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

Ph.D. Thesis

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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 | https://doi.org/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, but in the last decades less invasive approaches were presented. Beside the former thoracotomy the three, two and one port Video-Assisted Thoracoscopic Surgery (VATS) techniques came in use. Apart from the number of incisions another less invasive modification of anesthesia, the non-intubated and non- relaxed method was also developed.

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, non-relaxed approach (non-intubated thoracic surgery – NITS). We hypothesize that, apart from its anesthesiological advantages, this assessment has also positive 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 also impact on the development of chronic pain. During the 12 months follow period we focused the reported painkiller consumption after intubated, relaxed and non-intubated, non-relaxed uniportal VATS lobectomy and compared the two surgical approaches.

II. EVOLUTION OF VIDEO-ASSISTED THORACIC SURGERY

In Europe, the worst cancer death is registered in Hungary, which based on the high cancer-related death of lung cancer (Bogos et al 2020). In case of early tumor stage, only 42% 5 years and 24% 10 years overall survival can be reached with proper anatomical surgical resection (Schussler et al. 2022)

In the past few decades, instead of the traditional open thoracotomy, the video-assisted thoracic surgery (VATS) came in focus (Agócs et al. 2020). This technique has also changed a lot during this period. After the initially three ports VATS technique, the lobectomies were performed through two ports (one port and utility incision) and later only one utility incision (Gonzalez-Rivas D. et al. 2012). This so called uniportal technique has many advantages, like less invasiveness, milder postoperative pain and faster recovery (Wang L. et al 2017)

Beside the reduction of the number of the incisions, a new anesthetical assessment, the non-intubated, non-relaxed technique (NITS) was presented in 2004, which was different from the traditional intubated and relaxed VATS (iVATS) approach under general anaesthesia (Pompeo et al 2004). During the operation, the lungs are breathing and the surgery is performed without intubation, under local anaesthesia with vagus and intercostal nerve blockade. The main advantages are the low mortality, early hospital discharge and patients has no tube-associated discomfort or complications of tube insertion including tracheal damage, vocal cold palsy, atelectasis, and alveolar barotrauma (Janik et al. 2021). The NITS has also better immune response and milder effect on immunsupression. (Furák et al. 2022). The risk of diaphragm

dysfunction with associated lung atelectasis is lower, decreasing the potentially intrapulmonary shunt perfusion and hypoxemia (Rao M et al. 2023). After NITS, the compliance for adjuvant chemotherapy is better after lobectomy with statistically significantly lower incidence of toxicity (Furák et al 2020).

The above-mentioned evolution could be seen also in the Department of Thoracic Surgery at the Szeged University Hospital. After the initial three ports approach the uVATS and the NITS technique were started to perform lobectomy for patients with lung cancer.

In this part of the thesis we reviewed the patients data underwent iVATS uniportal or NITS uniportal lobectomy and compared the results.

II.1. Method

We collected the demographic, preoperative and histological data of 211 iVATS and 118 NITS uniportal VATS lobectomized patients, who underwent operation between 03 July 2015 and 27 November 2018, in the Department of Thoracic Surgery at the Szeged University Hospital. The exclusion criteria were the same: 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). . The patients who underwent conversion for some kind of reason were also not part of this study. We compared the differences between the two groups with Mann-Whitney U test. After that, in each group 70-70 patients were selected with propensity score match (caliper=0,05) with the following factors: age, sex, BMI, Charlson Comorbidity Index, FEV1, histology and type pf lobe resection. After the selection we made the same statistical comparison between this two groups.

II.2. Surgical procedure

All the patients were operated through uniportal approach. The main difference was the anesthetical assessment. In NITS procedure the skin was infiltrated with local anesthetic (2% lidocaine, 5 mg/kg) between the 5th and 6th rib on the middle axillary line before the incision. 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. In iVATS group endotracheal intubation was performed with double lumen tube under general anesthesia for single lung ventilation. 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. 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.

II.3. Results

In all patient's cohort, between the iVATS and NITS group there was no statistically significant difference in sex ratio (p=0,057) and in age (p=0,474). In iVATS group the mean BMI was nearly 3 unit higher than in NITS group and this difference was statistically significant (p=<0.001), although in both groups only patients under 30 BMI were measured. The mean FEV1 between the two group showed also statistically significant difference (p=0,017). The difference between the two mean DLCO% was statistically not significant (p=0,211). The incidence of diabetes mellitus and cardiac disease showed statistically not significant differences (p=0,315 and p=0,657). The difference in mean Charlson Comorbidity Index was statistically significant (p=0,022).

