care of patients with non-small-cell lung cancer stage III – the Central European real-world experience. Radiol Oncol. 2020 May 28;54(2):209-220. **IF:2,99, Quartile: Q3**
11. Kas J, Bogyó L, **Farkas A**, Fehér Cs, Ghimessy Á, Gieszer B, Karskó L, Kecskés L, Lungu V, Mészáros L, Molnár M, Németh P, Pataki Á, Radeczky P, Szegedi R, Tallósy B, Török K, Vágvölgyi A, Rózsa Cs, Török K, Komoly S, Elek J, Fillinger

J, Agócs L, Rényi-Vámos F, Kocsis Á. Application of video-assisted thoracoscopy in the surgical treatment of myasthenia gravis in adults without thymoma. Magy Seb. 2020 Dec 12;73(4):125-139. **Quartile: Q3**

12. Furák J, Németh T, Budai K**, Farkas A**, Lantos J, Romy Glenz J, Fabó Cs, Shadmanian A, Buzás A. Spontaneous ventilation with double-lumen tube intubation for video- assisted thoracic surgery thymectomy: a pilot study. Video-assist Thorac Surg 2023.. **IF:0,2, Quartile:Q4**
13. **Farkas A,** Tolvaj B, Andrási K, Kecskés L, Furák J. Left pneumonectomy for intrapulmonary unicentric Castleman disease. Orv Hetil. 2023 Sep 17;164(37):1476-1483. **IF:0,6, Quartile:Q4**
14. Szabo Z, Fabo Cs, Szarvas M, Matuz M, Oszlany Á, **Farkas A**, Paróczai D, Lantos J, Furák J. Spontaneous Ventilation Combined with Double-Lumen Tube Intubation during Thoracic Surgery: A New Anesthesiologic Method Based on 141 Cases over Three Years. J. Clin. Med. 2023, 12, 6457. **IF: 4,96, Quratile: Q1**

I. INTRODUCTION

Although many specific immune and chemotherapeutic agents are available in lung cancer treatment the best overall survival is still based on thoracic surgery. The proper anatomical resection of the lung lobe with radical lymphadenectomy is still the gold standard and most widely used operation in lung cancer surgery. The development of technique has shown other opportunities beside the former major thoracotomies. The Video-Assisted Thoracoscopic Surgery (VATS) technique as minimal invasive approach has many advantages compared with the classical open surgery. Nowadays most of the operation can be performed by VATS, without changing the most important oncological key points.

The initially three ports VATS technique has changed a lot and many other subtypes appeared also in the last decades. Different approaches offer different kind of view and method during the surgery and some of them with less incisions are more tissue-friendly. Uniportal approach with one single incision is widely used even for the most complicated cases as well.

Apart from the number of incisions some other modification in connection with anesthesia developed also to improve the outcome of VATS surgery. Non-intubated and non-relaxed method is a relatively new and less invasive technique avoiding the complication of intratracheal intubation.

In the first part of our thesis we review the evolution of VATS technique, the potential subtypes and we examine the benefits of uniportal non-intubated and non-relaxated VATS technique.

In the second part we review the literature of chronic postoperative pain after thoracic surgery, the related immunological activation and the connection between immune response and chronic pain. We examine the influence of the non-intubated and non-relaxated technique on the development of long lasting pain after thoracic surgical procedure.

I.1. Setting of objectives

[1] Among the many surgical techniques we tried to find the answer if there is any surgical benefits of the tubeless, non-intubated thoracic surgery approach. Beside the main advantage of non-intubated VATS technique (non-intubated thoracic surgery - NITS), the less postoperative anesthetic complication, we hypothesize that this anesthesiological assessment has also effect on the surgical results. We evaluate the advantages of uniportal NITS VATS lobectomy by the comparison of demographic, surgical and histological data of the patients operated in the last three years.

[2] In our study we investigated if there is a difference between intubated relaxed and non-intubated non-relaxed surgery in connection with chronic postoperative pain. Our hypothesis was, that the type of anesthesia has impact also on the development of chronic pain. It's based on the fact, that the long lasting pain is strongly influenced by the activation of immune system which response is different between intubated and non-intubated operated patients. During the 12 months follow period we focused the reported painkiller consumption after intubated, relaxed and non-intubated, non-relaxed uniportal VATS lobectomy and excluded the other demographic and surgical parameters to compare the two surgical approaches.

II. EVOLUTION OF VIDEO-ASSISTED THORACIC SURGERY

The worst cancer death rate in Europe is still registered in Hungary. The most important cause is the high cancer-related death of lung cancer. The mortality is 30,6/100.000 among women and 58,6/100.000 among men, which is the highest among all cancer mortality (1, 2). Although nowadays the tumors are identified more and more in early stage (3, 4), with proper anatomical surgical resection only 42% 5 years and 24% 10 years overall survival can be reached (5).

In 1910 Jacobeus, a swedish internist described his method to explore the pleura surface with his special endoscopic instrument (6). After that in the 20th century, the technological and scientific advancements lead to the development of VATS with the aim to invent a less invasive thoracic surgical approach. Finally, the use of endoscopy in the chest made possible the surgical interventions through smaller incisions than before (7). In 1991 the first VATS lobectomy was published as a lung lobe resection through a 4-5 cm utility incision, with an additional anterior camera and another posterior ports (8). Since then many advantages of this technique were published and confirmed from various authors from all over the world. Most important and widely accepted of them are the reduced acute and chronic postoperative pain with lower functional impairment after the surgery, the early removal of chest tube, the faster functional recovery, the shorter hospital stay (9) and the improved pulmonary outcomes (10). Nevertheless, the 5-year overall survival showed better results after VATS lobectomy compared to open thoracotomy in patients who underwent surgery for early-stage lung cancer (11) .

During the past few decades, beside the initially three ports VATS technique, some other modified thoracoscopic approaches have been presented and became standard in many thoracic surgery departments worldwide. The connection between less trauma and better postoperative outcome lead the surgeons to leave first the posterior port (12) and later the anterior camera port as well. In this so-called uniportal VATS approach (uVATS), the camera and all the other instruments are placed in one single utility incision (Figure 1), which means a very different point of view for the thoracic surgeons (13).

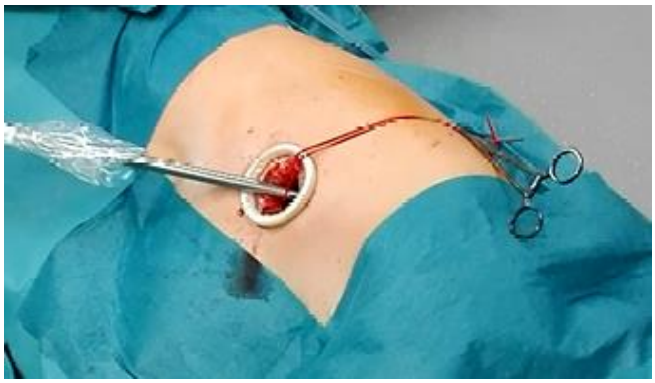

Figure 1.: Uniportal approach

In the process of evolution, beside the reduction of the number of the incisions, a new anesthetical assessment was presented, as a less invasive technique than "gold standard" intubated and relaxed VATS (iVATS) approach under general anaesthesia. In 2004, Pompeo et al. published their initial experiments on non-intubated, non-relaxed video-assisted thoracoscopic surgery (NITS) for solitary pulmonary nodule resection (14). In 2007, Al-Abdullatief et al. publiched the first awake, non-intubated lung lobe resection (15). Since then more and more anaesthetical advantages are clarified in connection with NITS. Patients has no tube-associated discomfort such as sore throat, nausea and are able to start earlier eating and drinking after the surgical intervention. The complications of tube insertion including tracheal damage, vocal cold palsy and respiratory function impairment can be also avoided. General anesthesia with intubation means a higher risk for secondary pneumothorax, intraoperative hypoxia, alveolar barotrauma, and ventilator dependence after the surgery, with the possibility of pneumonia, ARDS, multiple organ failure, septic infections, and intensive care unit induced neuromyopathy or polyneuropathy (16).

The more minimally invasive procedure the better impact on systemic inflammatory response after the surgery. NITS triggers the proinflammatory pathways less and has lower effect on immunosuppression (17). The changes in the level of natural killer cells and T-lymphocytes are milder (18) and less release of inflammatory cytokines, like inter-leukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) can be observed (19, 20). These benefits of less perioperative immune changes may lead to lower incidence of postoperative pneumonia and wound infection (21). The risk of diaphragm paralysis and dysfunction with the associated lung atelectasis is lower, decreasing the potentially intrapulmonary shunt perfusion and hypoxemia (22). Better effect on cardiopulmonary stability was also found during the surgery, which may have benefits on patients with underlying cardiovascular diseases (23). As less invasive procedure the compliance for adjuvant chemotherapy is better after lobectomy with statistically

significanty lower incidence of toxicity(24). Nevertheless, the contamination of medical staff by airways secretions could be avoided without the process of intubation, which was extremely important during the Covid-19 pandemic (25). Obviously, the most important disadvantage of this approach is that the conversion in case of surgical complication to iVATS is technically difficult (26). On the other side, the conversion rate is generally low, which not increases statistically significant the postoperative mortality and morbidity (27).

The above-mentioned evolution could be seen also in the Department of Thoracic Surgery at the Szeged University Hospital. After the learning curve of video-assisted approach, the priority of VATS and the step by step the daily use of less invasive techniques were a major key points. After the initial three ports approach in 2015 the uVATS and in 2017 the NITS technique were started to perform lobectomy for patients with lung cancer.

In this part of the thesis we review the patients pre- and postoperative data underwent eiher iVATS uniportal or NITS uniportal lobectomy and compare the results to evaluate the potential benefits of NITS approach and to share our experiences.

II.1. Method

Between 03 July 2015 and 27 November 2018, 329 patients were lobectomized with uVATS technique in the Department of Thoracic Surgery at the Szeged University Hospital. Until the start of NITS technique (24, January, 2017), all patients had lobe resection with iVATS. After the NITS technique was started, till the end of the period, if the anesthesiologia care team in charge was familiar with the NITS procedure, the lobectomy was performed without intubation and relaxation, but if not, then the traditional uniportal iVATS was our choice. Finally, 118 patients with uniportal NITS approach and 211 patients with uniportal iVATS technique were operated. We collected their demographic, pre- and postoperative and histological data to statistically compare them. After that, in each group 70-70 patients were selected with propensity score match (caliper=0,05) to reduce bias and avoid distortional variables for statistical analysis. The following factors were used for propensity score match: age, sex, BMI, Charlson Comorbidity Index, FEV1, histology and type pf lobe resection. We compared the differences between two groups with Mann-Whitney U test. Age-adjusted Charlson Comorbidity Index was calculated with regard to comorbidities and weighted it based on patient age. In this period all the patients underwent uVATS lobectomy, except in case of one or more exclusion criteria existence, which were similar in both groups: tumors greater than 7 cm or central location, radiological or histological confirmed mediastinal (N2) lymph node disease, previous open thoracotomy, less than 30% FEV1 or DLCO, anticoagulation in

therapeutic range, unstable or non-controlled cardiac disease, severe psychiatric disorders or uncooperative patients , persistent cough or large amounts of airway secretions, high chance of regurgitation, increased intracranial pressure, or Class II and III obesity with 35< body mass index (BMI). From the anesthesiologists point of view, the patients with the possibility of difficult intubation were also excluded from NITS procedure. The patients who underwent conversion from NITS to iVATS or from uVATS to open method for some kind of reason were also not part of this study.

