ALMA MATER STUDIORUM – UNIVERSITA' DI BOLOGNA

DOTTORATO DI RICERCA IN

SCIENZE MEDICHE SPECIALISTICHE

Ciclo 28°

Settore Concorsuale di afferenza: MED21
Settore Scientifico disciplinare: 06/E01

IMPACT OF THE VIDEO-ASSISTED LOBECTOMY APPROACH ON MAXIMAL OXYGEN CONSUMPTION, PULMONARY FUNCTION AND QUALITY OF LIFE OF LUNG CANCER PATIENTS

Presentata da: **Dr. M. Salati**

Coordinatore Dottorato
Prof. R. Di Bartolomeo

Relatore
Prof. S. Mattioli

Correlatore
Dr. A. Brunelli

Esame finale anno 2015-2016

TABLE OF CONTENT

I. STATE OF THE ART

Lung cancer is the most common cancer in the world with about 1.3 million new cases diagnosed every year (1,2).

Lung cancer mortality is among the highest, with a male/female ratio that is 4:3 nowadays (1,2) .

It is generally agreed that surgery is the best treatment option for lung cancer as it offers the only real potential for cure. Despite that, the survival rate after surgical therapy is extremely low (60 to 30% dependently by the stage of disease) (3,4).

Moreover the surgical treatment exposes lung cancer patients to the risk of a postoperative deterioration of their functional status and quality of life (5).

The traditional surgical option offered to cure patients with lung neoplasm is represented by an anatomic lung resection (lobectomy/ bilobectomy/ pneumonectomy) performed through a thoracotomic incision.

During the last two decades, the literature has proposed evidence supporting alternative minimally invasive technique to perform major anatomic pulmonary resection. In particular, the video-assisted thoracic surgery (VATS) lobectomy seems to represent a valuable approach for selected patients as treatment of early-stage lung cancer. In fact, this technique reduces the hospital stay, allows a more rapid postoperative recovery with less pain and, above all, could offer a more favorable oncologic result as compared with the traditional thoracotomy approach (6).

Nevertheless scanty information is available about the impact of VATS lobectomy on the physical and mental status of lung cancer patients. So it appears crucial verifying the relapses of such an innovative technique on the actual postoperative pulmonary function tests (PFTs), lung diffusion capacity (DLCO), cardiorespiratory reserve, and quality of life of patients submitted to lung resection for cancer.

I.1 *Role of VATS lobectomy*

In 2007 the American College of Chest Physicians evidence-based clinical practice guidelines for Diagnosis and Management of Lung Cancer recommend that "In patients with stage I NSCLC who are considered appropriate candidates for thoracoscopic anatomic lung resection (lobectomy or segmentectomy), the use of VATS by surgeons experienced in these techniques is an acceptable alternative to open thoracotomy" (6).

This statement is a consequence of the growing evidence that, in the last 15 years, showed not only comparable but also better results of VATS lobectomy vs the standard open technique in terms of short- and long-term outcomes.

In particular, operative mortality after VATS lobectomy ranges from 0% to 2.7%, which is comparable to the reported mean modern mortality for open lung cancer surgery (7) . Moreover the VATS lobectomy is associated with an acceptable morbidity rate. Similarly to the open lobectomies, arrhythmias, prolonged air leak, and pneumonia are the most common complications (8).

On the other hand, the minimally invasive approach seems to represent an advantage for some early outcomes of primary importance after thoracic surgery, such as the chest tube duration, the length of stay and the postoperative pain (7,9).

Although in the past the long-term results initially reported limited the use of the thoracoscopic lobectomy, more recent papers reviewed the role of minimally invasive approach even from this point of view. Different studies demonstrated the advantages of the VATS lobectomy in terms of immunologic impact, compliance to adjuvant therapies and consequently of long-term oncologic results (10,11).

I.2 *Role of pulmonary function test and lung diffusion capacity*

Recently, two task forces, one represented by the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) and the other by the British Thoracic Society (BTS) and the Society for Cardiothoracic Surgeons of Great Britain and Ireland (SCTS), published different guidelines about preoperative functional evaluation of patients undergoing lung resection (12,13).

As stated in both the ERS/ESTS and BTS/SCTS algorithms, the physic assessment of lung resection candidates should begin with the evaluation of lung function, by the systematic measurement of forced expiratory volume in the 1^{st} second (FEV1) and carbon monoxide lung diffusing capacity (DLCO) (regardless of the FEV1 values).

In fact, these parameters are still crucial in the effort of quantifying the post-surgery mortality risk and the perioperative risk of complications.

Despite some limitations highlighted by several studies published by the end of the 90s, the preoperative FEV1 and DLCO are still pivotal parameters used in clinical practice to define the surgical risk in lung cancer patients and, in some cases, to exclude patients from a potentially curative surgical therapy (14-18).

As well as for the quantification of the operative risk, FEV1 and DLCO have been used in several studies to determine the longitudinal impact of major pulmonary resections for lung cancer on respiratory function (19).

These studies showed that pulmonary resections led to different levels of functional impairment depending on the extent of resection and variable on the time-point of postoperative evaluation. Considering in particular the open standard lobectomy, this procedure results in reduction of respiratory function in the early postoperative period with a subsequent significant recovery after 3-6 months after the operation (19,20).

I.3 *Role of cardiopulmonary exercise test*

Over the past 10 years, the cardiopulmonary exercise tests have taken a central role to overcome the limitations of the above mentioned surgical risk assessment parameters in patients undergoing lung resection (21,22).

In particular the high-tech maximal cardiopulmonary exercise test (CPET) is increasingly used to assess the aerobic capacity of a candidate for pulmonary resection (23-26). The rationale is that the patients with a preoperative impaired aerobic reserve could experience a greater difficulty dealing with the multiple pathophysiologic changes that accompany major surgical procedures. In fact, during the normal postoperative period a rise in oxygen consumption of a variable extent is expected and the onset of a complication may further increase the oxygen requirements beyond that which the patient can provide. This postoperative situation inevitably induces an oxygen debt, which, remaining critically high over specified periods of time, could lead to a multiorgan failure.

Increasing evidence has supported the use of CPET (especially the VO2max value, that can be directly measured by this test) for the quantification of operative risk in lung surgery, in particular for those patients with marginal respiratory functions. So, the ergometric evaluation has acquired such importance that the ERS/ESTS task force recommended a more liberal use of cardiopulmonary exercise test, which became crucial in guiding the preoperative functional assessment strategy (12).

I.4 *Role of quality of life assessment*

Especially from the patient's perspective, the risk of an impaired quality of life (QOL) after surgery is an important consideration when deciding whether to proceed with surgery. Some patients may be ready to face the risk of immediate perioperative complications (even death) but are not prepared to accept significant postoperative debility.

As a consequence, the potential benefit (survival) of an operation should be weighed not only against morbidity and mortality, but also against residual health-related QOL measures. Therefore a more comprehensive patient counseling should also include reliable information about the anticipated residual QOL.

Although the need exists for a more comprehensive understanding of the effects of thoracic surgery on patients' functional and QOL outcomes, at present very few studies have addressed this subject.

Some recently published papers demonstrated that candidates for lung resection with lung cancer had a worse preoperative quality of life compared with the general population (27,28). Moreover it has been verified that the QOL measures had poor correlation with those parameters traditionally used to assess the postoperative functional loss (such as FEV1, DLCO, VO2max), in patients submitted to open major pulmonary resection for lung cancer (29). Therefore, the functional variables cannot substitute for specific evaluation instruments apt at measuring the subjectively perceived QOL. At the same time, scarce evidence analyzed the longitudinal changes and the mechanisms of recovery of QOL patients submitted to major lung resection for neoplasm.

Unfortunately, both in the preoperative risk stratification and in the evaluation of the postoperative impact of lung surgery, the vast majority of the published works takes into account pulmonary resections performed with the traditional technique (standard thoracotomic lobectomy). Therefore, there is a lack of knowledge about the impact of the vats lobectomy on patients functional and mental recovery after the operation and on the surgical risk specific for this approach.

II. PROJECT DESCRIPTION AND METHODS

This project was aimed at verifying the long-term impact of the VATS lobectomy technique on physical and mental status of patients undergoing lung resection for lung cancer.

