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Research Article

Postoperative Complications and Outcome for all Stages with Non-Small Cell Lung Cancer after Video-Assisted Thoracoscopic Lobectomy and Open Lobectomy: A Propensity-Score Matched Analysis

Julia Zimmermann[1*], Julia Walter[2], Johannes Schön[1], Julia Kovács[1], Gökce Yavuz[1], Valentina Pfeiffer[1], Christian Ketscher[1], Niels Reinmuth[3,4], Rudolf A Hatz[1,4], Amanda Tufman[2,4], Christian P Schneider[1,4]

[1]Division of Thoracic Surgery, LMU University Hospital, LMU Munich and Asklepios Lung Clinic Gauting, Germany

[2]Department of Internal Medicine V, LMU University Hospital, LMU Munich, Germany

[3]Department of Thoracic Oncology, Asklepios Lung Clinic Gauting, Germany

[4]Comprehensive Pneumology Center Munich, German Center of Lung Research (DZL), München, Germany

[*]**Corresponding author:** Julia Zimmermann, Division of Thoracic Surgery, Ludwig-Maximilians-University Munich, Marchionini Street 15 81377 Munich, Germany

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Abstract

Background: Postoperative complications and long-term outcomes after Video-Assisted Thoracoscopic (VATS) lobectomy and thoracotomy are still debated controversially in Non-Small Cell Lung Cancer (NSCLC). In this study we compared both surgical approaches in a retprospective propensity-score matched analysis.

Methods: We reviewed data of all patients undergoing VATS or open lobectomy at the Lung Cancer Center Munich between 2011 and 2020. We excluded patients with conversion to thoracotomy. We used propensity score matching adjusted for difference in patient and tumor characteristics of VATS and thoracotomy patients. They were compared before and after matching using standardized differences. Surgical outcomes and complication rates were compared using paired t-test and McNmear test for paired samples. Survival was determined using Kaplan-Meier curves with LogRank test.

Results: Of 1680 patients**,** we matched 434 with VATS to 434 patients with thoracotomy. Blood loss (>200ml) was significant less frequent after VATS. Other complication rates did not differ significantly between the two groups. Length of stay after resection was longer in thoracotomy (14.6 vs. 13.2, p=0.002), additionally the overall secretion via chest tube was higher (2330.6 ml vs. 1944.9 ml, p=0.01). The length of chest tube duration did not differ significantly. The surgery in minutes was longer in VATS (185.5 vs. 173.3, p=0.002). Overall survival was better in patients with VATS (p=0.04).

Conclusion: VATS and open lobectomy are still an indispensable part in the treatment of NSCLC in all operable tumor stages. Compared to the postoperative complications and survival both approaches can be performed as a safe and life-prolonging procedure.

Keywords: Minimally invasive surgery; Outcome; Propensity-score matched analysis; Postoperative complications; Thoracotomy

Introduction

Both Video-Assisted Thoracoscopic (VATS) and open lobectomy are established procedures in the treatment of NSCLC. Due to technical developments, there is a shift towards minimally invasive surgery in the last decades. It has been demonstrated that minimally invasive lung surgery results in cosmetic advantages, less pain, shorter chest tube duration and shorter postoperative hospital stay for early stage Non-Small Cell Lung Cancer (NSCLC). [1-3] It is still controversial whether VATS or open lobectomy is better regarding perioperative outcomes and long-term survival. Studies show different results, but with a tendency that both surgical approaches are equivalent, especially in early stage NSCLC. [4-9] Most of the published studies were retrospective, which always involves limitations regarding surgeon biases. For example, larger tumors or tumors with assumed nodal involvement are more likely to be operated with a thoracotomy than VATS, although studies showed that VATS is also a safe procedure in advanced NSCLC. [10-12] Furthermore, in case of large tumors or nodal involvement, a poorer prognosis is assumed, leading to sicker patients in the open lobectomy group. To compensate for this inequality, some studies have already applied Propensity-Score Matching (PSM) [1,2,6,8,9,11,13].