The mean operation time between the two procedure showed no statistically significant difference (p=0.857). The difference in prolonged airleak rate was statistically not significant (p=0,07), but in mean day of chest tube removal the difference was statistically significant (p<0.001). The need of redrainage and reoperation between the two group showed no statistically significant difference (p=0,624 and p= 0,393). The difference in morbidity was statistically not significant (p=0,065). 30 days mortality occurred only in one case. 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 demographic, surgical and histological data of the patients are presented in Table-1, Table-2 and Figure-1.

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

Table-2: Surgical and pathological data of all patients

	iVATS (n=211)	NITS (n=117)	p-value
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

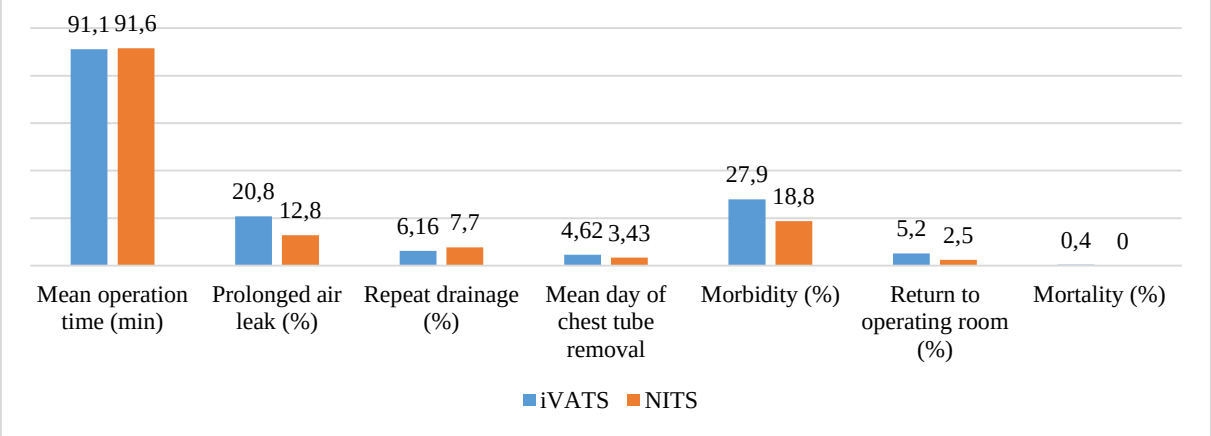

Figure 1.: Surgical data of all patient's cohort

After propensity score match analysis, the sex ratio showed no statistically significant difference (p=0,861). The difference in mean age was statistically not relevant (p=0,963). The mean BMI between the two goups showed no statistically significant difference (p=0,737). The difference in mean FEV1 and in mean DLCO were not statistically not significant (p=0,626 and p=0,721). The differences in the incidence of diabetes and cardiac disease were also statistically not significant (p=0,349 and p=1,0). The Charson Comobidiy Index between the two group showed no statistically significant difference (p=0,586).

Between the mean operation times the difference was not statistically significant (p=0,442). In prolonged air leak rate the difference showed no statistically significance (p=0,164). The difference in mean day of chest tube was statistically significant (p<0.01). Repeated drainage showed statistically not significant difference (p= 0,730). In reoperation rate the difference was statistically also not relevant (p= 0,681). The difference in morbidity was statistically not significant (p=0,099). 30 days mortality was not recorded in either group. The

demographic, surgical and histological data of the patients after propensity score match analysis are presented in Table-3, Table-4 and Figure-2.

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

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

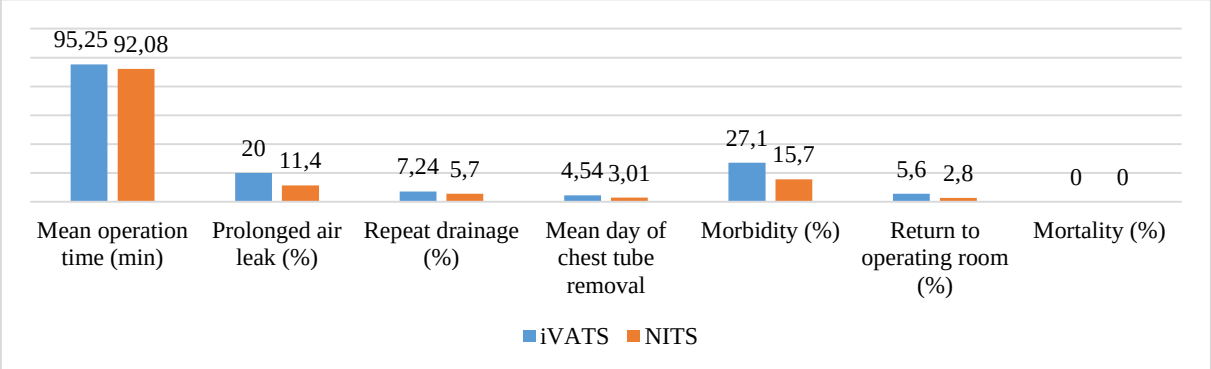

Figure 2.: Surgical data of the patients selected with propensity score match

II.4. Discussion

The NITS procedure seems to be more physiological and less invasive and can prevent the complication of intubation. The lower rate of immune activation can also contribute to the lower rate of complication (Furák et al. 2022).

