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FACULTY OF MEDICINE

Prediction of complications and lung ventilation function after lung cancer operation

Summary of promotion thesis to acquire a PhD degree in surgery, oncology and hematology

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Explanations of abbreviations.

Abbreviation	Explanation
Ca	carcinoma
DL _{CO}	CO diffusion capacity
FEV ₁	Forced expiratory volume in the 1th second
FEV ₁ %	Forced expiratory volume in the 1th second % predicted
FVC	Forced vital capacity
COPD	Chronic Obstructive Pulmonary Disease
HSM	Chronic Cardiac failure
BMI	body/mass index
MVV	Maximal voluntary ventilation
N, N1, N2	Nodus
pPa	Pulmonary artery pressure
paCO ₂	Arterial carbon dioxide pressure
paO ₂	Arterial oxygen pressure
ppo	Predicted post operative
PVR	Pulmonary vascular resistance
T, T1, T2, T3, T4	Tumor, according TNM clasification
TEA	Thoracic epidural analgesia
TNM	TNM classification for tumors staging
TUPAO	Temporary unilateral occlusion of pulmonary artery

Table of content

Table of content.....	1
Introduction	2
Currently applied methods for operative risk prediction.	5
Role of lung ventilation reserve.....	5
Statistical analysis of risk factors.....	6
Simultaneous analysis of several risk factors.	6
Hypotheses proposed for defense.....	7
Aim of research.	7
Objectives of research.	8
Material and methods.	8
Type of study, permission of ethics committee	8
Study population.....	8
Methods of patient examination	8
Data collection and methods of statistical processing.....	9
Results	10
General characteristics of patients.	10
Lung ventilation function early after the operation.....	16
Ventilation function after lobectomy	19
Ventilation function after pneumonectomy	20
Complication risk factors.....	20
Logistic regression.....	21
Discussion.	22
Preoperative findings.....	22
Lung ventilation function changes as a result of the operation...	24
Operation risk factors	26
Binary logistic regression.	29
Conclusions.	30
Novelty of research.....	31
Practical importance of research.....	32
Publications on the research theme.....	33
Reports on research theme.....	34
Approbation of research work.	38
Appendix.	39

Introduction

Lung cancer worldwide takes the leading position as to mortality rate among other oncological diseases (Skuladdottir and Olsen, 2001; Sakkaraiappan and Belani, 2002), as to the incidence rate, lung cancer takes the 10th place in the cause of mortality, it causes about 1 million deaths a year (Lange and Vestbo, 2000). In Latvia lung cancer is also the most common oncological disease among males (Baško, 2001) and one of the most common among females (Cancer Register, 2002). Successful lung cancer resection is the best and, in fact, the only way to treat this disease completely (Anderson and Allen, 2001). If diagnosed early, limited tumor extirpation accounts for 80% 5-year survival time (Deslauriers, 2002), on average the survival time after nonsmall cell lung cancer operations makes 50% (Osaki, Oyama et al., 2001; Deslauriers, 2002), while for non-operated patients, treated by other methods available – radiotherapy and chemotherapy, 5-year survival time is only 3-5% (Skuladottir and Olsen, 2001; Birim, Kappetein et al., 2005). One can conclude that radical operative treatment is the best choice, since patients show better survival rates (Rocmans, 2001; Szoke, Trojan et al., 2004). However, according to the literature and State Centralized Cancer register data, at present in Europe and in Latvia as well, only 10-20% patients with nonsmall cell lung cancer, being diagnosed for the first time, are operated on (Brutsche, Spiliopoulos et al., 2000; Rocmans, 2001; Baško, 2002; CancerRegister, 2002; Rostad, Strand et al., 2006). Why 80-90% patients are refused the operation? Contraindications for the operation in lung cancer cases are of two types (Semik, Schmid et al., 2001). Firstly, resectability, which is also called surgical resectability, i.e. – whether the tumor can be technically removed completely. Unfortunately, in lung cancer cases, majority of patients at the time of making a diagnosis are found to have distant stages (Kudaba and Žītare, 1999; Baško, 2001; Cancerregister, 2002; Rostad, Naalsund et al., 2002; Spiro and Silvestri, 2005), when no operation can be done (extension into the heart, second side major bronchus, spine), or it is unpurposeful – tumor invasion N3 in lymph nodes or distant metastases are present.