The focus was often placed on the long-term outcome. [6,9,13,14] Studies dealing with postoperative complications are available, but often include only a small cohort or only early stage NSCLC. [1-3,11,15,16] The aim of our study was to link all important aspects in a large cohort including all stages of NSCLC. Primary endpoint is the comparison of VATS and open lobectomy with regard to possible postoperative complications. Second endpoint is the long-term outcome. We used the propensity score matching in order to include all tumor stages (I-III) and matched on tumor size, lymph node involvement and metastasis. This allowed us to ensure comparable groups.

Methods

Study Design, Patient Cohort and Data Collection

In this retrospective analysis, we used data of all lung cancer patients undergoing lobectomy through thoracotomy or VATS at the Lung Cancer Center Munich between 2011 and 2020. Patients with conversion to thoracotomy were excluded. Additionally, for patients having had more than one tumor lobectomy we only used the first resection in our analysis. We also excluded patients with missing information regarding comorbidities. All information in the dataset was extracted from electronic patient records and patient archive. This data included information about patient characteristics namely age at resection, sex, performance status defined by the American Society Anesthesiologists Risk Classification (ASA), comorbidities, Body Mass Index (BMI), year of lobectomy, and smoking status. Tumor characteristics covered clinical and pathological tumor stage, histological type, tumor location, as well as tumor grading, lymphovascular space invasion (L status) and vascular invasion (V status).

Surgery Outcomes, Complications and Survival

To compare VATS and thoracotomy we analyzed the length of surgery in minutes, length of hospital stay after surgery in days (LOS), secretion via chest tube in ml, and the length of chest tube duration. If patients had two or more chest tubes we used the number of days until the last chest tube was removed. Complications after surgery included repeated thoracic puncture or repeated placement of a chest tube, fistula more than five days after surgery, pneumonia, cardiac arrhythmia, readmission to the intensive care unit, blood loss, and need for blood transfusion. Blood loss was categorized as less than 200ml, 200ml or more, and unknown. We compared Overall Survival (OS) and Progression-Free Survival (PFS) between patients with VATS and thoracotomy using time until death and first progression (either local or distant) or time until last follow-up.

Categorization of Variables and Handling of Missing Data

We categorized histological types into Adenocarcinoma (ACC), Squamous-Cell Carcinoma (SCC), and neuroendocrine carcinoma (including carcinoids and large-cell neuroendocrine carcinomas) (NEC). All other histological types were summarized under the category "other histology". As BMI was missing in 37 patients we used multiple imputation to fill in the missing values. For outcomes with missing information in numerical variables we used pairwise exclusion of cases in the statistical analysis. For categorical outcomes we created a category unknown in the analysis.

Statistical Analysis

Patient characteristics are presented as mean values with Standard Deviation (SD) for metric variables and absolute and relative frequencies for categorical variables. We assessed the balance of the distribution of baseline characteristics and tumor characteristics using standardized differences. Using PSM we matched patients with VATS to patients with thoracotomy including all variables with a standardized difference of greater than 0.1 in the estimation of the propensity scores. For the matching we used nearest neighbor method with a caliper of 0.2. Conditional multiple imputation was performed using the R package mice, to impute missing values of BMI. Variables used in the imputation process were age, sex, and all assessed comorbidities. We compared numerical outcomes in the matched cohort using paired t-test, and categorical outcomes using McNemar test. OS and PFS was compared with Kaplan-Meier curves and LogRank test. Data analysis was performed using R Version 4.0.0 and RStudio Version 1.4. Tables and figures were created in RStudio and Microsoft Excel.