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 to control bias and made the same statistical comparison. In all patient's 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 not statistically relevant. In both analysis, the rates of reoperation were two more higher after iVATS procedure, but these differences were statistically not significant. In all patients cohort, in iVATS groupthe morbidity 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 clinically and statistically not relevant. In all patients 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.

In the literature several similar studies were published to compare iVATS and NITS technique. 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 patient's 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 difference in prolonged air leak was statistically not significant (Jakraphan Yu et al. 2024)..Zeead M. AlGhamdi et al. found that the difference in mean operation time was statistically not significant. In their study the morbidity and mortality rate were the same in both groups. In the mean day of chest tube removal the difference was statistically also not significant (Zeead M. AlGhamdi et al. 2018). Jianqi Zheng et al. found statistically not significant difference in mean operation time, and in the mean day of chest tube removal (Jianqi Zheng et al 2021). Lan Lan et al. showed 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 (Lan Lan et al. 2018). In the study of Jun Liu et al. there was statististically not significant difference in mean operation time, in mean day of chest tube removal and in

morbidity (Jun Liu et al. 2016). 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 (Xue et al. 2021).

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 thoracic surgical incisions are considered as a high risk of development of long lasting pain. In general, 25% of all operated patients, including open- and VATS might report chronic pain after the surgery, but this rate can be 67% after thoracotomy (Bruce J et al 2011). The development of persistent paint is still complex: Damage of the intercostal nerve during the thoracotomy is considered the primary source, but the placement of pericostal sutures or wires at closure, the 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 (Marshall K. et al 2020). As a result of the nerve injury, neuropathic component like hyperalgesia, allodynia and dysesthesia can associate with the chronic pain and may reduce more the daily activity (Rosenberger DC et al. 2022). 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: age, sex, BMI, Charlson Comorbidity Index, histology, type pf lobectomy and FEV1. We compared the differences between the 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. The exclusion criteria

were similar, like in our previous study, but we have to remark, that none of the patients had chest pain before the surgery.

III.2. Surgical procedures

The intubated, relaxed and non-intubated, non-relaxed anesthetic approach were presented in the previous study but here we focus on the postoperative analgesic therapy. 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. 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. The intensity of pain can be different from mild to severe and neuropathic component and sensory disturbances of the wound can be added to this sense (Schug et al. 2019).

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. The p-values presented no statistically significant differences in the 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. Demographic, surgical data, pathological subtypes are presented in Table-5 and Table-6.

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

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. (%)			0.351
Adenocarcinoma	24 (75%)	24 (68.5%)	
Squamous cell carcinoma	5 (15.6%)	5 (14.3%)	
Other	3 (9.4%)	6 (17.2%)	
Pathological staging no. (%)			0.984
I A	19 (59.4%)	19 (54.3%)	
I B	6 (18.8%)	4 (11.4%)	
II A	2 (6.2%)	3 (8.6%)	
II B	3 (9.4%)	3 (8.6%)	
III A	2 (6.2%)	5 (14.3%)	
III B	0 (0%)	0 (0%)	
IVA	0 (0%)	1 (2.8%)	

Chronic pain showed slightly female predominance, without statistically significance (p-value=0.616), The mean total operation time among the patients with chronic pain was 7 minutes longer than in the total cohort which 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, and this difference was statistically significant (p=0.057). Perioperative morbidity was also suggested to be a clinical risk factor for developing persistent but 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 and the difference showed statistical significance (p-value=0.03). Cardiac disease also associated more likely with analgesic consumption for persistent pain after the surgery but this result was statistically not significant (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 was statistically not significant (p-value=0.868). At 6 months 9.4% of NITS and 11.4% of iVATS patients needed analgesic medications. The difference was statisticaly not significant (p-value=0.785). At 12 months 3.3% of NITS and 5.9% of iVATS patients reported daily analgesic use. This difference was also statistically not significant (p-value=0.633). The association between the presence of chronic pain and the two surgical technique presented in Table 8 and Figure-3.