For this purpose, we identified the following endpoints of the study:

PRIMARY ENDPOINTS

to verify the physical status variation after the VATS lobectomy, comparing the preoperative and the 3 months postoperative patients physical examinations (PFTs, DLCO, CPET)

to verify the mental status variation after the VATS lobectomy, comparing the preoperative and the 3 months postoperative QoL questionnaire measurement (EORTC C30)

SECONDARY ENDPOINT

to verify the differences between the VATS lobectomy and the standard open lobectomy in terms of physical status variation, using a propensity score matching analysis

We prospectively enrolled in the present study the surgical patients referred to the Unit of Thoracic Surgery - AOU Ospedali Riuniti of Ancona since June 2012 to June 2015 and treated by the VATS lobectomy approach.

The specific inclusion and exclusion criteria used for the prospective patients enrollment are shown below:

Inclusion criteria:

1. All patients (both sex and adults) candidates for elective surgical treatment (lobectomy) for primary or secondary lung cancer
2. Informed consent obtained

Exclusion criteria:

1. Previous thoracic operations
2. Candidates to pneumonectomy or resection less than lobectomy
3. Cardiological contraindications to CPET
4. Incontrollable hypertension
5. Incontrollable diabetes
6. Inability to perform CPET (musculoskeletal, cerebrovascular, neurologic, psychiatric, severe peripheral vascular diseases)

The enrollment of each patient was decided during the weekly clinical meeting for the discussion of new lung resection candidates.

Considering the secondary endpoint (functional comparison between open and VATS lobectomy patients 3 months after the operation), we queried our institutional prospectively maintained database in order to retrospectively obtain data about patients treated by the open lobectomy approach since January 2010 to May 2012. These data were used for the comparative analysis between open and VATS lobectomy patients. We adopted the following query as retrospective inclusion criteria: patients (both sex and adults) submitted to elective open pulmonary lobectomy for primary and secondary lung cancer which performed a preoperative and postoperative (3 months) functional evaluation.

Only those patients with a complete preoperative and postoperative functional evaluation (FEV1, DLCO and VO2max concurrently available) within both VATS and open lobectomy groups were selected for the matched analysis.

Fifteen days before and three months after the operation the patients were evaluated to assess their physical status (PFTS, DLCO measurement, CPET) as well as their quality of life perception (quality of life questionnaire EORTC C30).

The parameters used to verify the variation of the patients' physical status after the VATS lobectomy were: FEV1%, DLCO% and VO2max.

Pulmonary function tests were performed according to the American Thoracic Society criteria. The DLCO was measured by the single-breath method. Results of spirometry and DLCO were collected after bronchodilator administration and were expressed as percentage of predicted for age, sex, and height according to the European Community for Steel and Coal prediction equations (30).

Chronic obstructive pulmonary disease (COPD) was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (FEV/forced vital capacity [FVC] < 0.7) (31).

For the maximal oxygen consumption measurement, a symptom-limited CPET was systematically performed in all patients on an electronically braked cycle ergometer, using a ramp-pattern increase in work rate to reach an exercise test duration between 8 and 12 minutes. The exercise test was stopped when 1 or more of the following criteria were present: fatigue, dyspnea, excessive systemic blood pressure increase (ie, > 230/130 mm Hg), a greater than 2-mm ST depression in at least 2 adjacent leads, or angina). The VO2max was the average VO2 during the last 15 seconds of exercise.

In order to measure the patients' health related quality of life and its variation after the VATS lobectomy, we used the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) (32). Answering the questions reported within the EORTC QLQ-C30 module, it was possible to obtain several scales able to measure different aspects of the perceived quality of life (Tab.1).

For the purpose of the present study we recorded and analyzed the variation of the preoperative and postoperative Global Health Status and the variation of the five Functional Scales (i.e. Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning and Social Functioning).

Tab.1. Psychological parameters measured by the EORTC C30 module

	Definition
Global health status	
QL2	General Quality of Life
Functional scales	
PF2	Physical Functioning
RF2	Role Functioning
EF	Emotional Functioning
CF	Cognitive Functioning
SF	Social Functioning
Symptom scales	
FA	Fatigue
NV	Nausea and Vomiting
PA	Pain
DY	Dyspnoea
SL	Insomnia
AP	Appetite Loss
CO	Constipation
DI	Diarrhea
FI	Financial Difficulties

The definition of the patient surgical risk and the consequent selection of the optimal surgical therapy were obtained taking into account the following preoperative evaluation protocol:

ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy) (12).

During the study period, the VATS lobectomy was performed using both the uniportal or biportal technique. In case of a minimally invasive videoassisted biportal approach, a single port incision for the camera and a 5 cm incision (utility incision) for the passage and manipulation of instruments were used. In case of the uniportal approach a unique 4-5 cm incision was performed at the level of the fifth intercostal space in the anterior axillary line. Through this single incision all the operative instruments as well as the 5-mm thoracoscope were inserted.

The ribs were not resected or spread.

Mediastinal systematic nodal dissection or at least nodal sampling was performed for all cases.

The pulmonary veins, pulmonary artery (PA) branches, and bronchus were divided individually with endoscopic staplers.

All operating steps were performed through direct observation on the monitor and not by direct examination through the utility incision.

The open traditional approach was performed through a muscle sparing and intercostal nerve sparing lateral thoracotomy, in order to avoid nerve crushing during the operation. The ribs were spread using a Finocchieto retractor and closed at the end of the operation by two single non-absorbable stitches, preserving the nerves of the intercostal spaces above and below the thoracotomy.

After the surgical procedure, both in the VATS and in the open approach, a single chest tube was placed to drain the pleural cavity. In case of the uniportal VATS, the tube was inserted through the operative incision.

All the patients were managed using intraoperative and postoperative standardized protocols, aimed at a fast-tracking the patients after major lung resection.

The postoperative complications were classified adopting the definitions proposed by the ESTS Database Committee (33,34). According to these definitions the “major cardiopulmonary morbidity” included any of the followings:

- pulmonary complications: pneumonia, atelectasis requiring bronchoscopy, adult respiratory distress syndrome, mechanical ventilation longer than 24 h, pulmonary edema, pulmonary embolism;
- cardiac complications: myocardial ischemia, cardiac failure, arrhythmia, stroke, acute renal insufficiency.

Postoperative complications and mortality were considered as those occurring within 30 days postoperatively, or over a longer period if the patient was still in the hospital.

An electronic prospective database was designed for the collection and management of patients’ clinical data. During the study period the data quality of the registry was routinely checked using task independent quality metrics.

At the end of the data collection phase, the base of data was revised using standardized and registered procedures of data cleaning.

The present study project has been developed taking into account the ethical principles of Good Clinical Practice.

At the same time the researchers followed the ethical rules for the medical research involving humans, as stated in the Declaration of Helsinki by the World Medical Association.

The present study was approved by the local Institutional Review Board.

II.1 *STATISTICAL ANALYSIS*

Normal distribution of numerical variables was assessed by the Shapiro Wilk normality test. Numerical variables with normal distribution were compared by the unpaired Student's t-test and those without normal distribution by the Mann–Whitney test. Categorical variables were compared by the chi-square test or Fisher's exact test as appropriate.

In order to compare the postoperative (three months) physical and mental variation between open lobectomy and VATS lobectomy patients, we matched them according to their baseline characteristics. The conditional probability to be managed by the VATS technique (propensity score) was estimated by logistic regression analysis incorporating the following variables: age, gender, body mass index, smoking history-pack-years, Charlson's Comorbidity Index, Eastern Cooperative Oncology Group score, Zubrod score, forced expiratory volume in one second to forced vital capacity ratio (FEV1/FVC ratio), presence of coronary artery disease, hypertension, history of arrhythmia, presence of arterial vascular disease, primary or secondary lung cancer diagnosis, pT status, pN status.

All variables were at least 95% complete and sporadic missing values were imputed by taking the most frequent response category or averaging non-missing values for continuous variables.

The VATS lobectomy patients were matched to the open lobectomy counterparts by choosing the patient with the nearest propensity score (35).

The procedure yielded 83 well-matched pairs of open and VATS patients. The categoric variables of the two groups of propensity score matched patients were compared by the chi-square test or Fisher's exact test as appropriate. Numeric variables were compared using the unpaired t-test (normal distribution) or the Mann–Whitney test (non-normal distribution).

III. RESULTS

III.1 *General population*

From January 2010 through June 2015, 319 patients submitted to pulmonary lobectomy for primary or secondary lung cancer at our unit matched the inclusion criteria and were enrolled in the present study.