Results

Patient Population

In total, 1680 patient underwent lobectomy at our center between 2011 and 2020. After exclusion of patients with conversion to thoracotomy (n=190), patients with multiple lobectomies (n=17), and patients with missing information on comorbidities (n=8), 1465 patients were left for PSM. Of these, 544 (37.1%) had received VATS and 921 (54.8%) thoracotomy. PSM found 434 matches for patients with VATS and thoracotomy; hence data of 868 patients were analyzed. Patient and tumor characteristics of before and after matching are summarized in Tables 1,2 and Figures 1. Figure 2 (A) shows that the distribution of propensity scores was not well-balanced before matching. PSM resulted in a well-balanced cohort of VATS and thoracotomy patients regarding the propensity score as shown in Figure 2 (B). Year of surgery had a standardized difference of over 0.1 after PSM, all other variables had standardized difference of <0.1.

	VATS (n = 544)		open (n = 921)		stdiff	VATS (n = 434)		open (n = 434)		stdiff
	mean	sd	mean	sd		mean	sd	mean	sd	
age in years	66.1	10.6	65.2	10.9	0.09	66.2	10.7	65.3	11.1	0.08
BMI	25.5	4.6	26.1	4.7	0.13	25.7	4.6	25.8	4.7	0.03
CCI score	3.5	2	3.4	2	0.06	3.5	2	3.5	2.1	0.005
	n	%	n	%	stdiff	n	%	n	%	stdiff
sex										
male	227	41.70%	559	60.70%		202	46.50%	211	48.60%	
female	317	58.30%	362	39.30%	0.39	232	53.50%	223	51.40%	0.04
current smoker										
yes	130	23.90%	230	25.00%		108	24.90%	116	26.70%	
no	403	74.10%	664	72.10%		315	72.60%	311	71.70%	
unknown	11	2.00%	27	2.90%	0.07	11	2.50%	7	1.60%	0.07
ASA										
1	29	5.30%	20	2.20%		15	3.50%	15	3.50%	
2	157	28.90%	223	24.20%		117	27.00%	118	27.20%	
3	315	57.90%	518	56.20%		260	59.90%	252	58.10%	
4	4	0.70%	17	1.80%		4	0.90%	2	0.50%	
unknown	39	7.20%	143	15.50%	0.33	38	8.80%	47	10.80%	0.09
year of surgery										
2011	15	2.80%	57	6.20%		13	3.00%	22	5.10%	
2012	47	8.60%	95	10.30%		43	9.90%	33	7.60%	
2013	41	7.50%	113	12.30%		39	9.00%	48	11.10%	
2014	48	8.80%	136	14.80%		43	9.90%	54	12.40%	
2015	46	8.50%	135	14.70%		37	8.50%	62	14.30%	
2016	66	12.10%	97	10.50%		59	13.60%	46	10.60%	
2017	79	14.50%	69	7.50%		62	14.30%	31	7.10%	
2018	69	12.70%	86	9.30%		50	11.50%	59	13.60%	
2019	71	13.10%	68	7.40%		48	11.10%	41	9.40%	

2020	63	11.60%	65	7.10%	0.41	40	9.20%	38	8.80%	0.35

Patient characteristics of lung cancer patients with lobectomy between 2010 and 2020 stratified by resection approach prior to and after Propensity score matching. Means with standard deviation of numerical variables and absolute and relative frequency of categorical variables. Standardized difference as a measure of balance between the two groups. VATS = video-assisted thoracoscopic surgery, stdiff = standardized difference, sd = standard deviation, BMI = body mass index, ASA = American Society of Anesthesiologists risk classification, NYHA = New York Heart Association, PAD = peripheral artery disease, COPD = chronic obstructive pulmonary disease, HIV/AIDS = Human Immunodeficiency Virus, AIDS = Acquired Immunodeficiency Syndrome.

Table 1: Patient characteristics of study population before and after matching.