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

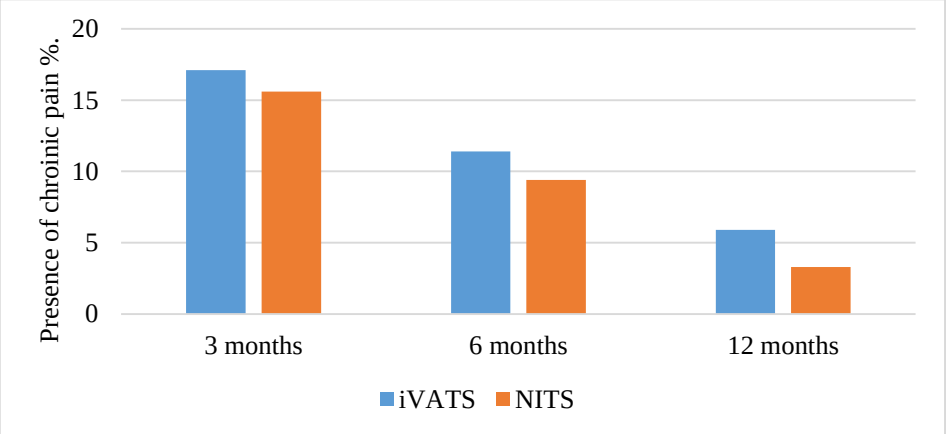

Figure-3: Relationship between the presence of chronic pain and the type of surgery performed

III.5. Discussion

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. Sommer C. et al 2018). Consequently, disturbed activation of immune- and inflammatory

system may contribute to the development and progress of long lasting pain. Interruption of tissue continuity implicate the infiltration of inflammatory cells, many various inflammatory mediators are secreted and this stimulation can lead to sensitization of the primary afferent neurons. This process may contribute to the onset of persistent pain (Moalem G et al. 2006). 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) promotes the chronic pain with hyperalgesia and allodynia(Li QY et al. 2017) and nerve growth factor (NGF) contributes to the hypersensitivity(Bannwarth B. et al 2014). On the other hand, reduction of the anti-inflammatory cytokines like interleukin-4 (IL-4) and interleukin-10 (IL-10) is also crucial in neuropathic pain (Uceyler N et al. 2007)

In general, minimal invasive surgery is considered a less invasive and traumatic approach than traditional open techniques and the risk of chronic pain is lower. This statement was confirmed in the last few decades from several authors, with 3-36 months follow up period volt (Wildgaard K. et al. 2016, Peng J. et al. 2022, Wildgaard K. et al. 2022, Landreneau RJ. et al. 1994, Handy JR. et al. 2010, Bendixen M. et al. 2016). 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 (Furák et al. 2022) VATS reduces circulating $CD3^+$, $CD4^+$, and $CD8^+$ T cells (Zhang LB. et al. 2015, Ng CS et al 2005) while thoracotomy increases the immune suppression of NK cells and T lymphocytes (Ng CS et al. 2005). IL-6 is also significantly increased in patients after thoracotomy than in those who undergo VATS, (Nagahiro I et al. 2001).

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 (Tacconi F . et al.. 2022), but the development of chronic postoperative pain is significantly less frequent after the uniportal approach(Cheng YF. et al. 2022, Homma T. et al 2022, Jin J.et al. 2022). 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 (Mineo TC et al. 2017). 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. 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 (Wang ML. et al 2017, Hung MH. et al. 2014, Hung WT. et al. 2016).Pompeo et al. assessed the acute pain intensity in two studies with visual analog scale (VAS) score in 24 hours after wedge resection or talc pleurodesis. They found that the pain score level is lower after non-intubated, non-relaxed than after intubated, relaxed VATS technique.(Pompeo at al. 2004, Pompeo et al. 2013) The results of patients underwent bullectomy through uniportal acces for primary spontaneous pneumothorax showed significant differences with VAS score in the first hour between general anaesthesia and tubeless technique, but this was not significant after 24 hours (Hwnag et al. 2018). 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(Zang et al. 2021). However, other authors published different results and conclusions; 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 (Yang et al. 2021). 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..

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. 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. Our results showed 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. Our result showed statistically significant higher incidence of the chronic pain during the follow-up period

among the diabetic patients. 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 (Kehlet H.et al. 2006, Ochroch EA. Et al 2006, Zhang Y. et al 2022). 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. Former other study has found a significantly higher incidence of chronic pain in patients with prolonged air leakage in their retrospective study (Peng et al. 2014), but other authors found no association between them (Mongardon et al. 2011, Fiorelli et al. 2020).

In summary, similar to previous publications we confirmed that the onset of chronic pain was less frequent in NITS compared to iVATS technique. Although the analgesic consumption did not show a statistically significant difference between the two groups, but the mean 2% lower rate during the follow up is an other advantage of non-intubated, non-relaxed technique .

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.