II.2. Surgical procedure

The preoperative examinations were the same for all patients according to local protocol. Patients were premedicated with a benzodiazepine (midazolam 0.02- 0.05 mg/kg) before the operation. At the beginning of the procedure bispectral index (BIS)-guided (target 40-60), target-controlled intravenous (TCI) propofol sedation was started, with opioid (fentanyl 1-2 mcg/kg body weight) administration. After reaching the target BIS, in case of iVATS a bilumen tube was inserted in the trachea to provide selective ventilation of the patients. In the NITS group a laryngeal mask was inserted and the patients could breathe spontaneously without relaxation (Figure 2). During the surgery, routine monitoring with electrocardiogram , invasive blood pressure measurement, pulsoximetry, end-expiratory carbon dioxide and respiratory rate were used with permanent oxygen supplementation and regular arterial blood gas monitoring.

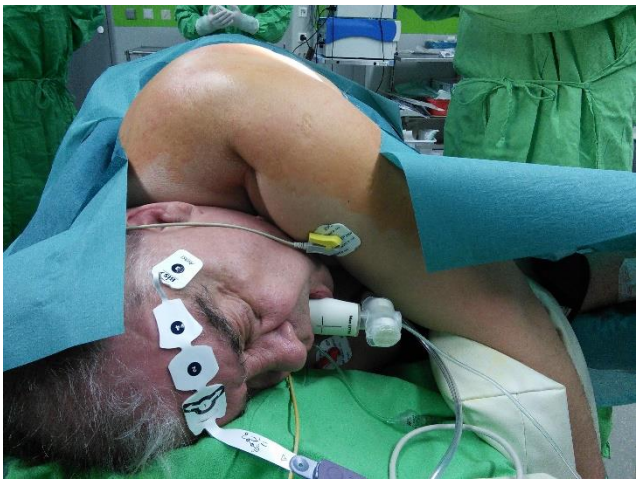

Figure 2.: NITS procedure

Although the anesthetic considerations were different, all patients were operated via uniportal approach: After positioning the patient in lateral decubitus an approximately 4 cm long utility incision was performed in the 5th intercostal space. No additional port was made to perform the surgery. The local anesthesia with nerve blockade was a crucial point in connection

with NITS: Before the incision, the skin was infiltrated with local anesthetic (2% lidocaine, 5 mg/kg) between the 5th and 6th rib on the middle axillary line. In NITS cases after entering the thorax, vagus nerve blockade was performed with 0,5% bupivacaine (0.5 mL/kg) on the right upper mediastinum or on the aortopulmonary window on left side (Figure 3). After a few minutes, the lung could be gently moved with instruments without developing cough reflex. In both group, paravertebral blockade was administered with 4–5 mL of bupivacaine alongside the thoracic spine, blocking the 2nd to the 5th intercostal nerves.

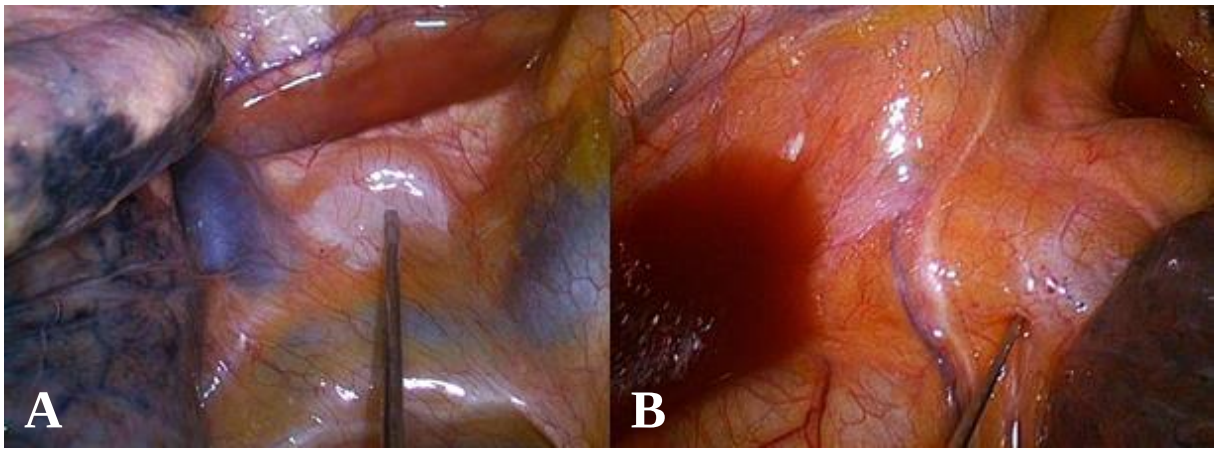

Figure 3.: Vagus nerve blokade on the right (A) and on the left (B) side

After that, the surgical steps of lung resection were similar in both groups; All the patients underwent uVATS lobectomy and radical lymph node dissection. At the end of the surgery a plastic chest tube was placed through the utility incision, and the wound was closed. The duration of paravertebral blockade was 24 hours. After that intravenous Neodolpasse (diclofenac) and Paracetamol infusion were used to reduce acute postoperative pain. On the second day we switched to oral diclofenac therapy.

II.3. Results

In all patient's cohort the sex ratio was fast equal in iVATS group (55,9% female and 44,1% male), while in NITS group two third of the patients was female (66,7%) and one-third was male (33,3%). A difference was statistically not significant (p=0,057). The mean age was 64,28 years among iVATS and 65,08 years among NITS patients, which was statistically not significant difference (p=0,474). In iVATS group the mean BMI was nearly 3 unit higher than in NITS group (27,4 vs. 24.6) and this difference was statistically significant (p=<0.001), although in both groups only patients under 30 BMI were measured. The mean FEV1 was 84,75% in iVATS and 90,5% in NITS group respectively. This result showed also statistically significant difference (p=0,017). On the contrary, the mean DLCO% was higher among iVATS

patients (74,18% vs. 69,68%), but this difference was statistically not significant (p=0,211). The incidence of diabetes mellitus was 8,5% among iVATS, and 11,9% among NITS patients. This parameter showed statistically not significant difference (p=0,315). The presence of cardiovascular disease in the patient's history was 20,8% in iVATS, and 18,8% in NITS group. The p-value was also in this case under the significance level (p=0,657). The mean Charlson Comorbidity Index was 4,64 and 5,18 respectively, which was statistically significant difference (p=0,022). The demographic data of the patients are listed in Table-1.

The mean operation time was 91,1 minutes with- and 91,6 minutes without intubation and relaxation, which difference was statistically not significant (p=0.857). The mean day of chest tube removal was 4,62 days after iVATS and 3,43 days after NITS procedure. This difference was statistically significant (p<0.001). The prolonged airleak rate was also higher in iVATS group (20,8% and 12,8%), but this result showed no statistically significant difference (p=0,07). The need of redrainage was 6,16% after iVATS and 7,7% after NITS procedure, which difference was not significant (p=0,624). The reoperation rate was more than two times higher among iVATS patients (5,2% vs. 2,5%), but this difference was also statistically not significant (p= 0,393). The morbidity was 27,9% in iVATS and 18,8% in NITS group respectively, which was statistically not significant difference (p=0,065). 30 days mortality occurred only in one case (0,4%) in iVATS group. The differences between the histological subtypes and the distribution of the stages were under the level of statistical significance ((p=0,36 and p=0,024). The surgical and histological data of the patients are presented in Table-2 and in Figure 4.

Table-1: All patients demographic

	iVATS (n=211)	**NITS (n=117)**	**p-value**
Numbers based on gender (%) **Female** **Male**	 118 (55.9%) 93 (44.1%)	 78 (66.7%) 39 (33,3%)	0.057
Mean age	64.28 (37–86)	65.08 (42–81)	0.474
BMI (kg/m^2)	27.4 (18.0–38.5)	24.6 (17.3–35.4)	<0.001
FEV1 (%)	84.75% (41–144)	90,5% (39–136)	0.017
DLCO (%)	74,18% (35–132)	69,68% (30–105)	0.211
Diabetes mellitus no. (%)	18 (8.5%)	14 (11.9%)	0.315
History of cardiac disease no. (%)	44 (20,8%)	22 (18,8%)	0.657
Charlson Comorbidity Index point	4.64 (1–15)	5.18 (2–11)	0.022

* BMI, body mass index; FEV1, forced expiratory volume in 1 second, DLCO, diffusing lung capacity for carbon monoxide

Table-2: Surgical and pathological data of all patients

	iVATS (n=211)	**NITS (n=117)**	**p-érték**
Mean operation time (min)	91.1 (40–215)	91.6 (60–185)	0.857
Prolonged air leak no. (%)	44 (20,8%)	15 (12.8%)	0.07
Repeat drainage no.(%)	13 (6,16%)	9 (7,7%)	0.624
Mean day of chest tube removal	4.62 (1–32)	3,43 (1–22)	<0.001
Morbidity no (%)	59 (27,9%)	22 (18.8%)	0.065
Return to operating room no. (%)	11 (5,2%)	3 (2,5%)	0.393
Mortality no.(%)	1 (0,4%)	0 (0%)	-
Pathological types no. (%) **Adenocarcinoma** **Squamosus cell carcinoma** **Other**	 137 (64,9%) 22 (10,4%) 52 (24.6%)	 84 (71,8%) 12 (10.3%) 21 (17.9%)	0.360
Pathological staging no. (%) **I A** **I B** **II A** **II B** **III A** **III B** **IVA**	 79 (47.0%) 15 (8,9%) 16 (9,5%) 19 (11.3%) 27 (16,1%) 9 (5,4%) 3 (1,8%)	 61 (56.0%) 18 (16.5%) 6 (5.5%) 11 (11.0%) 12 (11.0%) 0 (0%) 0 (0%)	0.024