The mean age was 67 years and 72.4 % of the patients were male.

Most of the operations were performed for treating primary lung cancer (90.3%) and 45.5% of patients (142) were operated on using the VATS lobectomy approach.

From the functional point of view, the patients had good spirometric parameters (mean FEV1: 86.7%), but a suboptimal lung diffusion capacity (mean DLCO: 78.6%). On average, the patients experienced VO2max values over the threshold to perform safe major lung resections.

This group of lung cancer surgical patients had a perceived global health status lower than the general population of the same mean age (QL2: 71.5) (36).

Table 2 summarises several baseline characteristics of our patents.

Tab 2. General characteristics of the entire population

VARIABLE	nbr.val	mean	std.dev
age	319	67,3	10,6
bmi	319	26,2	4,4
fev1	319	86,7	19,1
fev1/fvc	319	0,7	0,1
dlco	319	78,6	19,7
vo2max (ml/kg/min)	254	16,4	3,7
pack-years	319	40,1	38,0
QL2 pre	149	71,6	18,6
PF2 pre	150	90,2	12,5
RF2 pre	148	92,4	13,7
EF pre	149	80,1	17,0
CF pre	149	91,4	13,2
SF pre	147	93,0	13,6
	nbr.val	**percent**	**number**
open/vats	319	55,5 / 44,5	177 / 142
sex (m/f)	319	72,4 / 27,6	231 / 88
asa (low/high)	319	61,7 / 38,3	197 / 122
ecog (low/high)	319	63 / 37	201 / 118
cci (low/high)	319	57 / 43	182 / 137
res. Estesa	319	5,3	17
chest wall	319	0,9	3
morphology (prim/sec)	319	90,3 / 9,7	288 / 31
pT (low/high)	319	53,6 / 46,4	171 / 148
pN (low/high)	319	94,7 / 5,3	302 / 17

III.2 *VATS lobectomy patients*

Table 3 shows the characteristics of those patients treated by the VATS lobectomy approach. Even in this case the preoperative functional status of the patients was of high level (FEV1: 90.4%, VO2max: 16.6 ml/kg/min) with the exception of the DLCO. Again the patients reported an impaired perceived global quality of life (QL2: 72.7). A great proportion of the patients was affected by cardiovascular diseases (hypertension 52.8%, coronary artery disease 39.4% arrhythmia: 15.5%, cardiac failure: 5.6%, cerebrovascular disease: 5.6%, peripheral arterial vascular disease: 7%), and about 40% of the patients had a Charlson's Comorbidity index >2.

The mean operation time for performing the VATS lobectomy procedure was 197 min. During the postoperative period the patients experienced a mean air leak duration of about 2 days and the mean hospital stay was 5.4 days.

The rate of major cardiopulmonary complications was 9.1%, with a great proportion of pulmonary adverse events (5.6%).

Tab. 3. Baseline, surgical and postoperative characteristics of the VATS lobectomy patients' group

baseline characteristics			
VARIABLE	**nbr.val**	**mean**	**std.dev**
age (years)	142	68,5	10,2
bmi	142	26,1	4,4
fev1	142	90,4	20,1
fev1/fvc	142	0,7	0,1
dlco	142	76,6	19,0
vo2max (ml/kg/min)	105	16,6	3,8
pack-years	142	33,5	34,3
QL2 pre	111	72,7	19,1
PF2 pre	112	89,5	13,5
RF2 pre	110	92,6	14,0
EF pre	111	79,5	17,1
CF pre	111	91,7	13,1
SF pre	110	93,0	14,0
	nbr.val	**percent**	**number**
sex (M)	142	62,7	89
asa (low)	142	95,1	135
ecog (low)	142	68,3	97
cci (low)	142	59,1	84
IA (yes)	142	52,8	75
CAD (yes)	142	39,4	56
aritmia.pre (yes)	142	15,5	22
cardiac.fail.pre (yes)	142	5,6	8
cerebrovasc.pre (yes)	142	5,6	8
vasculop.pre (yes)	142	7	10
renal.pre (yes)	142	12	17
liver.pre (yes)	142	14,1	20
surgical and postop characteristics			
VARIABLE	**nbr.val**	**mean**	**std.dev**
operation time (min)	142	197,4	50,4
air-leak (days)	142	1,9	4,8
pleural effusion (ml)	142	459,6	231,4
hospital stay (days)	142	5,5	3,8
	nbr.val	**percent**	**number**
extended resection (yes)	142	2,1	3
chest wall (yes)	142	0,7	1
morphology (primary)	142	90,8	129
pT (low)	142	64,1	91
pN (low)	142	92,2	131
compl.tot (yes)	142	20,4	29
compl.cardiopulm (yes)	142	9,1	13
compl.cardiac (yes)	142	3,5	5
compl.pulm (yes)	142	5,6	8

Considering the variation of the physical indicators three months after the operation, we found a general reduction in comparison to the preoperative values. In particular the DLCO had a negative variation of 12.4%. (Tab. 4).

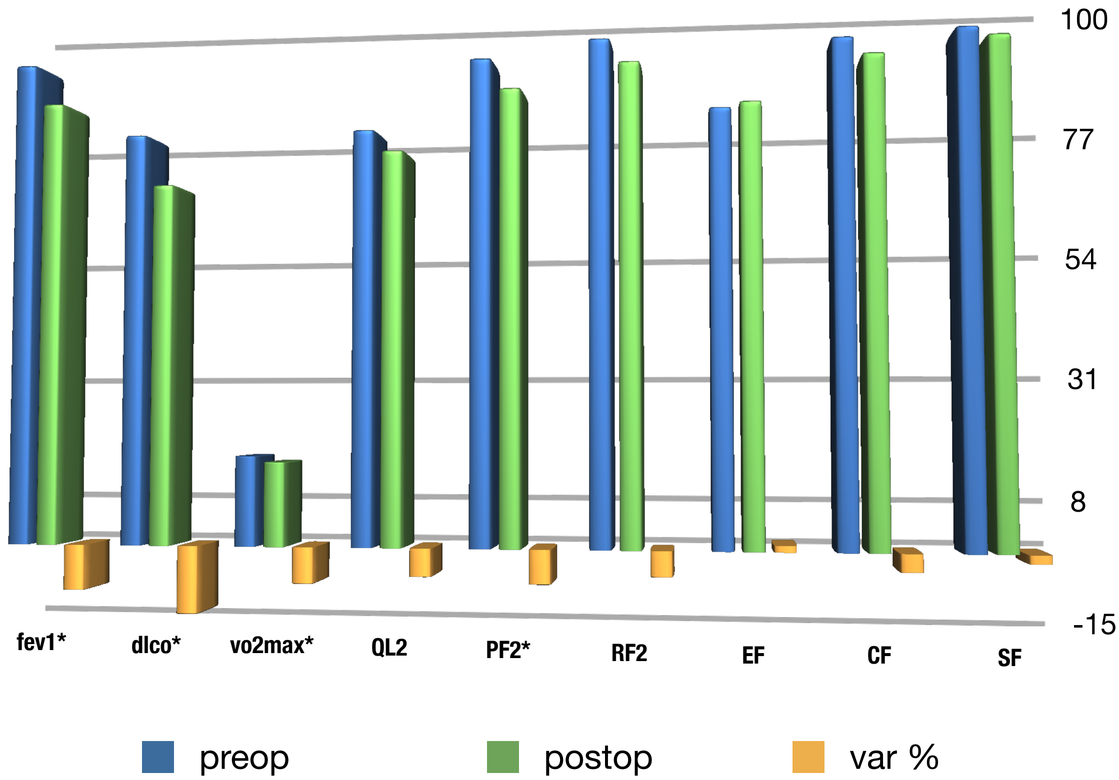
A similar negative trend was found for the psychological indicators, even though the only parameter with a significative worsening was the perceived physical functioning (reduction: 6.2%, p <0.001).

Tab. 4. Physical and psychological variation of the VATS patients 3 months after the operation.