Secondly, operability or functional resectability, i.e., whether a patient's lung functional reserve, the heart status allow to perform the operation, whether the patient can endure the operation (Semik, Schmid et al., 2001).

In difference to other surgeries, lung parenchyma resection operation does not affect the appearance (e.g., in cosmetic surgery), or a patient's working capabilities (e.g., in traumatology), but actively affects vital functions. Patients, who are going to have a lung surgery, are at risk of complications due to two reasons connected with lungs: firstly, due to reduction of alveolar surface and, secondly, due to increase of pressure in the lesser circulatory system. Besides these two factors we have to add limitations caused by operation trauma. The operation trauma, because of pain syndrome, restricts thoracic excursions and causes additional ventilation failure, which has to be taken into consideration in the postoperative period. Such operations like lobectomy or pneumonectomy, as a result of which the functioning part of parenchyma gets reduced, decreases the lung functional reserves. If the lung function prior to the operation is not essentially impaired, then even pneumonectomy does not produce a health threatening lung function failure. However, the evacuation of a part of the lung to a patient with the existing lung functional failure may cause essential gas exchange disorders. Unfortunately, many patients who need surgical management because of lung cancer are smokers with a long smoking history and a concomitant disease – COPD (chronic obstructive pulmonary disease). As a result, irreversible airways obstruction develops which results in ventilation failure.

The advances in surgical and anaesthesiological technologies make it possible to operate on more elderly patients (Akopov and Chernyi, 2005; Dienemann, Hoffmann et al., 2005; Fukuse, Satoda et al., 2005; Mery, Pappas et al., 2005; Ramesh, Pope et al., 2005; Yamashita and Haga, 2005), as well as on such patients, who due to concomitant diseases seemed earlier to be inoperable (McKenna, Fischel et al., 1996; Riedel and Schulz, 1999; Wyser, Stulz et al., 1999; Gaballo, Corbo et al., 2004).

However, despite a comprehensive preoperative examination, risk factor assessment and the intensive therapy in the postoperative period, lung resection operations are characteristic of a comparatively great complication rate – 30-50% (Stephan,

Boucheseiche et al., 2000; Uramoto, Nakanishi et al., 2001) and a high perioperative mortality – 1.6 – 5% after lobectomies (Harpole, DeCamp et al., 1999; Brutsche, Spiliopoulos et al., 2000; Osaki, Oyama et al., 2001) and 5-12% after pneumonectomy (Harpole, DeCamp et al., 1999; Spiliopoulos and de Perrot, 2000; Stephan, Boucheseiche et al., 2000; Alexiou, Onyeaka et al., 2002; Toker, Dilege et al., 2004). Besides, lethality early after operations is found usually not to be connected with a primary oncological disease, but just with the operation trauma (Welch and Black, 2002).

The most common causes of death in the early postoperative period are: acute respiratory distress syndrome, bronchopleural fistula with empyema, cerebrovascular disorders, acute coronary syndrome, cardiac arrhythmias (Rostad, Naalsund et al., 2004; Watanabe, Asamura et al., 2004).

A very important role in the assessment of the preoperative status is the operability, or functional resectability, and this role is increasing. More and more often the possibility to perform a radical operation is determined by concomitant diseases (Jeremic, 2003; Birim, Kappetein et al., 2005; Iwasaki, Shirakusa et al., 2005). The average age of patients with lung cancer is constantly growing (Varela, Novoa et al., 2000; Kudaba, 1999 #1511; Baško, 2001; Lopez-Encuentra, 2002), the outcome of a vast operation, which has to be done in extended tumor cases, to a great extent depends on a patient's ability to endure it (Dyzkiewicz, Piwkowski et al., 2004).

There is a border between a patient who can still be operated on, and who cannot be operated any more. This border is determined by a size of reduced lung parenchyma on one hand, and the patient's vital function reserve on the other hand. Doctors' aim is to try to foresee how the lung is going to function after the planned reduction of parenchyma size, whether the patient does not develop a severe respiratory failure, pulmonary hypertension, or some other complications. Since non-surgical lung cancer treatment results are still very poor, one should put a maximum effort to state this border of operability, and to identify those patients who can endure the operation.

Currently applied methods for operative risk prediction.

Role of lung ventilation reserve.

The development of operative and intensive therapeutic technologies has made it possible to decrease mortality and complication rate after lung cancer operations. Many factors are identified which allow to predict the development of an increased complication risk.

Patients with a normal ventilation function or a mild ventilation function failure and without a cumbersome cardiac history can endure any lung operation, even a pneumonectomy, without having any additional examination.