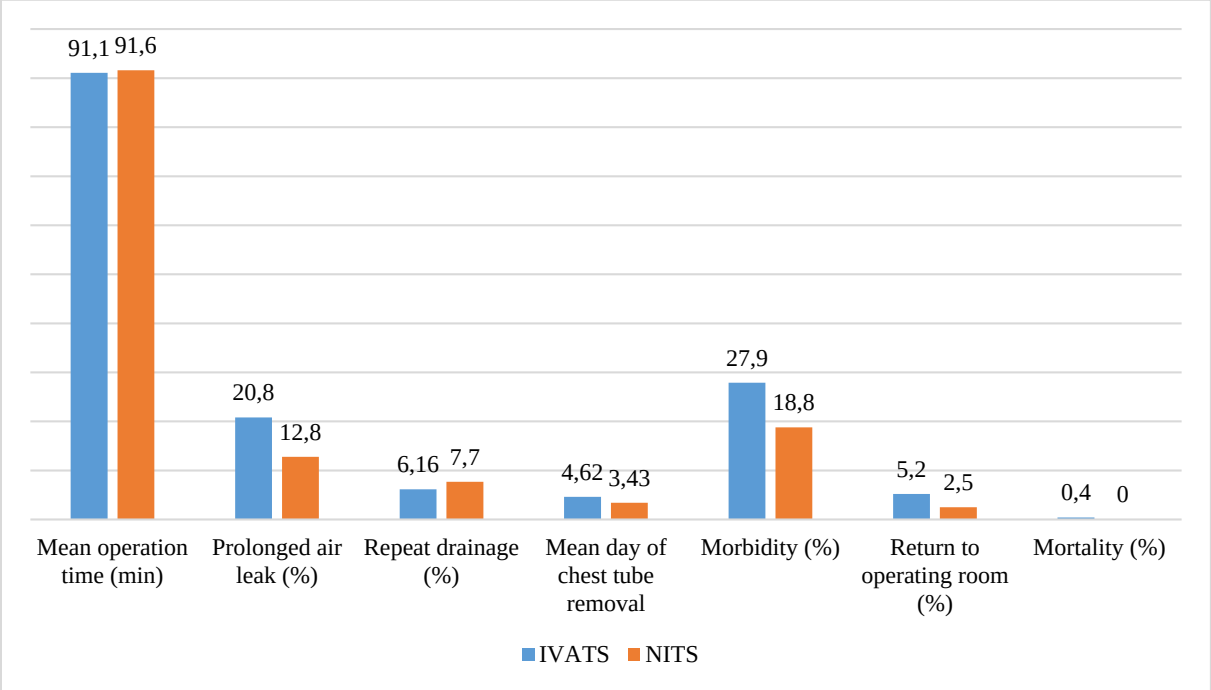

Figure 4.: Surgical data of all patient's cohort

After propensity score match analysis, the sex ratio showed no statistically significant difference (p=0,861). The mean age was 65,19 in iVATS and 65,11 in NITS group which difference was statistically not relevant (p=0,963). The mean BMI was 25,23 in the iVATS and 25,45 in NITS group which was statistically not significant difference (p=0,737). The mean

FEV1 was 87,83% in iVATS and 89,58% in NITS group, and the mean DLCO was 70,34% in iVATS and 72,08% in NITS group respectively. These differences were statistically not significant (p=0,626 and p=0,721). The differences in the incidence of diabetes mellitus (8,5% among iVATS and 12,8% among NITS patients) and cardiac disease (21,4% among iVATS and 21,4% among NITS patients) were also statistically not significant (p=0,349 and p=1,0). The Charson Comobidiy Index was 4,73 in iVATS and 4,9 in NITS group with no statistically significant difference (p=0,586). The demographic data of the selected patients are listed in Table-3.

The mean operation time was 95,25 minutes in iVATS and 92,08 minutes in NITS group. This difference showed no statistically significance (p=0,442). The mean day of chest tube removal was 4,54 days after iVATS and 3,01 days after NITS procedure and this difference was statistically significant (p<0.01). Prolonged air leak rate was 20% in iVATS group and nearly half (11,4%) in NITS group but the difference showed no statistically significance (p=0,164). Repeated drainage rate was 7,24% and 5,7%, which difference was statistically not significant (p= 0,730). Reoperation rate was 5,6% after iVATS and 2,8% after NITS procedure which result showed no statistically significant difference (p= 0,681). Morbidity was 27,1 and 15,7 %, in iVATS and NITS group respectively. The difference was statistically not significant (p=0,099). 30 days mortality was not recorded in either group. The surgical and histological data of the patients after propensity score match analysis are presented in Table-4 and in Figure 5.

Table-3: Demographic data of the patients selected with propensity score match

	iVATS (n=70)	**NITS (n=70)**	**p-value**
Number based on gender (%) **Female** **Male**	 45 (64.3%) 25 (35.7%)	 44 (62.8%) 26 (37,2%)	0.861
Mean age	65.19 (49–82)	65.11 (42–81)	0.963
BMI (kg/m^2)	25.23 (18.0–35.1)	25.45 (19.3–32.8)	0.737
FEV1 (%)	87.83% (48–144)	89.58% (39–112)	0.626
DLCO (%)	70.34% (35–114)	72,08% (42–96,4)	0.721
Diabetes mellitus no.(%)	6 (8.5%)	9 (12.8%)	0.349
History of cardiac disease no. (%)	15 (21,4%)	15 (21,4%)	1.000
Charlson Comorbidity Index point	4.73 (1–9)	4.90 (2–9)	0.586

* BMI, body mass index, FEV1, forced expiratory volume in 1 second, .DLCO, diffusing lung capacity for carbon monoxide

Table-4: Surgical and pathological data of the patients selected with propensity score match

	iVATS (n=70)	**NITS (n=70)**	**p-value**
Mean operation time (min)	95.25 (45–215)	92.08 (65–185)	0.443
Prolonged air leak no. (%)	14 (20,0%)	8 (11.4%)	0.164
Repeat drainage no.(%)	5 (7,24%)	4 (5,7%)	0.730
Mean day of chest tube removal	4.54 (1–20)	3,01 (1–13)	<0.01
Morbidity no (%)	19 (27,1%)	11 (15.7%)	0.099
Return to operating room no. (%)	4 (5,6%)	2 (2,8%)	0.681
Mortality no.(%)	0 (0%)	0 (0%)	-
Pathological types no. (%) **Adenocarcinoma** **Squamosus cell carcinoma** **Other**	 57 (81,4%) 9 (12,9%) 4 (5.7%)	 57 (81,4%) 8 (11.4%) 5 (7.1%)	1.000
Pathological staging no. (%) **I A** **I B** **II A** **II B** **III A** **III B** **IVA**	 40 (57.2%) 10 (14.3%) 6 (8.6%) 5 (7.1%) 8 (11.4%) 0 (0%) 1 (1.4%)	 37 (52.9%) 13 (18.6%) 4 (5.6%) 9 (12.9%) 7 (10.0%) 0 (0%) 0 (0%)	0.682

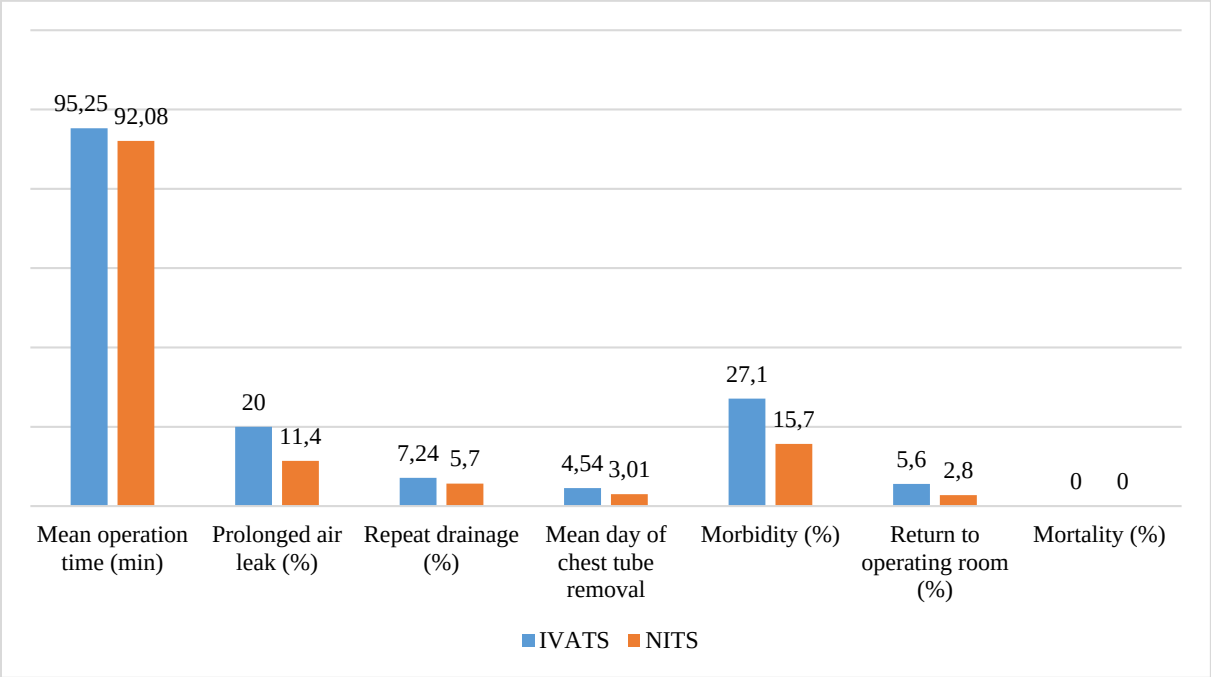

Figure 5.: Surgical data of the patients selected with propensity score match

II.4. Discussion

The minimal invasive thoracic surgery approach is the first choice in lung cancer treatment depending on the clinical or pathological stage of the tumor. The international recommendations favor none of the different surgical or anaestesiological VATS approaches against the other, generally the departments have their own preferred technique in the daily practice. The NITS procedure seems to be more physiological and less invasive. The tubeless technique can prevent the complication of intubation and the lower rate of immune activation can contribute to the lower rate of complication (17). In our retrospective study the demographic, pre- and postoperative and histological data of 211 intubated, relaxed and 117 non-intubated, non-relaxed uVATS lobectomized patients were collected and statistically analyzed. After that with propensity score match we selected 70-70 patients in each group and made the same statistical comparison.

In all patients cohort there was no 1 minute difference between the two technique, and with propensity score match the iVATS was 3 minutes longer than NITS. Both differences were clinically and statistically not significant. The rate of redrainage was approx. 1,5% higher after NITS procedure in all patients and in propensity score match group as well, which was also statistically not relevant. In both analysis, the rates of reoperation were two more higher after iVATS procedure, but these differences were statistically not significant. In all patient's cohort the morbidity in iVATS group was higher with 9%, and after propensity score match with 12%. Although these differences were clinically relevant, the two statistically analysis showed no significance. 30 days mortality occurred only in one case in all patients cohort, which was not clinically and statistically relevant. In all patient's cohort, the mean chest drain removal was more than one day earlier after NITS procedure. Without intubation and relaxation it was between 3. and 4. and in case of intubation and relaxation between 4. and 5. postoperative day. The statistically analysis showed significant difference in this parameter. After propensity score match the mean chest drain removal was on the 3. day after NITS, and between 4.-5. day after iVATS. This difference was also statistically and clinically relevant.