VARIABLE	preop (mean, SD)	postop (mean, SD)	var %	p.value	nbr.val
fev1	90,4 (20,1)	82,9 (18,6)	-8,3	<0,001	142
dlco	76,6 (18,9)	67,1 (17,3)	-12,4	<0,001	142
vo2max	16,6 (3,7)	15,5 (3,5)	-6,6	<0,001	84
QL2	76,7 (19,1)	72.8 (18,8)	-5,1	0,878	94
PF2	89,5 (13,5)	83,9 (13,5)	-6,2	<0,001	94
RF2	92,6 (14,1)	88,3 (17,6)	-4,6	0,115	94
EF	79,5 (17,1)	80,5 (17,2)	1,2	0,3872	94
CF	91,7 (13,1)	88,7 (14)	-3,3	0,2115	94
SF	93 (14)	91,5 (15,1)	-1,6	0,4678	94

The figure 1 shows the mean physical and psychological values highlighting their lower level in the postoperative period, with the exception of the variation registered for the emotional functioning indicator (increase: 1.2% p: 0.39)

Fig. 1. Comparison of the preoperative and postoperative physical and psychological indicators and their variation



The tables 5, 6, 7, and 8 show the variations of the physical and psychological indicators in particular risk groups of patients (elderly, COPD patients, patients with cardiovascular disease and complicated patients) within the VATS lobectomy population and the comparison with the variations for the correspondent counterparts (young, non-COPD patients, patients without cardiovascular disease and non-complicated patients).

For all the considered subgroups we observed a constant reduction of the physical indicators. The negative trend was again mostly evident for the DLCO reduction.

In the comparison between young and elderly patients the percentage of the FEV1 variation ((FEV1pre - FEV1post) / FEV1pre) was higher for the young ones (FEV1 variation young: -10.5% vs FEV1 variation elderly: -4.6%, p value: 0.02) (Tab.5).

Tab. 5. Physical and psychological variation for young and elderly patients within the VATS group

	young (61)			elderly (81)			variation comparison		
VARIABLE	preop	postop	p.value	preop	postop	p.value	young	elderly	p.value
fev1	89,7 (20,4)	78,8 (16,1)	< 0.001	91 (19,9)	86 (19,8)	0,001	-10,5	-4,6	0,02
dlco	78,5 (17)	68 (15,9)	< 0.001	75,1 (20,2)	75,1 (18,4)	< 0.001	-12,2	-10	0,4
vo2max	17,4 (4,4)	16,1 (4,4)	0,06	16,1 (3,1)	15,2 (2,7)	0,003	-7,2	-6,7	0,9
QL2	70,5 (17,1)	70,4 (18)	0,6	74,4 (20,6)	74,6 (19,4)	0,9	3,2	7,7	0,5
PF2	90,8 (10,8)	85,1 (12,2)	0,001	88,3 (15,3)	82,9 (14,5)	0,002	-5,2	-3,7	0,7
RF2	92,6 (13,5)	88,4 (16,5)	0,09	92,5 (14,5)	88,2 (18,7)	0,5	-3,2	2,7	0,3
EF	77,3 (17,4)	79,5 (17,4)	0,3	81,3 (16,7)	81,5 (17)	0,7	5,8	4,2	0,8
CF	94,3 (10,4)	90,8 (11,4)	0,4	89,6 (14,6)	87 15,7	0,3	0,1	-0,4	0,9
SF	91,1 (15,6)	87,8 (18,7)	0,3	94,5 (12,4)	94,6 10,6	0,9	0,6	0,4	0,5

Results are expressed as mean and standard deviation (in brackets) when indicated

COPD and non-COPD patients experienced a similar trend of variation for all the analyzed parameters.

Tab. 6. Physical and psychological variation for COPD and non-COPD patients within the VATS group

	COPD (68)			**non-COPD (74)**			**variation comparison**		
VARIABLE	preop	postop	p.value	preop	postop	p.value	COPD	nonCOPD	p.value
fev1	83,9 (18,5)	79,3 (18,6)	0,002	96,4 (19,8)	86 (18)	<0.001	-4,7	-9,4	0,07
dlco	72,1 (19,9)	63,7 (18,4)	<0.001	80,7 (17,2)	70 (15,8)	<0.001	-11	-11	0,9
vo2max	16,1 (3,52)	16 (3,1)	0,1	17,2 (3,93)	15 (3,8)	0,002	-3,4	-10,0	0,1
QL2	72,3 (20,2)	74,7 (17,8)	0,6	73,0 (18,3)	71 (19,6)	0,4	9,8	1,8	0,3
PF2	88,7 (15,7)	84,5 (13,9)	0,007	90,1 (11,3)	83,4 (13,2)	<0.001	-2,5	-6,0	0,3
RF2	92,8 (14)	91,2 (15,0)	0,8	92 (14,3)	85,6 (20)	0,08	3,1	-2,8	0,3
EF	79,0 (16,9)	82,9 (16,0)	0,3	79,9 (17,3)	78,3 (18)	0,8	7,4	2,7	0,4
CF	90 (14,8)	89,5 (14,1)	0,9	93,5 (11,2)	87,9 (14)	0,03	3,0	-2,9	0,2
SF	94,1 (14,8)	93,8 (12,3)	1,0	92,1 (13,3)	89,5 (17,1)	0,3	5,00	-0,90	0,3

Results are expressed as mean and standard deviation (in brackets) when indicated

Patients with cardiovascular disease had a postoperative negative variation of the VO2max index significantly higher than their counterparts (VO2max variation pts with cardiovascular disease: -10.7% vs VO2max variation pts without cardiovascular disease: -2.2%, p value: 0.04) (Tab. 7).

Tab. 7. Physical and psychological variation for cardiovascular disease and non-cardiovascular disease patients within the VATS group

	cardiovascular disease (86)			non-cardiovascular disease(56)			variation comparison		
VARIABLE	preop	postop	p.value	preop	postop	p.value	cardiov	non cardiov	p.value
fev1	90,6 (20,7)	83,1 (18,4)	<0,001	90,3 (19)	82,6 (19)	<0,001	-6,8	-7,5	0,8
dlco	76,3 (20,1)	67 (17)	<0,001	77,1 (17,1)	67,3 (17,9)	<0,001	-10,7	-11,3	0,9
vo2max	16,2 (3,2)	14,6 (3,2)	<0,001	17,3 (4,3)	16,6 (3,5)	0,3	-10,7	-2,2	0,05
QL2	73,7 (19,2)	72,3 (18)	0,7	71,4 (19,1)	73,4 (19,6)	0,9	4,4	7,1	0,7
PF2	86,6 (15,6)	82 (14,3)	0,02	93,3 (8,8)	86,3 (11,9)	<0,001	-1,9	-7,7	0,08
RF2	90,3 (16,4)	88 (17,4)	0,6	95,5 (9,6)	89,1 (18,2)	0,07	3,7	-4,8	0,2
EF	79,8 (16,8)	80 (17,4)	0,4	79,2 (17,5)	81,6 (16,9)	0,7	3,8	6,3	0,7
CF	89,4 (13,2)	86,7 (13,7)	0,1	94,8 (12,5)	91,8 (14,1)	0,7	-1,5	1,5	0,5
SF	91,9 (14,4)	92 (12,7)	0,6	94,4 (13,5)	90,5 (18,3)	0,1	5,4	-2,7	0,2

Results are expressed as mean and standard deviation (in brackets) when indicated

The complicated patients reported a greater reduction of the postoperative physical functioning scale in comparison to the non-complicated ones (PF2 variation complicated: -14.9% vs PF2 variation non-complicated: -3.6% p value: 0.04) (Tab.8).

Tab. 8. Physical and psychological variation for complicated and non-complicated patients within the VATS group

	complicated (13)			non complicated (129)			variation comparison		
VARIABLE	preop	postop	p.value	preop	postop	p.value	compl	non-compl	p.value
fev1	87,3 (20,8)	78,7 (11,9)	<0,001	90,8 (20,1)	83,3 (19,1)	<0,001	-6,4	-7,2	0,9
dlco	84,5 (24)	68,8 (16,2)	0,01	75,8 (18,3)	67,0 (17,5)	<0,001	-16,5	-10,4	0,2
vo2max	16 (2,6)	13,6 (3,3)	0,1	16,7 (3,9)	15,7 (3,4)	0,002	-13,6	-6,2	0,4
QL2	79,8 (13,5)	80,3 (15,5)	0,8	72,2 (19,4)	72 (19)	0,8	7,1	5,5	0,9
PF2	91,4 (7,4)	80,0 (12,4)	0,01	89,3 (13,8)	84,3 (13,6)	<0,001	-14,9	-3,6	0,05
RF2	85,7 (24,4)	87,5 (17,6)	1	93,0 (13,1)	88,4 (17,7)	0,09	1,8	-1,4	0,6
EF	84,5 (21,2)	79 (12,6)	0,4	79,2 (16,8)	80,7 (17,6)	0,3	-2,7	5,5	0,4
CF	88,1 (18,5)	83,3 (15,9)	0,4	92 (12,7)	89,3 (13,8)	0,3	-4,3	-1,6	0,4
SF	95,2 (8,1)	91,7 (24,1)	0,6	92,9 (14,3)	91,5 (14)	0,6	-6,2	2,4	0,5

Results are expressed as mean and standard deviation (in brackets) when indicated

III.3 *Open vs VATS comparison*

The 85 VATS patients able to entirely complete the preoperative evaluation as well as the 3 months follow up were then matched to the open ones (112 patients), in order to compare the functional loss (FEV1, DLCO and VO2max reduction) after VATS vs open lobectomy.