	VATS (n = 544)		open (n = 921)		stdiff	VATS (n = 434)		open (n = 434)		stdiff
	mean	sd	mean	sd		mean	sd	mean	sd	
tumor size in cm	2.6	1.3	4.2	2.7	0.76	2.7	1.4	2.7	1.5	0.003
number of affected lymph nodes	0.5	1.7	1.4	3.2	0.38	0.6	1.9	0.7	2.1	0.07
	n	%	n	%	stdiff	n	%	n	%	stdiff
histological type										
adenocarcinoma	384	70.6%	492	53.4%		294	67.7%	279	64.3%	
SCC	84	15.4%	275	29.9%		80	18.4%	92	21.2%	
NEC	66	12.1%	116	12.6%		53	12.2%	54	12.4%	
other	10	1.8%	38	4.1%	0.40	7	1.6%	9	2.1%	0.08
location										
middle lobe	48	10.8%	45	4.9%		33	7.6%	33	7.6%	
upper lobe	184	41.4%	600	65.1%		248	57.1%	257	59.2%	
lower lobe	212	47.7%	276	30.0%	0.28	153	35.3%	144	33.2%	0.05
N										
N0	79	14.5%	344	37.4%		76	17.5%	93	21.4%	
N1,2,3	465	85.5%	577	62.6%	0.54	358	82.5%	341	78.6%	0.10
M										
M0	531	97.6%	872	94.7%		422	97.2%	419	96.5%	
M1	13	2.4%	49	5.3%	0.15	12	2.8%	15	3.5%	0.04
grading										
1	42	7.7%	43	4.7%		32	7.4%	33	7.6%	
2	279	51.3%	392	42.6%		211	48.6%	199	45.9%	
3	165	30.3%	332	36.0%		139	32.0%	147	33.9%	
4	3	0.6%	22	2.4%		3	0.7%	2	0.5%	
unknown	55	10.1%	132	14.3%	0.28	49	11.3%	53	12.2%	0.07

lymphovascular space invasion										
0	414	76.1%	714	77.5%		334	77.0%	348	80.2%	
1	105	19.3%	177	19.2%		85	19.6%	71	16.4%	
unknown	25	4.6%	30	3.3%	0.07	15	3.5%	15	3.5%	0.08
vascular invasion										
0	448	82.4%	756	82.1%		358	82.5%	366	84.3%	
1	71	13.1%	134	14.5%		61	14.1%	53	12.2%	
unknown	25	4.6%	31	3.4%	0.07	15	3.5%	15	3.5%	0.06

Tumor characteristics of lung cancer patients with lobectomy between 2011 and 2020 stratified by resection approach prior to and after Propensity score matching. Means with standard deviation of numerical variables and absolute and relative frequency of categorical variables. Standardized difference as a measure of balance between the two groups. VATS = video-assisted thoracoscopic surgery, stddiff = standardized difference, sd = standard deviation, NEC = neuroendocrine carcinoma, SCC = squamous-cell carcinoma.

Table 2: Tumor characteristics of study population before and after matching.