Year by year more and more studies were published about minimal invasive, non-intubated thoracoscopic surgery, mostly from the Asian continent. Jakraphan Yu et al. compared 152 intubated, relaxed and non-intubated, non-relaxed patients with VATS anatomical resection. After propensity score match they found the same significant difference in mean day of chest tube removal, which was not observed in all patients cohort. Their experiences showed, that among all patients the NITS procedure was 30 minutes shorter than iVATS, which was statistically significant, but after propensity score match analysis the

difference was less and statistically not relevant. The prolonged air leak was 5,2% higher in case of intubation and relaxation, but this difference was statistically not significant (28). Compare to our results, patients after iVATS had 8% and 8,6% more likely prolonged air leak than after NITS. Zeead M. AlGhamdi et al. compared 30 intubated and 30 non-intubated VATS lobectomized patients. The mean operation time was 16 minutes longer in NITS procedure, which was clinically and statistically not significant. In their study the morbidity and mortality rate were the same in both groups. The mean day of chest tube removal was between 5. and 6. postoperative day in iVATS and in NITS group respectively, therefore the difference was statistically not significant (29). On the contrary, in our study the mean day of chest tube removal was between 3. and 4. in all patients cohort and between 4, and 5. day after propensity score match analysis and the two differences were statistically significant. Jianqi Zheng et al. selected 200 intubated and 200 non-intubated patients with prospensity score match analysis and compared their data retrospectively. They found statistically not significant difference in mean operation time, which was 13 minutes longer with traditional intubation and relaxation. Although the mean day of chest tube removal was earlier after NITS procedure, but in both groups was between 3. and 4. day and the difference was statistically not significant (30). Lan Lan et al. selected with propensity score match analysis 119 intubated and 119 non-intubated patients after VATS lobectomy and found that, the mean operation time in NITS procedure was statistically significant lower with 42 minutes. The incidence of atelectasis, pneumonia and pleural fluid was also statistically significant higher in this group (31). Jun Liu et al. selected with the same method 136 intubated and 136 non-intubated VATS lobectomized patients and they found, that the mean operation time was 5-6 minutes longer in case of intubation and relaxation, which was statistically not relevant. They found no statistically significant differences in mean day of chest tube removal, which was between 3.-4. postoperative day in both group respectively. The morbidity after the procedure was 1,7% higher after intubation and relaxation, which showed also no statistically significance (32). In our cohort the morbidity was 12% higher in iVATS group which although clinically remarkable, but statistically not. The meta-analysis of 8 studies from Xue et al. confirmed the same result as our study: the mean day of chest tube removal is statistically significantly shorter after NITS, meanwhile the difference in mean operation time, morbidity and mortality showed no statistically significance(33) .

In conclusion, our study in accordance with the previous international results confirmed that in case of non-intubated and non-relaxed video- assisted lung anatomical resection the mean operation time is shorter, the chest tube could be removed earlier and the

incidence of prolonged airleak is lower. The morbidity was higher after conventional intubation and relaxation, but in connection with mortality no difference was observed.

III. CHRONIC PAIN SYNDROME AFTER THORACIC SURGERY INTERVENTIONS

The chronic postoperative pain is defined as pain around the surgical area with at least 2 months duration after the surgery and the additional exclusion of other sources of pain (34). Depending on the surgical intervention the incidences are different, but the thoracic surgical incisions are considered as a high risk of development of long lasting pain. Nearly 67% of patients after thoracotomy and 25% of all operated patients, including open- and and VATS might report chronic pain after the surgery (35, 36). Beside the number and localization of thoracic incisions, multiple risk factors are identified to contribute to the onset of postoperative pain: American Society of Anesthesiologists physical status classification (ASA), patients under the age of 60 years, female sex, preoperative hypertension, false acute pain management after the surgery, more than 4 days chest tube drainage, number of chest drains, and postoperative chemo- radiotherapy (37-39). The association between postoperative acute and long lasting pain is still not clear. Some studies reported that the intensity of acute pain (from 1 day to 1 week after the surgery) is predictive for chronic pain (38, 40-45), whereas others have found no correlation (39, 46). Nevertheless, psychosocial risk factors, like anxiety, fear against the surgery and catastrophizing can contribute to the presence of chronic pain(47).

The intensity is mainly low, but 3-16% of chronic pain can be moderate or severe (48). Approximately 50% of patients with chronic postoperative pain has some limitations in their daily life activities, and nearly 30% of them have sleeping disturbances (35). The development of persistent paint is still complex: Damage of the intercostal nerve during the thoracotomy is crucial and considered the primary source of pathological pain. Additionally, the placement of pericostal sutures or wires at closure can harm the nerve further (49). Skin incision, rib spreading and resection, muscle splitting, costovertebral joint disruption, and chest tube or surgical drain insertion can also contribute to the onset of long lasting pain (50). As a result of the nerve injury, neuropathic component associate with the chronic pain nearly in one-third of the patients (36). The most common forms are hyperalgesia, allodynia and dysesthesia, which can be extremely annoying and may reduce more the daily activity and the quality of life (51).

In our study, we compared the presence of persistent pain up to 12 months after surgery as defined by differences in analgesic consumption in patients who underwent lobectomy using the iVATS and NITS techniques.

III.1. Method

Using propensity score matching, 70 iVATS and 70 NITS from 328 patients were selected, who underwent uniportal lobectomy between July 3, 2015, and November 27, 2018, in the Department of Thoracic Surgery at the Szeged University Hospital. The same factors were used for propensity score match as in the previous study to control bias: age, sex, BMI, Charlson Comorbidity Index, histology, type pf lobectomy and FEV1. We compared the differences between two groups with Mann-Whitney U test. In this cohort 35 iVATS and 32 NITS patients had complete documentation of postoperative pain and use of painkiller medications up to 12 months after the procedure. Their data were used in our study. Routine laboratory, lung function test, blood gas test, chest CT, head CT, PET-CT, bronchoscopy and cardiac ultrasound were performed at all patients as a part of the preoperative pulmonary examinations. None of the selected patients had acute or chronic chest pain before the surgery. Between the beginning of the uniportal iVATS procedure (July 02, 2015) and the beginning of the uniportal NITS VATS procedure (January, 24, 2017), all the patients were operated with iVATS technique. After the NITS was started (at January, 24, 2017) till the end of the observed period (November, 27, 2018), if the anesthesiologist in charge was familiar with the NITS procedure, the lobectomy was made by NITS technique. Otherwise the patients were operated with iVATS. The exclusion criteria were similar, like in our previous study: centrally located tumors, diameter greater than 7 cm, cN2 lymph node stage, previous thoracotomy, therapeutic –dose anticoagulation, unstable cardiac disease, loss of cooperation, psychiatric disorders, or severe obesity with 35< body mass index (BMI). The patients who underwent conversion from VATS to open method or from NITS to IVATS were were not involved in this study. The patients with the possibility of difficult intubation were excluded from NITS procedure.

III.2. Surgical procedures

The intubated, relaxed and non-intubated, non-relaxed anesthetic approach were presented in the previous study. Now we focus on the surgical trauma and the analgesic therapy. The number of surgical incisions was the same in both groups: All patients were operated via one single incision without any additional port. All the skin incisions were less than or equal to 4 cm, which was performed in the 5th intercostal space. The most important difference, that in NITS technique the local and regional anaesthesia was the key point to perform the surgery: In NITS procedure before the incision, the skin was infiltrated with local anesthetic (2% lidocaine, 5 mg/kg) between the 5th and 6th rib on the middle axillary line. After the utility incision was completed, in the NITS cases the vagus nerve blockade was performed with 0,5% bupivacaine

(0.5 mL/kg) on the right upper mediastinum or on the aortopulmonary window. In both groups, 4–5 mL of bupivacaine alongside the thoracic spine between 2nd to the 5th intercostal nerves was used for paravertebral blockade.

Subsequently, the surgical steps were similar; however, the non-intubated patients were able to breathe spontaneously under the procedure. All the patients underwent uniportal VATS lobectomy with radical lymph node dissection. Finally, a plastic chest tube was placed through the utility incision, and the wound was closed. The duration of paravertebral blockade was 24 hours. Next we started intravenous Neodolpasse (diclofenac) and Paracetamol infusion on the first postoperative day. After the second day we switched to per os diclofenac therapy.

III.3. Data collection

All patients were interviewed and examined during the follow-up period in the observer pulmonology department at 3, 6, and 12 months after the surgery. General conditions, pain status, painkiller consumption, and current wound healing status were recorded. In our study the chronic pain was defined according to the International Association for the Study of Pain (IASP): pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process for at least 3 months after the surgery. Additionally, the pain is localized closely to the wound, but can spread to other part of the chest. Although intensity of pain can be different from mild to severe, neuropathic component and sensory disturbances of the wound can be added to this sense (52).

III.4. Results

As a result of propensity score match no significant differences were found in covariates including age, sex, BMI, Charlson Comorbidity Index, presence of cardiac disease and diabetes mellitus, FEV1 or DLCO in NITS and iVATS groups respectively. Patient’s demographics and preoperative pulmonary functions are listed in Table 5.

Table-5: Patient demographics and preoperative pulmonary functions

	NITS (n=32)	**iVATS (n=35)**	**p-value**
Numbers based on gender (%) **Female** **Male**	 22 (68.75%) 10 (31.25%)	 23 (65.72%) 12 (34.28%)	
Mean age	64.4 (52–78)	65.9 (56–80)	0.746
BMI (kg/m^2)	25.48 (18.5–32.8)	25.63 (19.5–37.2)	0.724
FEV1 (%, mean)	92.6% (42–125)	89.5% (48–144)	0.014
DLCO (%, mean)	72.73% (40–96.4)	73.66% (35–126)	0.525
Diabetes mellitus no. (%)	6 (18.75%)	4 (11.42%)	0.226
History of cardiac disease no. (%)	8 (25%)	6 (17.14%)	0.682
Charlson Comorbidity Index point	4.78 (2–9)	4.88 (2–9)	0.123

* BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing lung capacity for carbon monoxide

The p-values presented no statistically significant differences in mean operation time, mean day of chest tube removal, prolonged air leak, number of redrainages, reoperation, or morbidity. 30 days mortality was not observed in either group. Pathological subtypes and tumor stages showed also not significant differences among the patients. Surgical data, pathological subtypes, and stages are presented in Table 6.