The table 9 shows the comparison of the baseline, surgical and postoperative characteristics of the two groups before the matching procedure.

Considering the baseline characteristics, the VATS lobectomy patients seemed to be older, with higher FEV1 values (open FEV1: 84.8 vs VATS FEV1: 93.2) but lower DLCO (open DLCO: 82,8 vs VATS DLCO: 77). The mean VO2max was similar in the two groups.

Moreover there was an higher proportion of patients with cardiac disease within the VATS patients (CAD for VATS: 50.5% vs for open: 22.3% and cardiac failure rate for VATS: 5.6% vs for open 0.6%), but with low ECOG and CCI scores . Finally the pack-years indicator was higher for the open patients.

Tab. 9. Characteristics of open and VATS lobectomy patients before matching

VARIABLE	open (112)	vats (85)	p.value
baseline characteristics			
age (years)	66,2 (9,8)	69,3 (10,5)	0,04
bmi	26,3 (4,1)	25,8 (4,4)	0,47
fev1	84,8 (18,2)	93,2 (19,5)	0,003
fev1/fvc	0,7 (0,1)	0,7 (0,1)	0,76
dlco	82,8 (20,7)	77 (19,3)	0,05
vo2max	16,7 (4)	17 (3,7)	0,42
pack-years	45,9 (36)	32,3 (30,3)	0,005
sex (M)%	81	63,8	0,01
ecog (low)%	58	73,5	0,04
cci (low)%	58,0	61,4	0,7
IA (yes)%	47,3	48,2	0,9
CAD (yes)%	22,3	50,5	<0,001
aritmia.pre (yes)%	10,7	13,2	0,7
cardiac.fail.pre (yes)%	0,6	5,6	0,02
cerebrovasc.pre (yes)%	6,8	5,6	0,7
vasculop.pre (yes)%	8,0	4,8	0,5
surgical and postoperative characteristics			
operation time (min)	182 (64,8)	197,4 (50,4)	0,02
air-leak (days)	2,1 (5,2)	1,9 (4,7)	0,7
pleural effusion (ml)	671 (408)	460 (231)	<0,001
hospital stay (days)	7,1 (7,4)	5,4 (3,8)	0,01
extended resection (yes)%	7,9	2,1	0,04
chest wall (yes)%	1,1	1	0,7
morphology (primary)%	89,8	90,8	0,2
pT (low)%	45,1	64,1	<0,001
pN (low)%	96,6	92,2	0,1
compl.tot (yes)%	26,5	20,4	0,2
compl.cardiopulm (yes)%	14,7	9,1	0,1
compl.cardiac (yes)%	6,8	2,8	0,1
compl.pulm (yes)%	7,9	6,3	0,3

Results are expressed as mean and standard deviation (in brackets) when indicated

The propensity score yielded 83 well-matched pairs of open and VATS patients. The table 10 reports the results of the comparison between the open and VATS matched patients.

All the variables selected for the matching procedure resulted not different between the two groups, with the exception of the rate of patients with CAD, that was still grater for the VATS patients group (CAD rate open patients: 28.9% vs CAD rate VATS patients: 50.6%, p value: 0.01).

In the postoperative period the VATS patients experienced a lower pleural effusion and a shorter hospital stay than their open counterparts (hospital stay open patients: 6.3 days vs hospital stay VATS patients 4.6 days, p value < 0.001).

TABLE 10 Characteristics of open and VATS lobectomy patients after matching

VARIABLE	open (83)	vats (83)	p.value
baseline characteristics			
age (years)*	66,7 (10,2)	69,3 (10,5)	0,1
bmi*	26,3 (4,2)	25,8 (4,3)	0,5
fev1/fvc*	0,71 (0,1)	0,7 (0,1)	0,6
pack-years*	40,3 (30,1)	32,4 (30,3)	0,09
sex (M)%*	77,10	63,8	0,09
ecog (low)%*	65,10	73,40	0,3
cci (low)%*	56,60	61,40	0,6
IA (yes)%*	36,10	48,20	0,1
CAD (yes)%*	28,90	50,60	0,01
aritmia.pre (yes)%*	8,40	13,20	0,4
cardiac.fail.pre (yes)%	1,20	9,60	0,06
cerebrovasc.pre (yes)%	7,20	6,00	1
vasculop.pre (yes)%*	7,20	4,80	0,7
surgical and postoperative characteristics			
operation time (min)	189,9 (72,2)	200,9 (53,2)	0,3
air-leak (days)	2,1 (4,9)	1,1 (3)	0,1
pleural effusion (ml)	675,8 (329,6)	471,9 (239,2)	<0,001
hospital stay (days)	6,3 (3,7)	4,6 (2,4)	<0,001
extended resection (yes)%	8,4	3,6	0,3
chest wall (yes)%	0,0	1	1
morphology (primary)%*	94,0	95,2	0,5
pT (low)%*	42,2	56,6	0,08
pN (low)%*	94,0	90,4	0,6
compl.tot (yes)%	22,9	15,7	0,3
compl.cardiopulm (yes)%	16,9	9,6	0,6
compl.cardiac (yes)%	8,4	2,4	0,07
compl.pulm (yes)%	8,4	7,2	1

Results are expressed as mean and standard deviation (in brackets) when indicated

As reported in Tab. 11, even for the matched open and VATS patients, we found a decrease of the three months postoperative FEV1, DLCO and VO2max values in comparison to the preoperative ones (open patients' reduction: FEV1 -10%, DLCO -11.9%, VO2max -5.5%; VATS patients' reduction: FEV1 -7.2%, DLCO -10.6%, VO2max -6.9%).

The reductions in FEV1, DLCO and VO2max were similar in the matched open patients and VATS patients, with a Cohen effect size < 0.2 for all the comparisons, indicating negligible differences.

Tab.11 Comparison of FEV1, DLCO and VO2max variations between open and VATS matched patients

	open		**vats**		**variation comparison**			
	pre	post	pre	post	open	vats	p.value	choen
fev1	85,4	76,9	93,1	86,4	-10	-7,2	0,2	0,2
dlco	82,6	72,8	77	68,9	-11,9	-10,6	0,7	0,1
vo2max	17,4	16,4	17	15,8	-5,5	-6,9	0,6	0,1

These results are clearly demonstrated also by the bar charts and the box plots of Figure 2, 3 and 4. The box-plots show similar and consensual variations for both groups in all the functional variables. Moreover the bar charts have a similar trend of variation in the open and VATS matched patients and the columns are almost overlapping for the DLCO variation.