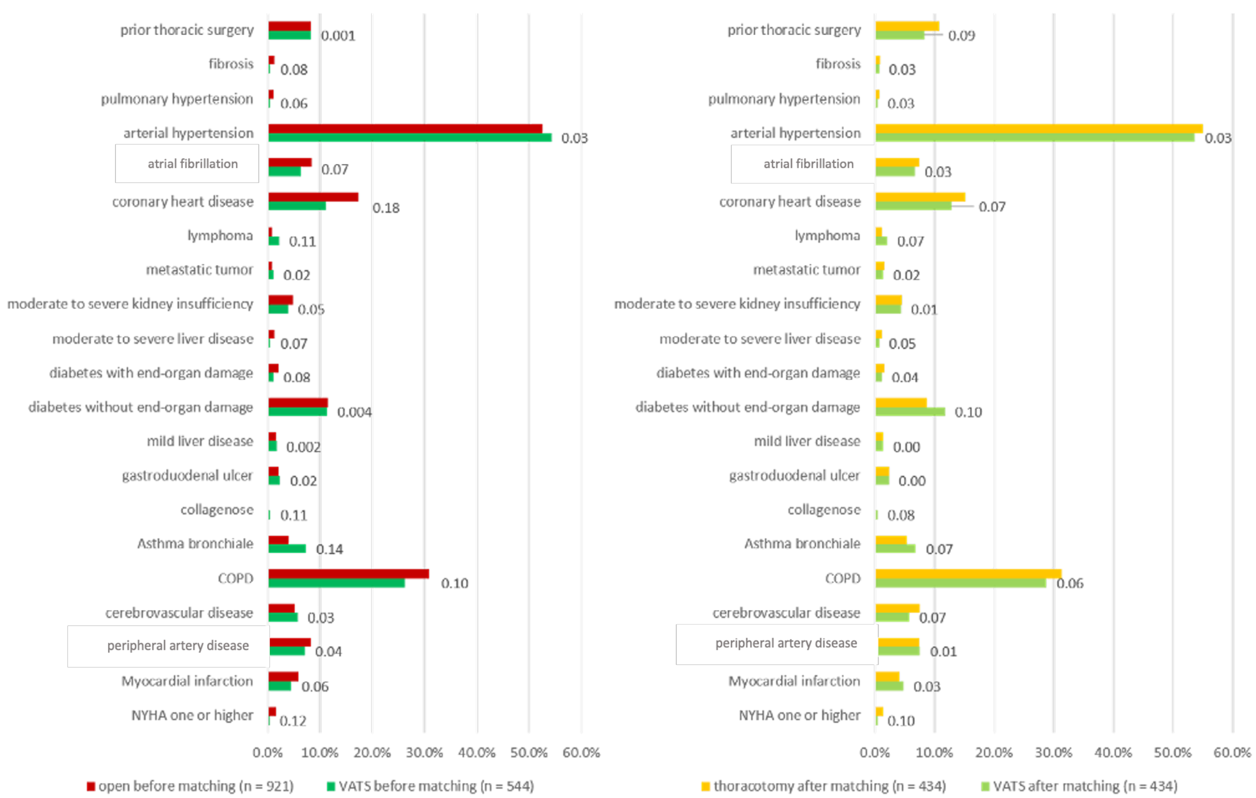


Figure 1: Preoperative comorbidities before and after propensity score matching. Distribution of prevalence of preoperative comorbidities stratified by surgical approach before and after propensity score matching. Data labels indicate standardized mean difference between the groups. COPD = chronic obstructive pulmonary disease, NYHA = New York Heart Association.

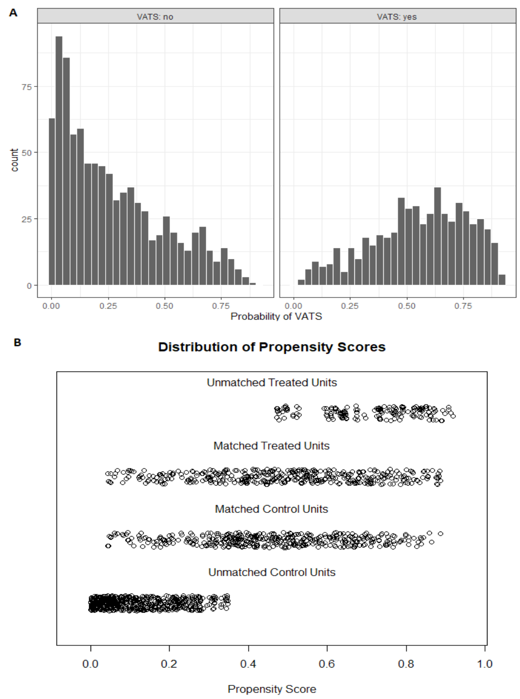


Figure 2: Distribution of propensity score before and after matching. Evaluation of the balance after matching. Plot A shows the distribution of the propensity score in VATS and thoracotomy patients prior to matching. Plot B shows the jitter plot of the propensity scores in matched and unmatched samples. VATS = video-assisted thoracoscopic surgery.