Table-6: Surgical and pathological data

	NITS (n=32)	**iVATS (n=35)**	**p-value**
Mean total operation time (min)	94.2 (60–175)	93.22 (45–160)	0.215
Prolonged air leak no. (%)	1 (3.1%)	5 (14.2%)	0.465
Repeat drainage no. (%)	0 (0%)	2 (5.6%)	0.173
Mean day of chest tube removal	2.4 (1–7)	4.2 (1–18)	0.602
Morbidity no. (%)	1 (3.1%)	9 (25.7%)	0.597
Return to operating room no. (%)	0 (0%)	1 (2.8%)	0.339
Mortality no. (%)	0 (0%)	0 (0%)	
Pathological types no. (%) **Adenocarcinoma** **Squamous cell carcinoma** **Other**	 24 (75%) 5 (15.6%) 3 (9.4%)	 24 (68.5%) 5 (14.3%) 6 (17.2%)	0.351
Pathological staging no. (%) **I A** **I B** **II A** **II B** **III A** **III B** **IVA**	 19 (59.4%) 6 (18.8%) 2 (6.2%) 3 (9.4%) 2 (6.2%) 0 (0%) 0 (0%)	 19 (54.3%) 4 (11.4%) 3 (8.6%) 3 (8.6%) 5 (14.3%) 0 (0%) 1 (2.8%)	0.984

Chronic pain showed slightly female predominance, without statistically significance (p-value=0.616), during the initial 2 follow-up periods (16.7% vs. 16% at 3 months and 11.9% vs. 8% at 6 months). Surprisingly, at the end of the follow up period at 1 year, no men reported the presence of long lasting pain (7.9% vs. 0%). The mean total operation time among the patients with chronic pain was 7 minutes longer than in the total cohort (93 minutes vs. 100 minutes). This difference was clinically and statistically not significant. Patients after prolonged air leaks (PAL) had higher chance to develop chronic pain in comparison to patients whose chest tubes were removed within 5 days: Persistent pain was observed at 33.3% of patient with PAL vs. 14.8% without PAL at 3 months, at 33.3% of patients with PAL vs. 8.2% of patient without PAL at 6 months, and at 16.7% of patients with PAL vs. 3.4% of patients without PAL at 12 months. This difference was statistically significant (p=0.057). Perioperative morbidity was suggested to be a clinical risk factor for developing persistent pain in the first 2 follow-up periods: 30% of patient with morbidity vs. 14% of patients without morbidity at 3 months and 20% of patient with morbidity vs. 8.7% of patient without morbidity at 6 months reported long lasting pain. After 12 months, no patient with morbidity reported analgesic consumption for chronic pain (0% vs. 5.2%). Despite of the clinical relevance, no statistically significant difference was calculated (p-value=0.228). One patient in the iVATS group required reoperation, and he later suffered from long lasting pain till the end of the follow-up period (p-value=0.003). Two patients needed repeated drainage in the postoperative period (both in iVATS group), but surprisingly none of them reported chronic pain (p-value=0.626). Presence of diabetes mellitus was an important risk factor: Chronic pain was recorded at 30% of patients with diabetes vs. 14% of patients without diabetes at 3 months, at 30% of patients with diabetes vs. 7% of patients without diabetes at 6 months and at 10% of patients with diabetes vs. 3.5% of patients without diabetes at 12 months. This difference showed statistical significance (p-value=0.03). Cardiac disease also associated more likely with analgesic consumption for persistent pain after the surgery: 28.5% of patients with cardiac disease vs. 13.2% of patients without cardiac disease at 3 months, 14.2% of patients with cardiac disease vs. 9.4% of patients without cardiac disease at 6 months, and 14.2% of patients with cardiac disease vs. 1.8% of patients without cardiac disease at 12 months suffered from chronic pain. Although this result was clinically significant, but statistically not (p-value=0.6). The reported chronic pain and the correlation with the several demographic and postoperative factors are listed in Table-7.

Table 7.: Relationship between the presence of chronic pain and various demographic and surgical factors.

	Presence of chronic pain (%)			**p-value**
	3 months	**6 months**	**12 months**	
Female (N=45) **Male (N=22)**	16.7% 16%	11.9% 8%	7.9% 0%	0.616
Prolonged air leak (N=6) **No prolonged air leak (N=61)**	33.3% 14.8%	33.3% 8.2%	16.7% 3.4%	0.057
Perioperative morbidity (N=10) **No perioperative morbidity (N=57)**	30% 14%	20% 8.7%	0% 5.2%	0.228
Reoperation (N=1) **No reoperation (N=66)**	100% 15%	100% 9%	100% 4.5%	0.003
Repeat drainage (N=2) **No repeat drainage (N=65)**	0% 16.4%	0% 10.4%	0% 4.4%	0.626
Diabetes mellitus (N=10) **No diabetes mellitus (N=57)**	30% 14%	30% 7%	10% 3.5%	0.03
Cardiac disease (N=14) **No cardiac disease (N=53)**	28.5% 13.2%	14.2% 9.4%	14.2% 1.8%	0.6

Comparison of the two surgical techniques showed at 3 months, that 15.6% of NITS and 17.1% of iVATS group reported long lasting pain. This results showed a 1.5% difference between the two groups, which was statistically not significant (p-value=0.868). At 6 months, both groups reported lower rates: 9.4% of NITS and 11.4% of iVATS patients needed analgesic medications. The difference was clinically (2%), and statisticaly (p-value=0.785) not significant. Further reduction was observed in pain at 12 months: only 3.3% of NITS and 5.9% of iVATS patients reported daily analgesic use. The difference was higher (2.6%) but was again statistically not significant (p-value=0.633). After NITS procedure, the ratio of patients suffered from chronic pain declined from 15.6% to 3.3% during the follow-up period. The patients in NITS group who reported use of analgesic at 3 months, 60% continued to use pain medications at 6 months, further decreasing to 20% at 12 months. In the iVATS group, the rate of long lasting pain also decreased from 17.1% to 5.9% in 12 months. iVATS patients who had chronic pain at 3 months, 66.6% reported use of analgesic at 6 months and 33% at 12 months. The association between the presence of chronic pain and the two surgical technique presented in Table 8 and in Figure-6.

Table 8.: Relationship between the presence of chronic pain and the type of surgery performed

	NITS (n=32)	**iVATS (n=35)**	**p-value**
Presence of chronic pain no. (%)			
3 months	5 (15.6%)	6 (17.1%)	0.868
6 months	3 (9.4%)	4 (11.4%)	0.785
12 months	1 (3.3%)	2 (5.9%)	0.633

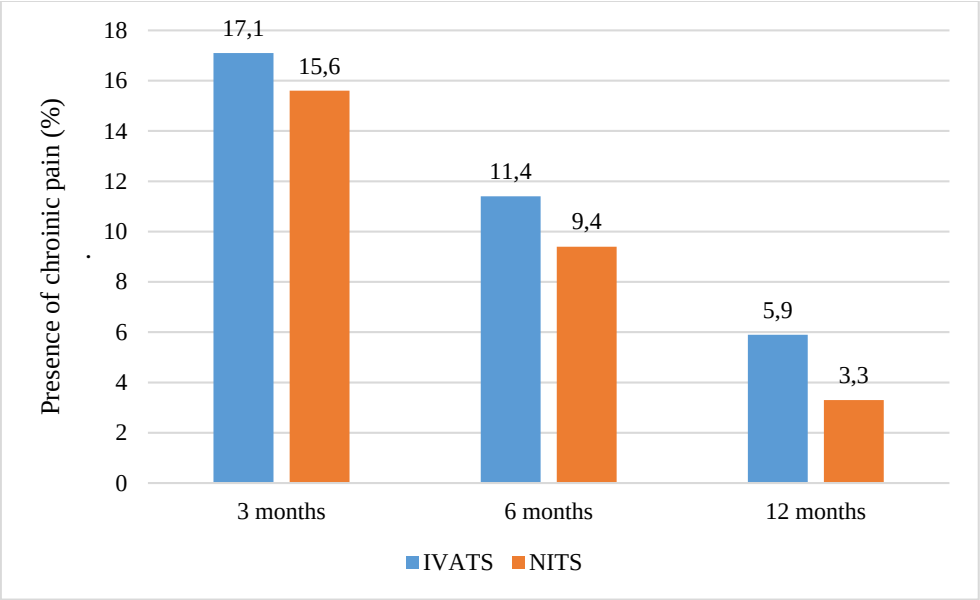

Figure 6.: Relationship between the presence of chronic pain and the type of surgery performed.

III.5. Discussion

Although many studies about the pathophysiology of wound healing and restoration of the normal (painless) function were published in the last few decades, many steps of this process is still unclear. The neuroinflammatory system plays a key role with the activation of pro- and anti-inflammatory cytokines and this process promotes regeneration and healing of the tissue. (53). Consequently, disturbed activation of immune- and inflammatory system in central and peripheral nervous system may lead to the development and progress of long lasting pain. Interruption of tissue continuity implicate the infiltration of inflammatory cells, mast cells, neutrophils, macrophages and T lymphocytes. As a response to the tissue damage many various inflammatory mediators are secreted, facilitating the activation of immune system. This stimulation can lead to sensitization of the primary afferent neurons, which may contribute to pathological sensation, to persistent pain (54). Dysregulated activation of the proinflammatory cytokines seems to be essential in the development of chronic pain. The increased expression of tumour necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) in the spinal cord and the dorsal root ganglion, promotes the chronic pain with hyperalgesia and allodynia (55). Nerve growth factor (NGF) has a cytokine-like action on mast cells, basophils, neutrophils, and lymphocytes, contributes the hypersensitivity (56). Reduction of the anti-inflammatory cytokines like interleukin-4 (IL-4) and interleukin-10 (IL-10) is also crucial in neuropathic pain compare to painless neuropathy (57). The decreased expression of another immunosuppressive

cytokine, the transforming growth factor-ß1 (TGF-ß1) plays a key role in skin cell fibromyalgia syndrome (58).

The tissue damage also facilitates the secretion of inflammatory mediators. The stimulation of nociceptive neurons with prostaglandin, histamine, and bradykinin contributes to a permanent activation and inappropriate control in pain threshold. This mechanism is called primary sensitization and leads to the development of acute postoperative pain. The increased activation of sensory receptors after the surgical procedure induces hyperexcitability of the dorsal horn neurones and the central nervous system amplifies its response. At the end of this progress, the increased neural reactivity lead to central sensitization and with neuropathic component can transform to pathological, chronic pain (59).

In general, minimal invasive surgery is considered a less invasive and traumatic approach than traditional open techniques. This statement is also accepted worldwide in connection with the thoracic surgical approaches. Apart from the number of the incisions, the smaller ports without rib spreading, fracture or resection reduce the nerve and tissue damage. In the last few decades several studies have been published about the higher chance of thoracotomy related, clinically significant persistent pain and pain associated difficulties in daily routine activities (mean follow-up time, 3–36 months) compared to VATS (60-65). The better postoperative outcome in terms of long lasting pain is in connection also with the decreased stimulation of immune system and cellular immune responds (17). VATS reduces circulating $CD3^+$, $CD4^+$, and $CD8^+$ T cells (66, 67) while thoracotomy increases the immune suppression of NK cells and T lymphocytes (68). Milder T-cell suppression decreases the risk of dysregulation of immune system, uncontrolled tumour growth, and late cancer recurrence. IL-6 is significantly increased in patients after thoracotomy than in those who undergo VATS, which may results the lower appearance of chronic persistent pain after minimally invasive surgery (69). On the contrary, some other studies found no differences between the VATS and thoracotomy approaches (mean follow-up time, 3–33.5 months) in the presence, severity and intensity of chronic pain after the surgical procedure (70-73). Hypothetically, less incision reduces more the immune activation and postoperative pain. The difference in respond of immunoinflammatory system between uVATS and multi-portal VATS approach is modest (74), but the development of acute (75) and chronic postoperative pain is significantly less frequent after the uniportal approach (45, 76, 77). A systematic review and meta-analysis presented also marginally better postoperative outcome for uVATS lobectomy compare to the traditional multi-portal approach in the treatment of lung cancer (78).