Fig. 2. FEV1 variation in open and VATS matched patients

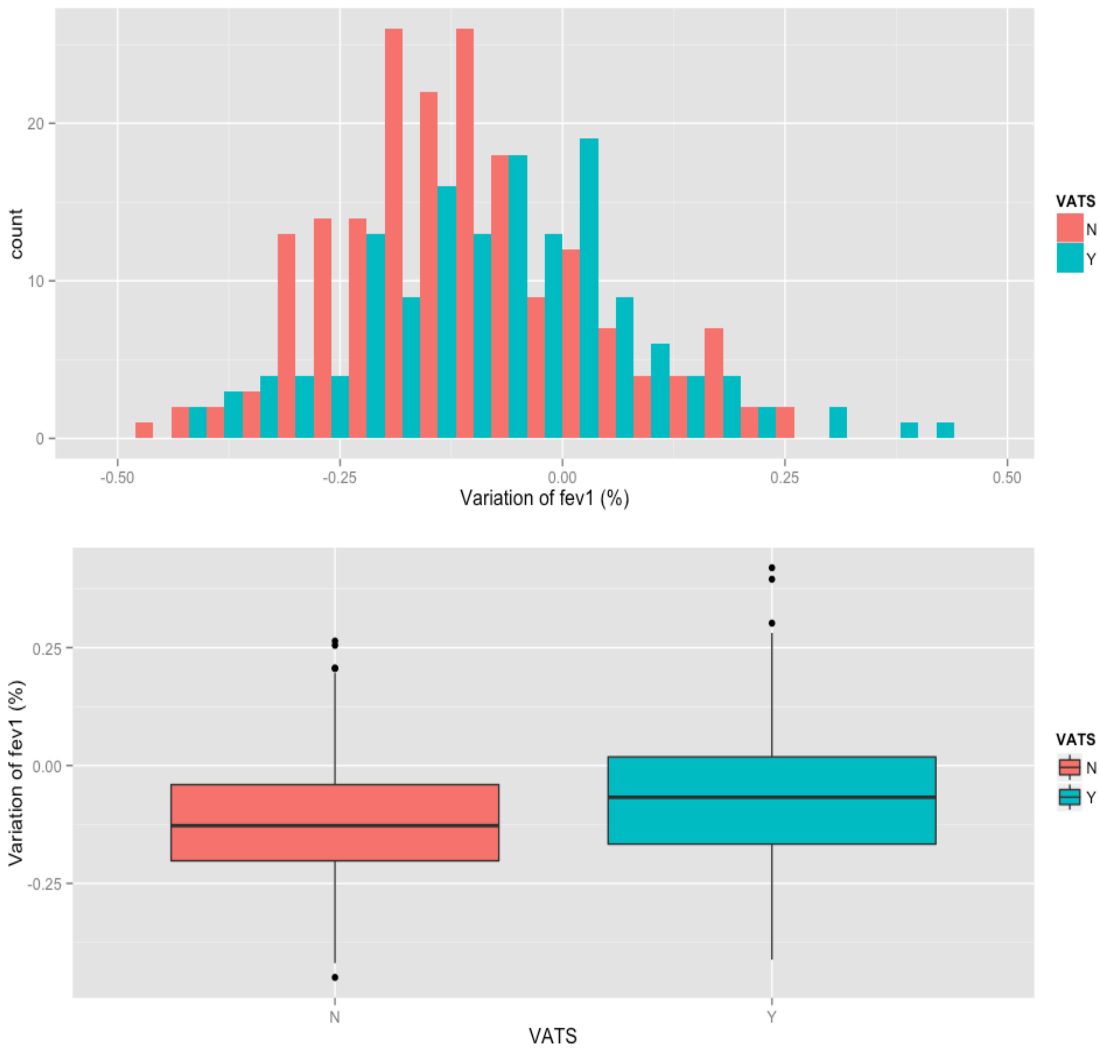


Fig. 3. DLCO variation in open and VATS matched patients

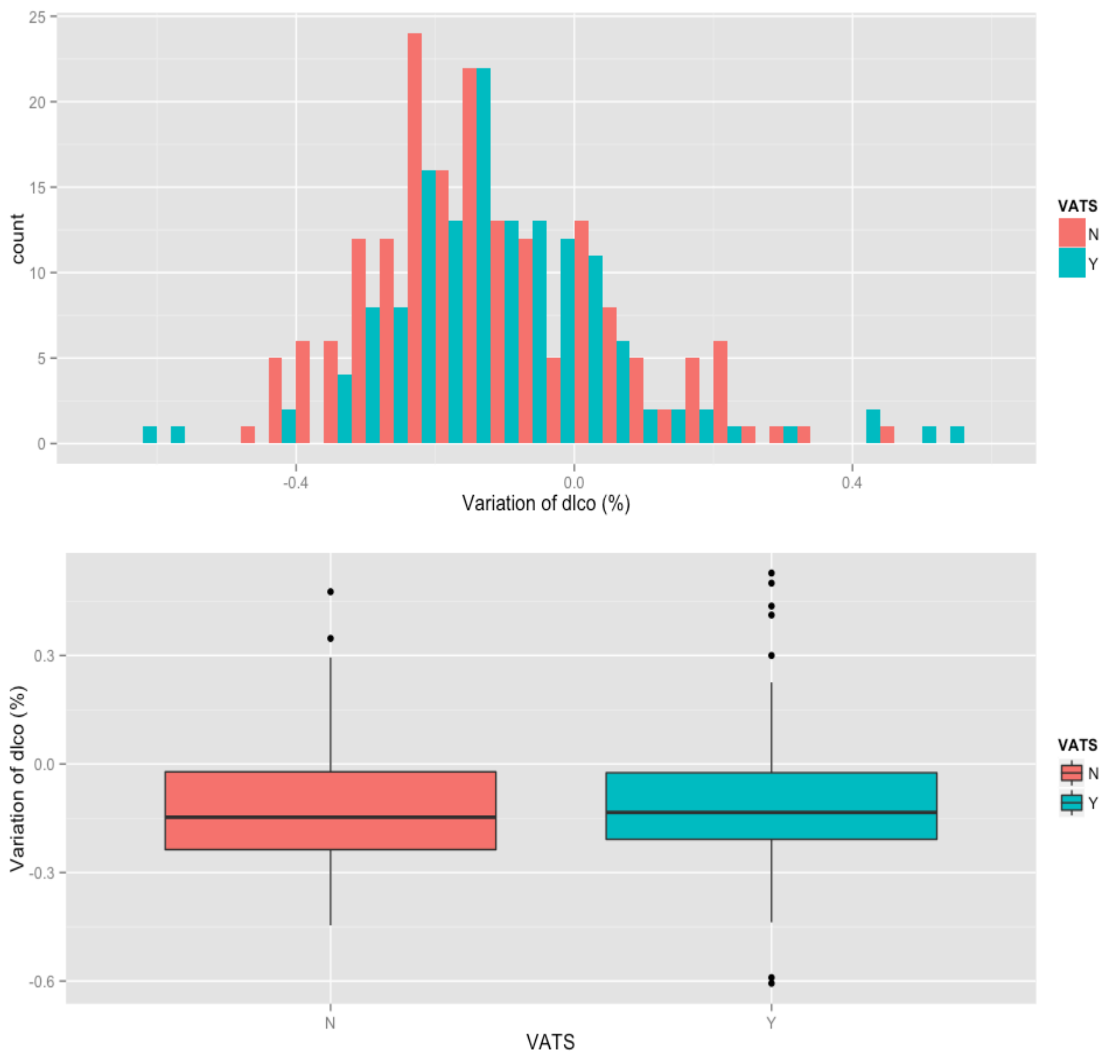
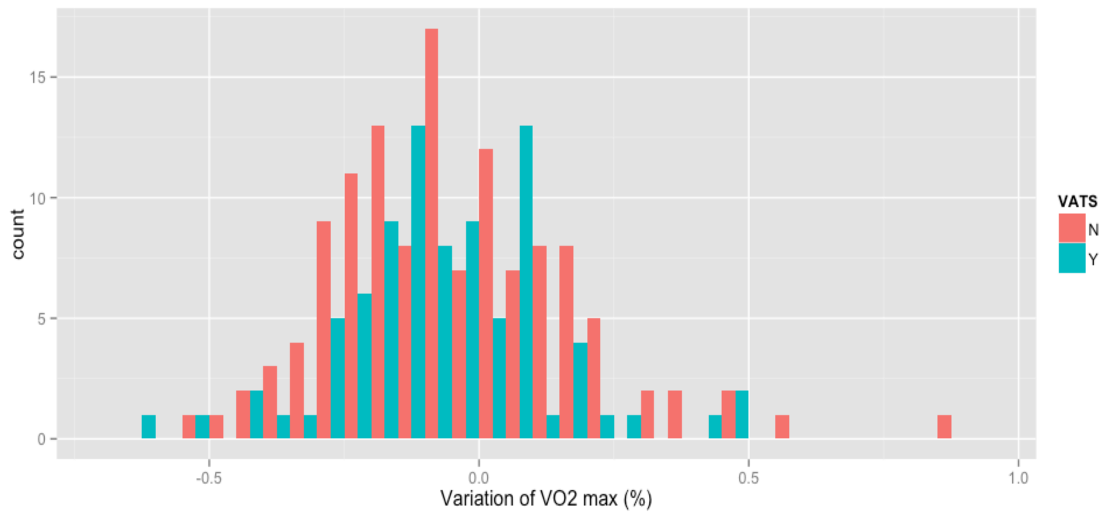
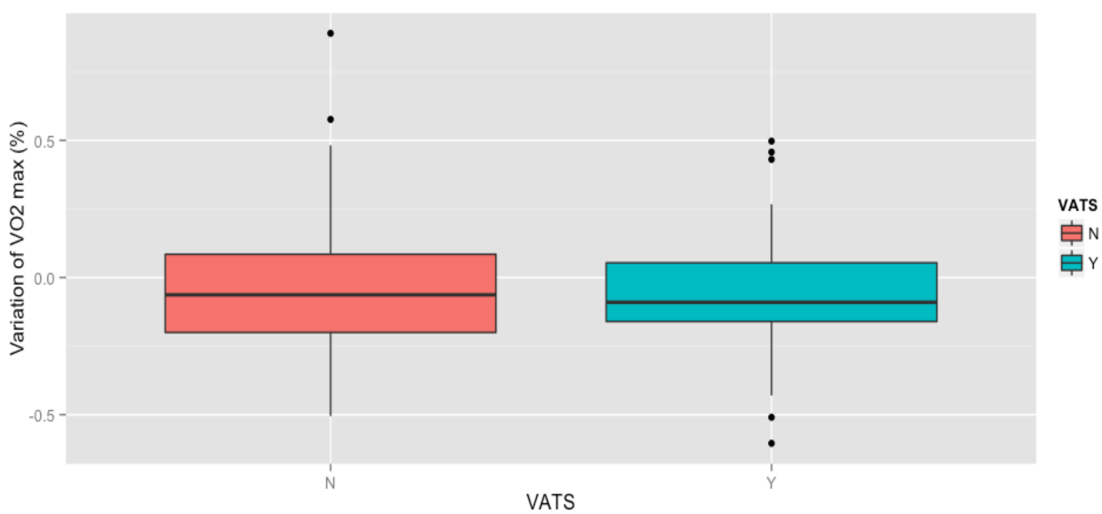