Surgical Outcomes and Complications

We found that the length of surgery in minutes was significantly longer in VATS compared to thoracotomy (185.5 min vs. 173.3 min, p=0.002). LOS after resection was significantly longer in thoracotomy compared to VATS (14.6 d vs. 13.2 d, p=0.002), as was more secretion via chest tube in ml (2330.6 ml vs. 1944.9 ml, p=0.01). The length of chest tube duration did not differ significantly between the two groups. The proportion of patients with a blood loss higher than 200ml was 27.4% in VATS and 38.5% in thoracotomy, which was a significant difference (p=0.001). All other complication rates did not differ significantly between the two groups. All surgical outcomes and complications are displayed in detail in Table 3.

	VATS (n = 434)		open (n = 434)		p-value
	mean	sd	mean	sd	
length of surgery in min	185.5	52.0	173.3	55.4	0.002
LOS after surgery	13.2	6.7	14.6	6.3	0.002
secretion via chest tube in ml	1944.9	1623.4	2330.6	1705.0	0.01
maximum duration of chest tube	6.4	4.3	6.7	3.4	0.33
	n	%	n	%	
repeated thoracic puncture/chest tube placement					
yes	36	8.3%	29	6.7%	
no	398	91.7%	405	93.3%	0.45

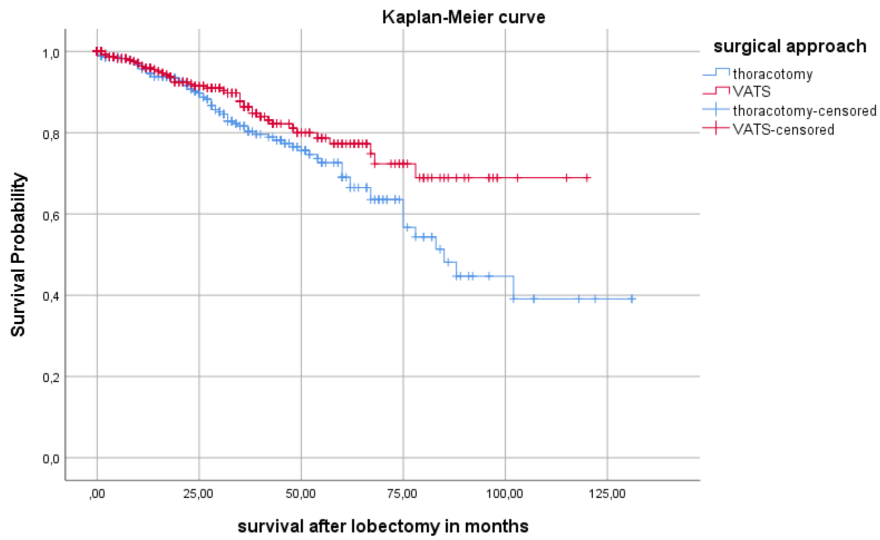
fistula > 5 days after surgery					
yes	42	9.7%	29	6.7%	
no	392	90.3%	405	93.3%	0.13
pneumonia					
yes	52	12.0%	63	14.5%	
no	382	88.0%	371	85.5%	0.30
cardiac arrhythmia					
yes	28	6.6%	33	7.7%	
no	399	93.4%	394	92.3%	0.58
readmission to ICU					
yes	26	6.1%	20	4.7%	
no	401	93.9%	407	95.3%	0.44
blood loss					
< 200 ml	242	55.8%	183	42.2%	
> 200 ml	119	27.4%	167	38.5%	
unknown	73	16.8%	84	19.4%	0.001
need for blood transfusion					
yes	5	1.2%	13	3.0%	
no	356	82.0%	336	77.4%	
unknown	73	16.8%	85	19.6%	0.17

Surgical outcomes and complications after lobectomies by surgical approach. Surgical outcomes as means with standard deviation, and complications as absolute and relative frequencies. P-values from McNemar test for frequencies and paired-test for number numerical outcomes. VATS = video-assisted thoracoscopic surgery, sd = standard deviation, LOS=length of stay, ICU = intensive care unit.

Table 3: Outcomes after surgery by surgical approach.