Activation and regulation of the immune system is influenced also by anaesthesia used during the surgery. NITS reduce the stimulation of the cellular and humoral immune responds, which play an important role in the occurrence of postoperative infections, neuralgic pain, and lung cancer progression (19, 79, 80). Our initial hypothesis based on the fact that, the tubeless surgical procedure without relaxation has milder effect on immune cell stimulation and reduce the systemic immune activation, therefore decreasing the incidence of chronic pain in comparison to patients who underwent intubation and relaxation. The positive effect of NITS in association with acute postoperative pain has been published yet. Apart from the number of incisions, the intensity of acute pain is stronger in patients who undergo thoracic surgery under general anaesthesia than is those who underwent NITS (81-83). Pompeo et al. assessed the acute pain intensity with visual analog scale (VAS) score in 24 hours after wedge resection of solitary pulmonary nodule with three port technique. They found that the pain score level is lower after non-intubated, non-relaxed than after intubated, relaxed VATS technique (14). Pompeo at al. also had the same results in patients with malignant pleural effusions who underwent talc pleurodesis using one, single flexible trocar (84). Hwang et al. observed patients underwent bullectomy through uniportal access for primary spontaneous pneumothorax. Their results showed significant differences with VAS score in the first hour between general anaesthesia and tubeless technique, but this was not significant after 24 hours (85). Zang et al. designed a meta-analysis based on 14 randomized controlled trials and showed that the VAS score was significantly lower in patients who underwent not intubated surgery (86). Wei et al., found in children aged 3–8 years that the acute pain was also lower after non-intubated VATS approach (87).

However, other authors published different results and conclusions; Kocatürk et al. presented no significant difference at 4, 8, 12, and 24 hours between tubeless and intubated patients who underwent diagnostic VATS procedure for pleural disease (88). According to Yang et al. there was no significant difference between acute and chronic pain at 3 months between non-intubated, non-relaxed and intubated, relaxed patients after uVATS lobectomy (79). Due to our findings this study is the only one in the literature when chronic pain (within 3 months) was compared between patients who underwent intubated, relaxed and non-intubated, non-relaxed uVATS lobectomies. In the other studies the acute postoperative pain was on the focus, and in general the mean operation time was relatively shorter than in case of lobectomy. Longer duration of interventions may stimulate the immune system more and keep the activation at an increased level for a longer period of time.

We designed our study to compare the differences in chronic pain between patients who underwent intubated and non-intubated lobectomy through one single incision with a follow-up period of 1 year. We assessed the presence of chronic pain based on analgesic consumption at 3, 6, and 12 months after surgery. No any type of pain scales were used, because our hypothesis was that the patients who continue to use pain medications months after the surgery, suffer from intensive pain resulting limitations in normal daily life activities. Best to our knowledge, our study was the first in this topic with 12 months follow up period. All patients underwent VATS uniportal lobectomy through one 4-5 cm incision, and there were no statistically significant differences in the patients demographic, pulmonary, surgical, or pathological data. The main difference between the two groups was the anaesthetic assessment; therefore, theoretically, all the measured differences in the onset of persistent pain originate from the anaesthetic management and the type of ventilation (mechanical single-lung ventilation vs. spontaneous ventilation) used. Our results showed that although there was no statistically significant difference between NITS and iVATS, an increased number of the intubated patients required analgesic treatment at home after the surgical procedure (1.5% more at 3 months, 2% more at 6 months, and 2.6% more at 12 months). This result correlate with the publication of Yang et al., but the length of our follow-up time was 9 months longer. Apart from the comparison of the two surgical technique, in our study more female patients reported chronic pain, but we could not confirm statistically significant differences in the development of chronic pain between female and male patients. Additionally, only female patients used pain medication at 12 months after surgery. Neuropathy and pathological neuropathic pain is strongly associated with the long term effect of diabetes. Although the pathophysiology is still uncertain the most important cofactors are the frequent high blood sugar level and oxidative stress, with consequent changes in cellular metabolism and microvascular damages (89). Our result showed statistically significant higher incidence of the chronic pain during the follow-up period among the diabetic patients. Therefore, diabetes may also contribute to neuropathic component of chronic persistent pain. In addition, perioperative morbidity and cardiac disease also seemed to be a higher risk factor of chronic pain; however, these differences were statistically not significant. Some previous published studies also confirmed these results (90-92). Our results showed that patients with prolonged air leak after the surgery had higher chance for development of chronic pain, but surprisingly we found that the redrainage was not associated with higher incidence of long lasting pain. Peng et al., found a significantly higher incidence of chronic pain in patients with prolonged air leakage in their retrospective study (36). Other authors like Mongardon et al. or Fiorelli et al. found no association between them

(39, 93). Only one patient required reoperation in our cohort, and he suffered from chronic pain during the 12 months. This number was too small for statistical analysis.

In summary, lower incidence and intensity of chronic pain lead to better quality of life, faster recovery, earlier return to daily life activity, and reduced analgesic consumption. Former publications showed that the intensity of acute pain is lower after non-intubated, non-relaxed VATS approach compared to intubated, relaxed VATS procedures. Our study similarly confirmed that the onset of chronic pain was less frequent in NITS procedure compared to iVATS technique. Although the analgesic consumption did not show a statistically significant difference between the two groups, but it was nearly 2% higher among the iVATS patients during the 12 months follow-up period.

IV. OUR RESULTS

[1] We retrospectively collected and analyzed first in Hungary the medical data of 328 patients underwent uniportal video-assisted lobectomy. The number of patients underwent tubeless VATS procedure is unique in our country. After this we selected 70-70 patients with propensity score match to control bias. We demonstrated with both statistical analysis that the intubated, relaxed and non-intubated, non-relaxed uniportal VATS approaches are safe and effective techniques in lung cancer surgery. Statistical analysis showed the benefits of less invasive non-intubated, non-relaxed VATS surgery compared to traditional VATS procedure under general anesthesia.

[2] We retrospectively collected and evaluated the pre-and postoperative data and analgesic use of patients underwent either non-intubated, non-relaxed or intubated, relaxed uniportal VATS lobectomy. We selected 70-70 patients with propensity score match to avoid the distortional data and we mainly focused on the present of chronic pain. First in literature, we compared the two surgical technique in connection with persistent pain with 12 months follow up. During this period, the rate of chronic pain was always lower after non-intubated, non-relaxed VATS lobectomy. We also examined the long lasting pain's relationship with the demographic and perioperative data to evaluate other risk factors of chronic, postoperative pain.

V. NEW FINDINGS

[1] We confirmed the feasibility and efficacy of intubated, relaxed and non-intubated , non-relaxed VATS uniportal technique in lung cancer surgery

[2] First in Hungary, we demonstrated the advantages of non-intubated, non-relaxed VATS technique compared to intubated, relaxed VATS procedure: Meanwhile there was was no significant difference in operation time, the mean day of chest tube removal was statistically significant shorter. The prolonged air leak, the rate of redrainage and reoperation and the morbidity was clinically also remarkable lower after non-intubated, non-relaxed uniportal VATS lobectomy.

[3] We examined first in the world the connection between anesthetic assessment of uniportal VATS lobectomy and chronic pain with 12 months follow up period. The present of long lasting pain was constant higher in case of intubation and relaxation after 3, 6 and 12 months from the surgery.

[4] The onset of chronic pain was more frequent among female patients. The rate of chronic pain was statistically significantly higher in patients with diabetes mellitus and after prolonged air leak. The incidence of persistent pain was also elevated in case of cardiac disease, redrainage, reoperation and morbidity.

VI. ACKNOWLEDGEMENTS

I would like to express my special gratitude to Professor György Lázár, Head of the Department of Surgery at the University of Szeged for giving me the opportunity to participate in Phd programme at University of Szeged.

Many thanks for my supervisor, Lecturer József Furák, for his help and support and strong professional guidance in my scientific work at the Ward of Thoracic Surgery, Department of Surgery.

I would like to offer my special thanks to my friend Ferenc Rényi-Vámos, whom without this would have not been possible.

I would like to thank László Kecskés for his advices, help and his contribution to my Phd thesis.

Last but not least, I would like to thank for my family and friends for their unwavering support and belief in me.

VII. REFERENCES

1. Bogos K, Kiss Z, Gálffy G, Tamási L, Ostoros G, Müller V, et al. Lung Cancer in Hungary. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2020;15(5):692-9.DOI: 10.1016/j.jtho.2019.11.001.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021;71(3):209-49.DOI: 10.3322/caac.21660.
3. Ágh T, Szilberhorn L, Csanádi M, Széles G, Vokó Z, Ádám G, et al. [The role of low-dose computed tomography in lung cancer screening]. Orvosi hetilap. 2022;163(37):1464-71.DOI: 10.1556/650.2022.32583.
4. Karácsony I, Bertókné Tamás R, Árváné Egri C, Fürtös VD, Szőllősi GJ, Surján O. [Summary of the Hungarian Mobile Health Screening Program data for 2021]. Orvosi hetilap. 2023;164(27):1070-6.DOI: 10.1556/650.2023.32763.
5. Schussler O, Bobbio A, Dermine H, Lupo A, Damotte D, Lecarpentier Y, et al. Twenty-Year Survival of Patients Operated on for Non-Small-Cell Lung Cancer: The Impact of Tumor Stage and Patient-Related Parameters. Cancers. 2022;14(4).DOI: 10.3390/cancers14040874.
6. Hoksch B, Birken-Bertsch H, Müller JM. Thoracoscopy before Jacobaeus. The Annals of thoracic surgery. 2002;74(4):1288-90.DOI: 10.1016/s0003-4975(02)03676-7.
7. Agócs L, Rényi-Vámos F. [What's new in the surgical treatment of lung cancer?]. Magyar onkologia. 2020;64(3):190-5.
8. Roviaro G, Varoli F, Rebuffat C, Vergani C, Maciocco M, Scalambra SM, et al. Videothoracoscopic staging and treatment of lung cancer. The Annals of thoracic surgery. 1995;59(4):971-4.DOI: 10.1016/0003-4975(95)00029-k.
9. Flores RM, Park BJ, Dycoco J, Aronova A, Hirth Y, Rizk NP, et al. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg. 2009;138(1):11-8.DOI: 10.1016/j.jtcvs.2009.03.030.
10. Kaseda S, Aoki T, Hangai N, Shimizu K. Better pulmonary function and prognosis with video-assisted thoracic surgery than with thoracotomy. The Annals of thoracic surgery. 2000;70(5):1644-6.DOI: 10.1016/s0003-4975(00)01909-3.
11. Yang CJ, Kumar A, Klapper JA, Hartwig MG, Tong BC, Harpole DH, Jr., et al. A National Analysis of Long-term Survival Following Thoracoscopic Versus Open Lobectomy for Stage I Non-small-cell Lung Cancer. Annals of surgery. 2019;269(1):163-71.DOI:

10.1097/sla.0000000000002342.

12. Onaitis MW, Petersen RP, Balderson SS, Toloza E, Burfeind WR, Harpole DH, Jr., et al. Thoracoscopic lobectomy is a safe and versatile procedure: experience with 500 consecutive patients. Annals of surgery. 2006;244(3):420-5.DOI: 10.1097/01.sla.0000234892.79056.63.

13. Bulgarelli Maqueda L, García-Pérez A, Minasyan A, Gonzalez-Rivas D. Uniportal VATS for non-small cell lung cancer. General thoracic and cardiovascular surgery. 2020;68(7):707-15.DOI: 10.1007/s11748-019-01221-4.