Fig. 4. VO2max variation in open and VATS matched patients





IV. DISCUSSION

The objective of the present study was to evaluate the changes of pulmonary function, exercise capacity and quality of life after pulmonary lobectomy for lung cancer performed through a VATS approach. Moreover we wanted to compare the physical changes of the VATS lobectomy patients to the ones registered in patients submitted to the traditional open lobectomy.

This study was conducted on a prospective series of patients operated on a single centre and managed preoperative and postoperatively using standardised protocols and pathways of care. Since we adopted (after completing during the previous two years the learning curve period) the VATS technique as the first choice approach for performing lobectomies in January 2012, we had the opportunity to study the functional and psychological impact of this novel approach in a three months follow up program. At the same time we could compare the VATS long term functional outcomes to the results obtained with the open lobectomies, performed since January 2010 and collected within our institutional prospective database.

At present, this represents the largest series of lung cancer surgical patients submitted to a systematic follow up program, where the physical examination consisted not only in a pulmonary function test and DLCO assessment but also in a direct measurement of the maximal oxygen uptake, using a formal high tech cardiopulmonary exercise test.

In order to investigate a stable postoperative physical and psychological condition minimising the dropout rate, we chose the 3-month period as evaluation time. In fact, the drop out rates could affect the results in follow-up studies as the patients who did not present at follow-up should presumably be considered the patients with worse conditions. This could falsely improve the results for a selection bias, elsewhere indicated as “cream-skimming” effect (37). Indeed, 26% of patients evaluated at 3 month dropped out for several reasons (recurrence, adjuvant chemotherapy, onset of further diseases, refusal to show at follow-up).

Focusing on the physical indicators variation three months after the VATS lobectomy operation, we found a reduction for each of them. The mean DLCO loss from the preoperative values was remarkable (-12.4%) and with potential clinical relapses, especially for those patients with a preoperatively impaired lung diffusion capacity (i.e. patients with pulmonary hypertension, interstitial lung disease, COPD) . This seems in line with the DLCO reduction observed in previously published papers, for patients submitted to pulmonary open lobectomy (38). Moreover we registered for the FEV1 and the DLCO an higher drop at three months in comparison to the one observed for the VO2max. This result corroborates the findings of other studies on patients submitted to open major lung resection, which argued that a more complete recovery of exercise tolerance, compared to the airflow and gas exchange capacities, is presumably due to compensatory mechanisms related to the cardiovascular system and the peripheral oxygen extraction capacity (38, 39).

Then we analysed the FEV1, DLCO and VO2max variation three months after the VATS lobectomy in some subgroups of patients, in order to verify the reliability of the results found on the general population.

The sub-analysis revealed a similar reduction of the functional parameters for all the groups considered. Nevertheless, we found that younger patients had an higher loss of the three months FEV1 than the one registered for the elderly. This finding may be explained by the fact that the lung resection in young patients implies the loss of more healthy pulmonary tissue, while the elderly sacrifice an higher proportion of emphysematous lung (which contributes less to the respiratory function). On the other hand we didn't observe a different level of FEV1 reduction when we compared the COPD vs non-COPD subgroups of patients.

Moreover we found that patients affected by cardiovascular disease had lower VO2max preoperative values than their counterparts. Furthermore, the cardiovascular patients experienced an higher reduction of their exercise capacity in comparison to the healthier patients.

This trend of postoperative reduction observed in the physical indicators was also perceived by the patients. In fact, the EORTC results showed that they experienced a relevant worsening of the physical functioning scale.

On the opposite site, the three months global health perception as well as the other functional scales evaluated by the EORTC were not different from the preoperative correspondent values. This suggest that, even after a minimally invasive major lung resection aimed at curing a neoplastic disease, the patients did't consider this treatment as a crucial step to improve their quality of life. They rather complained about an impairment of their preoperative physical performance. Moreover, in the subgroup analysis, we found that the patients which experienced postoperative complications perceived a even greater reduction of the postoperative physical functioning scale in comparison to the non-complicated ones. A similar trend of the perceived quality of life was found in other studies, although performed using different questionnaires and examining open lobectomy patients (40, 41).

The propensity score matching procedure gave us the possibility of comparing the physical parameters' variations three months after the operation between two homogeneous groups of open and VATS lobectomy patients.

We found a postoperative reduction of FEV1, DLCO and VO2max for both groups. Even in this case the rate of reduction was lower for the exercise capacity.

The most interesting results is represented by the consensual variation for all the physical parameters both in the open and VATS lobectomy patients. This means that the VATS lobectomy approach didn't offer any functional advantage in a three months perspective. The physical performance recovery seemed to reach the same level irrespectively to the surgical approach considering a long term follow up, in contrast to the findings reported by studies which analyses the short term recovery of the functional status after VATS lobectomy (42,43).

IV.1 *Limitations*

A possible limitation of this study is one common to most of the follow-up analyses and concerns the patients who dropped out. As these patients could have been patients with the worst functional status, their inclusion in the analysis could have perhaps changed the results, and this should be taken into account when interpreting the results.

A certain proportion of our patients received adjuvant chemotherapy. As chemotherapy has been proven to impair gas exchange, the inclusion of these patients could have influenced the results. However, only 17 patients studied at 3 months were submitted to adjuvant chemotherapy. We decided to include theme after a preliminary analysis that did not show differences in PFT results and VO2max at 3 months compared to the other patients

We couldn't compare the three months postoperative mental status of open vs VATS lobectomy patients as we didn't collect the EORTC C30 results of the open patients within our institutional prospective database.

IV.2 *Conclusions*

The VATS lobectomy influences a reduction of the preoperative functional status three months after the operation.

The reduction of FEV1 and DLCO is partially covered by compensatory mechanisms and the global exercise capacity is almost completely restored three months postoperatively.

The VATS lobectomy doesn't affect the postoperative perceived global quality of life. Nevertheless the patients, even after a minimally invasive approach, felt a worsening of their physical functioning.

In a three months perspective, the VATS lobectomy doesn't offer any advantage in terms of FEV1, DLCO and exercise capacity recovery in comparison to the muscle-sparing thoracotomy approach.

V. **REFERENCES**

1. World Cancer Report 2014. World Health Organization. 2014. pp. Chapter 1.1. ISBN 9283204298.

2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. Cancer J Clin 2012;62(1):10-29.

3. National Cancer Institute. Surveillance, epidemiology, and end results: US National Institutes of Health. http://seer.cancer.gov/statfacts/html/lungb.html Accessed February 2016.