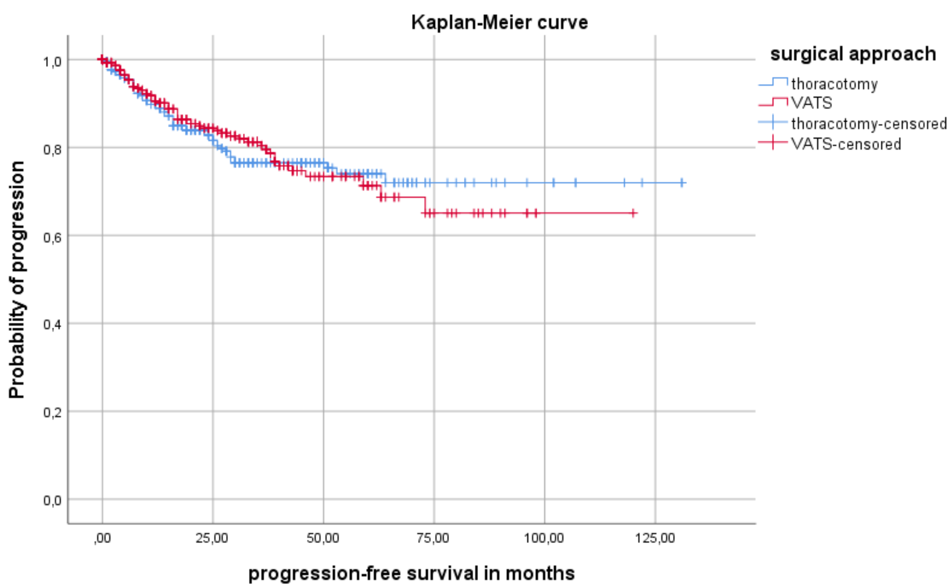
Survival Outcomes

Figure 3 shows that OS was significantly better in patients with VATS compared to thoracotomy (p=0.04). Median OS was not reached during follow-up in VATS patients. For thoracotomy patients OS was around 85 months. PFS did not differ significantly between the two groups. Median PFS was not reached in both groups during follow-up as can be seen in Figure 4.



p=0.04

Figure 3: Kaplan-Meier curve of overall survival by surgical approach Overall survival in months by surgical approach. P-value from LogRank test. VATS = video-assisted thoracoscopic surgery.



p=0.88

Figure 4: Kaplan-Meier curve of progression-free survival by surgical approach. Progression-free survival in months by surgical approach. P-value from LogRank test. VATS = video-assisted thoracoscopic surgery, PFS=progression-free survival.

Discussion

Although VATS is one of the established techniques in lung tumor resection, it is still under close observation with regard to postoperative complications and oncological outcome. It is up to the surgeons to decide which surgical approach is used to achieve the best oncological result with complete tumor resection and lymphadenectomy on the one hand, and a high level of patient satisfaction, usually accompanied by less postoperative complications, short hospital stay and minimization of postoperative pain, on the other hand. [3,17] The overall aim of every surgeon is to get the best out of all the factors mentioned previously, with a priority on the oncological outcome. Comparing VATS lobectomy with thoracotomy, not only in the early stages, will help to better understand the implications of both surgical approaches.

In order to get meaningful results when studying VATS and thoracotomy large patient cohorts with well-balanced comparison groups (VATS vs thoracotomy) are of need but not always available. Well-balanced cohorts can be achieved by means of PSM analysis. The importance of PSM in retrospective studies becomes evident when taking a closer look at the cohort data prior to the matching process. Prior to the matching process our results showed that, apart from sex, BMI and some comorbidities like NYHA >1 and bronchial asthma, there were differences in favor of the VATS group, especially with regard to the tumor characteristics. E.g. less lymph nodal involvement and G3/G4 status in the postoperative pathological report, as well as fewer distant metastases were found in the VATS group. Particularly such indicators do have a significant negative impact on the survival rate. [18-20] When evaluating retrospective results with unequal groups, any findings could be distorted compromising the statistical representation. I.e. without PSM the VATS group of our study would have better prerequisites even before the operation which would consequently impact the validity of our findings.