14. Pompeo E, Mineo D, Rogliani P, Sabato AF, Mineo TC. Feasibility and results of awake thoracoscopic resection of solitary pulmonary nodules. The Annals of thoracic surgery. 2004;78(5):1761-8.DOI: 10.1016/j.athoracsur.2004.05.083.

15. Al-Abdullatief M, Wahood A, Al-Shirawi N, Arabi Y, Wahba M, Al-Jumah M, et al. Awake anaesthesia for major thoracic surgical procedures: an observational study. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2007;32(2):346-50.DOI: 10.1016/j.ejcts.2007.04.029.

16. Kiss G, Castillo M. Nonintubated anesthesia in thoracic surgery: general issues. Annals of translational medicine. 2015;3(8):110.DOI: 10.3978/j.issn.2305-5839.2015.04.21.

17. Furák J, Németh T, Lantos J, Fabó C, Géczi T, Zombori-Tóth N, et al. Perioperative Systemic Inflammation in Lung Cancer Surgery. Frontiers in surgery. 2022;9:883322.DOI: 10.3389/fsurg.2022.883322.

18. Vanni G, Tacconi F, Sellitri F, Ambrogi V, Mineo TC, Pompeo E. Impact of awake videothoracoscopic surgery on postoperative lymphocyte responses. The Annals of thoracic surgery. 2010;90(3):973-8.DOI: 10.1016/j.athoracsur.2010.04.070.

19. Mineo TC, Sellitri F, Vanni G, Gallina FT, Ambrogi V. Immunological and Inflammatory Impact of Non-Intubated Lung Metastasectomy. International journal of molecular sciences. 2017;18(7).DOI: 10.3390/ijms18071466.

20. Jeon J, Sung S, Moon Y, Koo J, Hyun K, Han K, et al. Comparison of early postoperative cytokine changes in patients undergoing intubated and non-intubated thoracic surgery: a randomized controlled trial. Interactive Cardiovascular and Thoracic Surgery. 2021;32(3):343-50.DOI: 10.1093/icvts/ivaa265.

21. Villamizar NR, Darrabie MD, Burfeind WR, Petersen RP, Onaitis MW, Toloza E, et al. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. J Thorac Cardiovasc Surg. 2009;138(2):419-25.DOI: 10.1016/j.jtcvs.2009.04.026.

22. Rao M, Andrade R. The current status of non-intubated thoracoscopic lobectomy. Journal of thoracic disease. 2023;15(4):1544-7.DOI: 10.21037/jtd-23-282.

23. Furák J, Barta Z, Lantos J, Ottlakán A, Németh T, Pécsy B, et al. Better intraoperative cardiopulmonary stability and similar postoperative results of spontaneous ventilation combined with intubation than non-intubated thoracic surgery. General thoracic and cardiovascular surgery. 2022;70(6):559-65.DOI: 10.1007/s11748-021-01768-1.
24. Furák J, Paróczai D, Burián K, Szabó Z, Zombori T. Oncological advantage of nonintubated thoracic surgery: Better compliance of adjuvant treatment after lung lobectomy. Thoracic cancer. 2020;11(11):3309-16.DOI: 10.1111/1759-7714.13672.
25. Wang ML, Hung MH, Hsu HH, Cheng YJ, Chen JS. Non-intubated Thoracoscopic Surgery to Minimize Contamination From Airway Secretions During the COVID-19 Pandemic. Frontiers in surgery. 2022;9:818824.DOI: 10.3389/fsurg.2022.818824.
26. AlGhamdi ZM, Ahn S, Kim KC, Sung SW. Non-intubated uniportal VATS surgery is feasible approach. Journal of thoracic disease. 2020;12(3):1147-50.DOI: 10.21037/jtd.2019.11.40.
27. Ali JM, Volpi S, Kaul P, Aresu G. Does the 'non-intubated' anaesthetic technique offer any advantage for patients undergoing pulmonary lobectomy? Interactive Cardiovascular and Thoracic Surgery. 2019;28(4):555-8.DOI: 10.1093/icvts/ivy312.
28. Yu J, Tantraworasin A, Laohathai S. Non-intubated versus intubated video-assisted thoracoscopic lobectomy for lung cancer patients. Asian journal of surgery. 2024;47(1):402-6.DOI: 10.1016/j.asjsur.2023.09.038.
29. AlGhamdi ZM, Lynhiavu L, Moon YK, Moon MH, Ahn S, Kim Y, et al. Comparison of non-intubated versus intubated video-assisted thoracoscopic lobectomy for lung cancer. Journal of thoracic disease. 2018;10(7):4236-43.DOI: 10.21037/jtd.2018.06.163.
30. Zheng J, Liang H, Wang R, Zhong R, Jiang S, Wang W, et al. Perioperative and long-term outcomes of spontaneous ventilation video-assisted thoracoscopic surgery for non-small cell lung cancer. Translational lung cancer research. 2021;10(10):3875-87.DOI: 10.21037/tlcr-21-629.
31. Lan L, Cen Y, Zhang C, Qiu Y, Ouyang B. A Propensity Score-Matched Analysis for Non-Intubated Thoracic Surgery. Medical science monitor : international medical journal of experimental and clinical research. 2018;24:8081-7.DOI: 10.12659/msm.910605.
32. Liu J, Cui F, Pompeo E, Gonzalez-Rivas D, Chen H, Yin W, et al. The impact of non-intubated versus intubated anaesthesia on early outcomes of video-assisted thoracoscopic anatomical resection in non-small-cell lung cancer: a propensity score matching analysis. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2016;50(5):920-5.DOI: 10.1093/ejcts/ezw160.

33. Xue W, Duan G, Zhang X, Zhang H, Zhao Q, Xin Z, et al. Comparison of non-intubated and intubated video-assisted thoracoscopic surgeries of major pulmonary resections for lung cancer-a meta-analysis. World journal of surgical oncology. 2021;19(1):87.DOI: 10.1186/s12957-021-02181-x.

34. Bruce J, Quinlan J. Chronic Post Surgical Pain. Reviews in pain. 2011;5(3):23-9.DOI: 10.1177/204946371100500306.

35. Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. Acta anaesthesiologica Scandinavica. 1999;43(5):563-7.DOI: 10.1034/j.1399-6576.1999.430513.x.

36. Peng Z, Li H, Zhang C, Qian X, Feng Z, Zhu S. A retrospective study of chronic post-surgical pain following thoracic surgery: prevalence, risk factors, incidence of neuropathic component, and impact on qualify of life. PloS one. 2014;9(2):e90014.DOI: 10.1371/journal.pone.0090014.

37. Yoon S, Hong WP, Joo H, Kim H, Park S, Bahk JH, et al. Long-term incidence of chronic postsurgical pain after thoracic surgery for lung cancer: a 10-year single-center retrospective study. Regional anesthesia and pain medicine. 2020;45(5):331-6.DOI: 10.1136/rapm-2020-101292.

38. Pluijms WA, Steegers MA, Verhagen AF, Scheffer GJ, Wilder-Smith OH. Chronic post-thoracotomy pain: a retrospective study. Acta anaesthesiologica Scandinavica. 2006;50(7):804-8.DOI: 10.1111/j.1399-6576.2006.01065.x.

39. Mongardon N, Pinton-Gonnet C, Szekely B, Michel-Cherqui M, Dreyfus JF, Fischler M. Assessment of chronic pain after thoracotomy: a 1-year prevalence study. The Clinical journal of pain. 2011;27(8):677-81.DOI: 10.1097/AJP.0b013e31821981a3.

40. Gotoda Y, Kambara N, Sakai T, Kishi Y, Kodama K, Koyama T. The morbidity, time course and predictive factors for persistent post-thoracotomy pain. European journal of pain (London, England). 2001;5(1):89-96.DOI: 10.1053/eujp.2001.0225.

41. Van de Ven TJ, John Hsia HL. Causes and prevention of chronic postsurgical pain. Current opinion in critical care. 2012;18(4):366-71.DOI: 10.1097/MCC.0b013e3283557a7f.

42. Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. The Clinical journal of pain. 1996;12(1):50-5.DOI: 10.1097/00002508-199603000-00009.

43. Blichfeldt-Eckhardt MR, Andersen C, Ørding H, Licht PB, Toft P. From acute to chronic pain after thoracic surgery: the significance of different components of the acute pain response. Journal of pain research. 2018;11:1541-8.DOI: 10.2147/jpr.S161303.

44. Wang H, Li S, Liang N, Liu W, Liu H, Liu H. Postoperative pain experiences in Chinese adult patients after thoracotomy and video-assisted thoracic surgery. Journal of clinical nursing. 2017;26(17-18):2744-54.DOI: 10.1111/jocn.13789.

45. Tong Y, Wei P, Wang S, Sun Q, Cui Y, Ning N, et al. Characteristics of Postoperative Pain After VATS and Pain-Related Factors: The Experience in National Cancer Center of China. Journal of pain research. 2020;13:1861-7.DOI: 10.2147/jpr.S249134.

46. Kalso E, Perttunen K, Kaasinen S. Pain after thoracic surgery. Acta anaesthesiologica Scandinavica. 1992;36(1):96-100.DOI: 10.1111/j.1399-6576.1992.tb03430.x.

47. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. The Clinical journal of pain. 2012;28(9):819-41.DOI: 10.1097/AJP.0b013e31824549d6.

48. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2009;36(1):170-80.DOI: 10.1016/j.ejcts.2009.02.005.

49. Kolettas A, Lazaridis G, Baka S, Mpoukovinas I, Karavasilis V, Kioumis I, et al. Postoperative pain management. Journal of thoracic disease. 2015;7(Suppl 1):S62-72.DOI: 10.3978/j.issn.2072-1439.2015.01.15.

50. Marshall K, McLaughlin K. Pain Management in Thoracic Surgery. Thoracic surgery clinics. 2020;30(3):339-46.DOI: 10.1016/j.thorsurg.2020.03.001.

51. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain - update on incidence, risk factors and preventive treatment options. BJA Educ. 2022;22(5):190-6.DOI: 10.1016/j.bjae.2021.11.008.

52. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain. 2019;160(1):45-52.DOI: 10.1097/j.pain.0000000000001413.

53. Sommer C, Leinders M, Üçeyler N. Inflammation in the pathophysiology of neuropathic pain. Pain. 2018;159(3):595-602.DOI: 10.1097/j.pain.0000000000001122.

54. Moalem G, Tracey DJ. Immune and inflammatory mechanisms in neuropathic pain. Brain research reviews. 2006;51(2):240-64.DOI: 10.1016/j.brainresrev.2005.11.004.

55. Li QY, Xu HY, Yang HJ. [Effect of proinflammatory factors TNF-α,IL-1β, IL-6 on neuropathic pain]. Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica. 2017;42(19):3709-12.DOI: 10.19540/j.cnki.cjcmm.20170907.004.

56. Bannwarth B, Kostine M. Targeting nerve growth factor (NGF) for pain management: what does the future hold for NGF antagonists? Drugs. 2014;74(6):619-26.DOI: 10.1007/s40265-014-0208-6.