4. Goldstraw P, Crowley J, Chansky K et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumors. J Thorac Onc 2007; 2:706-14.

5. Handy, John R., et al. "What happens to patients undergoing lung cancer surgery?: Outcomes and quality of life before and after surgery." CHEST 2002: 122: 21-30.

6. Treatment Of Stage I And Ii Non-Small Cell Lung Cancer. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Chest 2013; 143 (5_suppl):e278S-e313S.

7. Raja M. Flores, Bernard J. Park, Joseph Dycoco, Anna Aronova, Yael Hirth, Nabil P. Rizk, Manjit Bains, Robert J. Downey, Valerie W. Rusch. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg. 2009 July; 138(1): 11–18.

8. Christopher Cao, Con Manganas, Su C. Ang, Sheen Peeceeyen, Tristan D.

Yan. Video-assisted thoracic surgery versus open thoracotomy for non-small cell lung cancer: a meta-analysis of propensity score-matched patients. Interact Cardiovasc Thorac Surg. 2013 March; 16(3): 244–249.

9. Subroto Paul, Art Sedrakyan, Ya-Lin Chiu, Abu Nasar, Jeffrey L. Port, Paul C. Lee, Brendon M. Stiles, Nasser K. Altorki. Outcomes after lobectomy using thoracoscopy vs thoracotomy: a comparative effectiveness analysis utilizing the Nationwide Inpatient Sample database. Eur J Cardiothorac Surg. 2013 April; 43(4): 813–817.

10. Emanuela Taioli, Dong-Seok Lee, Martin Lesser, Raja Flores. Long-term survival in video-assisted thoracoscopic lobectomy vs open lobectomy in lung-cancer patients: a meta-analysis. Eur J Cardiothorac Surg. 2013 October; 44(4): 591–597.

11. Natasha M. Rueth, Rafael S. Andrade. Is VATS lobectomy better: perioperatively, biologically and oncologically? Ann Thorac Surg. 2010 June; 89(6): S2107–S2111.

12. A. Brunelli, A. Charloux, C. T. Bolliger, G. Rocco, J-P Sculier, G. Varela, M. Licker, M. K. Ferguson, C. Faivre-Finn, R. M. Huber, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009 July; 34(1): 17–41.

13. Lim, E, Baldwin, D, Beckles, M et al. Guidelines on the radical management of patients with lung cancer. Thorax. 2010; 6: 1–27.

14. Markos J, Mullan BP, Hillman DR, Musk AW, Antico VF, Lovegrove FT, Carter MJ, Finucane KE. Pre-operative assessment as a predictor of morbidity, and

mortality after lung resection. Am Rev Resp Dis 1989; 139: 902 – 910

15. Brunelli, A., Fianchini, A. Predicted postoperative FEV1 and complications in lung resection candidates. Chest. 1997;111:1145–1146.

16. Ferguson, M.K., Little, L., Rizzo, L. et al, Diffusing capacity predicts morbidity and mortality after pulmonary resection. J Thorac Cardiovasc Surg. 1988;96:894–900.

17. Wang J, Olak J, Ferguson MK. Diffusing capacity predicts operative mortality but not long-term survival after resection for lung cancer. J Thorac Cardiovasc Surg 1999; 117: 581 – 587

18. Brunelli A, Al Refai MA, Salati M, Sabbatini A, Morgan-Hughes NJ, Rocco G. Carbon monoxide lung diffusion capacity improves risk stratifica- tion in patients without airflow limitation: evidence for systematic measurement before lung resection. Eur J Cardiothorac Surg 2006; 29: 567 – 570

19. Brunelli A, Refai M, Salati M, Xiumé F, Sabbatini A. Predicted versus observed FEV_1 and Dlco after major lung resection: a prospective evaluation at different postoperative periods. Ann Thorac Surg 2007;83:1134–9.

20. Brunelli, A., Xiumé, F., Refai, M., Salati, M., Marasco, R., Sciarra, V., & Sabbatini, A. (2007). Evaluation of expiratory volume, diffusion capacity, and exercise tolerance following major lung resection: a prospective follow-up analysis. CHEST Journal, 131(1), 141-147.

21. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery. ACCP evidenced-based clinical practice guidelines (2nd edition). Chest

2007;132: 161S–77S.

22. Holden DA, Rice TW, Stelmach K, Meeker DP. Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. Chest 1992;102: 1774 –9.

23. Brunelli A., Refai M., Xiume F., Salati M., Sciarra V., Socci L., Sabbatini A. Performance at Symptom-Limited Stair-Climbing Test is Associated With Increased Cardiopulmonary Complications, Mortality, and Costs After Major Lung Resection. Ann Thorac Surg 2008;86:240-248.

24. Benzo R, Kelley GA, Recchi L, et al. Complications of lung resection and exercise capacity: a meta-analysis. Respir Med. 2007;101:1790-1797.

25. Loewen GM, Watson D, Kohman L, et al. Preoperative exercise V̇o2 measurement for lung resection candidates: results of Cancer and Leukemia Group B Protocol 9238. J Thorac Oncol. 2007;2:619-625.

26. Brunelli A, Salati M. Preoperative evaluation of lung cancer: predicting the impact of surgery on physiology and quality of life. Curr Opin Pulm Med. 2008;14:275-281.

27. Pompili C. Quality of life after lung resection for lung cancer. Journal of Thoracic Disease. 2015;7(Suppl 2):S138-S144.

28. Salati M, Brunelli A, Xiume F, et al. Quality of life in the elderly after major lung resection for lung cancer. Interact Cardiovasc Thorac Surg 2009;8:79–83.

29. Pompili C, Brunelli A, Xiumé F, Refai M, Salati M, Sabbatini A. Predictors of postoperative decline in quality of life after major lung resections. Eur J Cardiothorac Surg. 2011 May; 39(5): 732–737.

30. Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party. Standardization of lung function tests. European Community for Steel and Coal. Official statement of the European Respiratory Society. Eur Respir J 1993;6(Suppl 16):5– 40.

31. National Institutes of Health, National Heart, Lung and Blood Institute. Global strategy for the diagnosis, manage- ment, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Workshop Report. Update 2003. www.goldcopd.com.

32. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.

33.Database report silver book 2011. Available on line: http://www.ests.org/documents/PDF/Database_silver_book_ 2011.pdf Accessed November 9, 2011.

34. Brunelli A, Rocco G, Van Raemdonck D, et al. Lessons learned from the European thoracic surgery database: the Composite Performance Score. Eur J Surg Oncol 2010;36Suppl 1:S93-9.

35. Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg 2002;123:8–15.

36. Michelson H, Bolund C, Nilsson B, Brandberg Y. Health-related quality of life measured by the EORTC QLQ-C30: reference values from a large sample of the Swedish population. Acta Oncologica, 2000;39:477-484. DOI: 10.1080/028418600750013384.

37. Bolliger CT, Jordan P, Soler M, et al. Pulmonary function and exercise capacity after lung resection. Eur Respir J 1996; 9:415– 421.

38. Brunelli, A., Xiume, F., Refai, M. et al, Evaluation of expiratory volume, diffusion capacity, and exercise tolerance following major lung resection: a prospective follow-up analysis. Chest. 2007;131:141–147.

39. Nugent AM, Steele IC, Carragher AM, et al. Effect of thoracotomy and lung resection on exercise capacity in patients with lung cancer. Thorax 1999; 54:334–338.

40. Win T, Sharples L, Wells FC, Ritchie AJ, Munday H, La Roche CM. Effect of lung cancer surgery on quality of life. Thorax 2005;60:234–8.

41. Brunelli A, Socci L, Refai M, Salati M, Xiumé F, Sabbatini A. Quality of life before and after major lung resection for lung cancer: a prospective follow-up analysis. Ann Thorac Surg 2007;84:410 – 6.

42. Pulmonary function after lobectomy: video-assisted thoracic surgery versus thoracotomy. Nakata, Masao et al. The Annals of Thoracic Surgery , Volume 70 , Issue 3 , 938 - 941.

43. Pulmonary function after pulmonary resection by posterior thoracotomy, anterior thoracotomy or video-assisted surgery.Hideki Endoh, Shigebumi Tanaka, Toshiki Yajima, Tomokazu Ito, Kohei Tajima, Akira Mogi, Yoshinori Shitara, Hiroyuki Kuwano. Eur J Cardiothorac Surg. 2010 May; 37(5): 1209–1214.