Some other studies which performed PSM had already shown that VATS has a better effect on blood loss, shorter duration of chest tube and shorter postoperative hospital stay. However, in contrast to our study, they were only able to include a small number of patients and examined early tumor stages. [1,2] After PSM the characteristics of our two groups were well balanced with standardized differences of lower than 0.1, with the exception on the year of surgery. In this large cohort of 868 patients, including all types of tumor stages, we observed significantly less blood loss, less secretion via chest tube and shorter postoperative hospital stay in VATS. The operation time was significantly longer in VATS compared to thoracotomy. In contrast to other studies, which have observed lower complications after VATS lobectomy [21], we could not find any differences except of the intraoperative blood loss. Fistula more than five days, pneumonia, repeated thoracic puncture due to increased intrathoracic fluid, repeated placement of a chest tube due to pneumothorax, cardiac arrythmia or readmission to an intensive care unit showed no significant differences between VATS and thoracotomy. Our data revealed, that the occurrence of postoperative complications is independent of the surgical approach. Less intraoperative blood loss and less secretion via chest tube, is an indirect sign of a smaller wound area, which goes well with VATS as a minimally invasive procedure. Median survival from lung cancer has improved significantly over the years [22].

Regarding our secondary end point, OS and PFS, VATS had a significant better OS than thoracotomy (p=0.04), but no significant association with PFS (p=0.88). Median OS was not reached during the observation period in VATS patients. In thoracotomy patients it was around 85 months. The improved OS after VATS cannot be explained satisfactorily. While the reduced loss of blood after VATS has a positive effect on OS, we have found at least one indicator which typically would impact OS negatively - the longer operation time for VATS. [23] Other factors typically impacting OS did not show significant differences. Lymph node involvement was slightly higher in the VATS group than in the thoracotomy group, which should have impacted OS even negatively. Likewise differences in tumor size must be excluded as a reason for the improved OS. In contrast to other studies we did not have any significant differences. Due to the matching, the above factors should not have any influence anyway, because we have created comparable groups through PMS. Hence, there might be other patient-unrelated factors influencing OS. Also the fact that there is no difference in PFS between the individual surgical approaches further relativizes the influence of VATS on OS and rather may indicate further influencing factors. Some limitations of this study have to be considered. First, this is a single center and a retrospective study. Second, although we did a PSM analysis surgeons selection bias might still exist. I.e. individual decisions preferring either VATS or thoracotomy may have an impact to our cohort selection or findings. Additionally, even after PSM year of surgery still had a standardized mean difference of graeter than 0.1. This reflects the growing importance of VATS in lung tumor resection. However, differences in year of surgery are small. Further, the cut-off value of 0.1 often used to assess balance of matching variables was set arbitrarily and researches suggest to also look at the distribution of the variables. Therefore we believe that our propensity matched cohort is still well balanced. Furthermore, the fact that the Lung Cancer Center Munich is an academic teaching hospital where young surgeons are well trained the effect of their learning curve on VATS may also become apparent. One strength of our study is the inclusion of all patients disregarding stage. Therefore, our cohort reflects results across all stages of resected patients and through PSM we were able to balance the cohort regarding stage. Additionally, by including all patients our cohort is quite large compared to other studies, leading to a higher statistical power.

Conclusion

VATS lobectomy and thoracotomy for NSCLC in all stages is a safe procedure. After PSM we have shown for a large cohort, that both surgical approaches can be performed effectively. Less complications and a good overall survival combined with a long period of PFS showed, that surgery for lung cancer is still an indispensable part in the treatment of lung cancer. Because the medical and oncological outcome is equal in both surgical approaches, the advantages of VATS surgery should be used in clinical practice with a shorter hospital stay. Nevertheless, the indications for thoracotomy should still be considered so that each patient receives the best treatment for them.

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