57. Uçeyler N, Rogausch JP, Toyka KV, Sommer C. Differential expression of cytokines in painful and painless neuropathies. Neurology. 2007;69(1):42-9.DOI: 10.1212/01.wnl.0000265062.92340.a5.

58. Evdokimov D, Kreß L, Dinkel P, Frank J, Sommer C, Üçeyler N. Pain-associated Mediators and Axon Pathfinders in Fibromyalgia Skin Cells. The Journal of rheumatology. 2020;47(1):140-8.DOI: 10.3899/jrheum.190248.

59. Mesbah A, Yeung J, Gao F. Pain after thoracotomy. BJA Education. 2016;16(1):1-7.DOI: https://doi.org/10.1093/bjaceaccp/mkv005.

60. Wildgaard K, Ringsted TK, Hansen HJ, Petersen RH, Kehlet H. Persistent postsurgical pain after video-assisted thoracic surgery--an observational study. Acta anaesthesiologica Scandinavica. 2016;60(5):650-8.DOI: 10.1111/aas.12681.

61. Peng J, Wang Z, Ma L, Ma W, Liu G, Zhang H, et al. Incidence and Influencing Factors of Chronic Postthoracotomy Pain in Lung Tumor Patients. Journal of healthcare engineering. 2022;2022:7584481.DOI: 10.1155/2022/7584481.

62. Wildgaard K, Ravn J, Nikolajsen L, Jakobsen E, Jensen TS, Kehlet H. Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. Acta anaesthesiologica Scandinavica. 2011;55(1):60-8.DOI: 10.1111/j.1399-6576.2010.02357.x.

63. Landreneau RJ, Mack MJ, Hazelrigg SR, Naunheim K, Dowling RD, Ritter P, et al. Prevalence of chronic pain after pulmonary resection by thoracotomy or video-assisted thoracic surgery. J Thorac Cardiovasc Surg. 1994;107(4):1079-85; discussion 85-6.DOI: 10.1097/00132586-199412000-00051.

64. Handy JR, Jr., Asaph JW, Douville EC, Ott GY, Grunkemeier GL, Wu Y. Does video-assisted thoracoscopic lobectomy for lung cancer provide improved functional outcomes compared with open lobectomy? European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2010;37(2):451-5.DOI: 10.1016/j.ejcts.2009.07.037.

65. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. The Lancet Oncology. 2016;17(6):836-44.DOI: 10.1016/s1470-2045(16)00173-x.

66. Zhang LB, Wang B, Wang XY, Zhang L. Influence of video-assisted thoracoscopic

lobectomy on immunological functions in non-small cell lung cancer patients. Medical oncology (Northwood, London, England). 2015;32(7):201.DOI: 10.1007/s12032-015-0639-2.

67. Ng CS, Whelan RL, Lacy AM, Yim AP. Is minimal access surgery for cancer associated with immunologic benefits? World journal of surgery. 2005;29(8):975-81.DOI: 10.1007/s00268-005-0029-6.

68. Ng CS, Lee TW, Wan S, Wan IY, Sihoe AD, Arifi AA, et al. Thoracotomy is associated with significantly more profound suppression in lymphocytes and natural killer cells than video-assisted thoracic surgery following major lung resections for cancer. Journal of investigative surgery : the official journal of the Academy of Surgical Research. 2005;18(2):81-8.DOI: 10.1080/08941930590926320.

69. Nagahiro I, Andou A, Aoe M, Sano Y, Date H, Shimizu N. Pulmonary function, postoperative pain, and serum cytokine level after lobectomy: a comparison of VATS and conventional procedure. The Annals of thoracic surgery. 2001;72(2):362-5.DOI: 10.1016/s0003-4975(01)02804-1.

70. Li WW, Lee TW, Lam SS, Ng CS, Sihoe AD, Wan IY, et al. Quality of life following lung cancer resection: video-assisted thoracic surgery vs thoracotomy. Chest. 2002;122(2):584-9.DOI: 10.1378/chest.122.2.584.

71. Furrer M, Rechsteiner R, Eigenmann V, Signer C, Althaus U, Ris HB. Thoracotomy and thoracoscopy: postoperative pulmonary function, pain and chest wall complaints. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 1997;12(1):82-7.DOI: 10.1016/s1010-7940(97)00105-x.

72. Rizk NP, Ghanie A, Hsu M, Bains MS, Downey RJ, Sarkaria IS, et al. A prospective trial comparing pain and quality of life measures after anatomic lung resection using thoracoscopy or thoracotomy. The Annals of thoracic surgery. 2014;98(4):1160-6.DOI: 10.1016/j.athoracsur.2014.05.028.

73. Bayman EO, Parekh KR, Keech J, Selte A, Brennan TJ. A Prospective Study of Chronic Pain after Thoracic Surgery. Anesthesiology. 2017;126(5):938-51.DOI: 10.1097/aln.0000000000001576.

74. Tacconi F, Carlea F, La Rocca E, Vanni G, Ambrogi V. Systemic Inflammation after Uniport, Multiport, or Hybrid VATS Lobectomy for Lung Cancer. The Thoracic and cardiovascular surgeon. 2022;70(3):258-64.DOI: 10.1055/s-0041-1731824.

75. Cheng YF, Huang CL, Hung WH, Cheng CY, Wang BY. The perioperative outcomes of uniport versus two-port and three-port video-assisted thoracoscopic surgery in lung cancer: a systematic review and meta-analysis. Journal of cardiothoracic surgery. 2022;17(1):284.DOI:

10.1186/s13019-022-02034-y.

76. Homma T, Shimada Y, Tanabe K. Decreased postoperative complications, neuropathic pain and epidural anesthesia-free effect of uniportal video-assisted thoracoscopic anatomical lung resection: a single-center initial experience of 100 cases. Journal of thoracic disease. 2022;14(9):3154-66.DOI: 10.21037/jtd-22-6.

77. Jin J, Du X, Min S, Liu L. Comparison of Chronic Postsurgical Pain Between Single-Port and Multi-Port Video-Assisted Thoracoscopic Pulmonary Resection: A Prospective Study. The Thoracic and cardiovascular surgeon. 2022;70(5):430-8.DOI: 10.1055/s-0042-1744546.

78. Harris CG, James RS, Tian DH, Yan TD, Doyle MP, Gonzalez-Rivas D, et al. Systematic review and meta-analysis of uniportal versus multiportal video-assisted thoracoscopic lobectomy for lung cancer. Annals of Cardiothoracic Surgery. 2016;5(2):76-84.DOI: 10.21037/acs.2016.03.17.

79. Yang F, Zhang X, Wang J, Mo N, Wu Y, Tang D, et al. The short-term outcomes of nonintubated anesthesia compared with intubated anesthesia in single-port video-assisted lung surgery in enhanced recovery after thoracic surgery: results from a single-center retrospective study. Journal of thoracic disease. 2022;14(12):4951-65.DOI: 10.21037/jtd-22-1689.

80. Huang Y, Bo Y, Li Y, Zhao Y, Li X, Chen D, et al. The impact of tubeless anesthesia versus intubated anesthesia on cerebral oxygen saturation and postoperative cognitive function in patients undergoing video-assisted thoracoscopic surgery: a randomized trial. Journal of thoracic disease. 2022;14(10):4012-30.DOI: 10.21037/jtd-22-1165.

81. Wang ML, Galvez C, Chen JS, Navarro-Martinez J, Bolufer S, Hung MH, et al. Non-intubated single-incision video-assisted thoracic surgery: a two-center cohort of 188 patients. Journal of thoracic disease. 2017;9(8):2587-98.DOI: 10.21037/jtd.2017.08.96.

82. Hung MH, Hsu HH, Chan KC, Chen KC, Yie JC, Cheng YJ, et al. Non-intubated thoracoscopic surgery using internal intercostal nerve block, vagal block and targeted sedation. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2014;46(4):620-5.DOI: 10.1093/ejcts/ezu054.

83. Hung WT, Hsu HH, Hung MH, Hsieh PY, Cheng YJ, Chen JS. Nonintubated uniportal thoracoscopic surgery for resection of lung lesions. Journal of thoracic disease. 2016;8(Suppl 3):S242-50.DOI: 10.3978/j.issn.2072-1439.2016.02.09.

84. Pompeo E, Dauri M. Is there any benefit in using awake anesthesia with thoracic epidural in thoracoscopic talc pleurodesis? J Thorac Cardiovasc Surg. 2013;146(2):495-7.e1.DOI: 10.1016/j.jtcvs.2013.03.038.

85. Hwang J, Shin JS, Son JH, Min TJ. Non-intubated thoracoscopic bullectomy under

sedation is safe and comfortable in the perioperative period. Journal of thoracic disease. 2018;10(3):1703-10.DOI: 10.21037/jtd.2018.02.10.

86. Zhang XX, Song CT, Gao Z, Zhou B, Wang HB, Gong Q, et al. A comparison of non-intubated video-assisted thoracic surgery with spontaneous ventilation and intubated video-assisted thoracic surgery: a meta-analysis based on 14 randomized controlled trials. Journal of thoracic disease. 2021;13(3):1624-40.DOI: 10.21037/jtd-20-3039.

87. Wei W, Fan Y, Liu W, Zhao T, Tian H, Xu Y, et al. Combined non-intubated anaesthesia and paravertebral nerve block in comparison with intubated anaesthesia in children undergoing video-assisted thoracic surgery. Acta anaesthesiologica Scandinavica. 2020;64(6):810-8.DOI: 10.1111/aas.13572.

88. Kocatürk C, Kutluk AC, Usluer O, Onat S, Çınar HU, Yanık F, et al. Comparison of awake and intubated video-assisted thoracoscopic surgery in the diagnosis of pleural diseases: A prospective multicenter randomized trial. Turk gogus kalp damar cerrahisi dergisi. 2019;27(4):550-6.DOI: 10.5606/tgkdc.dergisi.2019.18214.

89. Schreiber AK, Nones CF, Reis RC, Chichorro JG, Cunha JM. Diabetic neuropathic pain: Physiopathology and treatment. World journal of diabetes. 2015;6(3):432-44.DOI: 10.4239/wjd.v6.i3.432.

90. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet (London, England). 2006;367(9522):1618-25.DOI: 10.1016/s0140-6736(06)68700-x.

91. Ochroch EA, Gottschalk A, Troxel AB, Farrar JT. Women suffer more short and long-term pain than men after major thoracotomy. The Clinical journal of pain. 2006;22(5):491-8.DOI: 10.1097/01.ajp.0000208246.18251.f2.

92. Zhang Y, Zhou R, Hou B, Tang S, Hao J, Gu X, et al. Incidence and risk factors for chronic postsurgical pain following video-assisted thoracoscopic surgery: a retrospective study. BMC surgery. 2022;22(1):76.DOI: 10.1186/s12893-022-01522-1.

93. Fiorelli S, Cioffi L, Menna C, Ibrahim M, De Blasi RA, Rendina EA, et al. Chronic Pain After Lung Resection: Risk Factors, Neuropathic Pain, and Quality of Life. Journal of pain and symptom management. 2020;60(2):326-35.DOI: 10.1016/j.jpainsymman.2020.03.012.