Patients with moderately severe and severe ventilation function failure need calculations to be done as to the prospective postoperative function by using anatomical or radionucleoid methods.

If the prospective postoperative ventilation function, calculated by current methods is bigger than 40%, the patient can be operated on (BTS-guidelines, 2001; Fujiu, Kanno et al., 2003).

Patients, whose calculated prospective postoperative ventilation function, by using the current methods is less than 40%, are seen to have more commonly postoperative complications. However, when making a thorough patient selection, even such patients can be operated on (Magdeleinat, Seguin et al., 2005). If such patients are performed lobectomy, one can even observe the improvement of postoperative ventilation function comparing it to the preoperative one. The threshold value of prospective postoperative ventilation function, below which patients are definitely inoperable, has not been specified yet. The same refers to the risk factors which have not been precisely defined, because even the patient group with $ppoFEV1 < 40\%$ and other risk factors can reach sufficiently low postoperative mortality indicators (Wyser, Stulz et al., 1999; Myrdal, Gustafsson et al., 2001; Linden, Bueno et al., 2005; Magdeleinat, Seguin et al., 2005). For instance, in the group of 21 patients the mortality 0 (Choong, Meyers et al., 2004), or 1 from 57 patients (Linden, Bueno et al., 2005).

The authoritative British Thoracic Surgical Association (BTS – guidelines., 2001) recommends to discuss such cases at multidisciplinary council, although it has not said what factors to analyze (Onder, D'Arco et al., 2004), because the unanimity is governing in the literature, stating that TNM is correlating well with prognosis, yet all the other parameters in each publication, are different (Birim, Kappetein et al., 2006).

Statistical analysis of risk factors.

As a result, it is clear now, what patients are able to endure a radical lung cancer operation with a slight postoperative complication and mortality risk.

There are identified threshold group patients, stating that the operation for them is with an increased risk, but to say exactly how big the risk is, remains unclear. In the same way there is an unsolved question about patients with several risk factors. There are publications saying that each of them increases the risk, but the interaction of the factors is not clear, as well as their cumulative effect, because one can find publications in the periodicals also about successful operations on patients with many risk factors simultaneously.

In the publications available only separate attempts have been made to analyze the patient's condition as a whole, as well as all comorbidities simultaneously. Up to now, all these attempts in the studies made, have turned out to be failures.

Simultaneous analysis of several risk factors.

There have been attempts to apply physiologic, in order to analyze all possible risk factors simultaneously, by using the risk factors – pain, weight loss, T, FEV1, albumin concentration in serum, SaO2, smoking history, erythrocyte and leukocyte count. Authors, by analyzing 91 patient data, have succeeded to work out an acceptable complication prediction model (Turna, Mercan et al., 2005). When doing a multifactor analysis, no credible complication prediction

model has been worked out (Lopez-Encuentra, Pozo-Rodriguez et al., 2004).

In the literature one can find only 3 reports on binary logics being used for prediction of lung cancer operation outcome.

1. The author analyzes 37 pneumonectomies, and finds incompletely performed resection as being the risk factor (Dyszkiewicz, Piwkowski et al., 2004).

2. 108 patients are analyzed, but only separate risk factors are specified, not designing a total risk factor prediction model (Hollaus, Wilfing et al., 2003).

3. By inserting all probable risk factors into the model, one can conclude that the total model does not allow to predict the operation outcome (Varela, Jimenez et al., 2003).

The effect and duration of lung volume reduction operation, as well as optimal patient selection criteria are still not clearly defined. As a result, although experimentations are successful with a limited range of patients who have lung cancer and functional parameters correspond to the lung volume reduction to a patient, such patient selection criteria have not been worked out yet.

Hypotheses proposed for defense.

Currently used methods for predicting postoperative lung ventilation function are inaccurate, lung volume reduction effect must be taken in to account.

The operation risk for patients with several risk factors concomitantly could be established, using binary logistic analysis.

Aim of research.

To analyze nonsmall cell lung cancer operation risk factors in order to determine their effect on early development of postoperative complications.

Objectives of research.

To analyze radical lung cancer operation – lobectomy, bilobectomy and pneumonectomy complications.

To analyze lung ventilation function changes due to the operation.

To specify a formula for predicting the ventilation function changes.

To analyze the complication risk factors and to make an algorithm for predicting a high operation risk.

Material and methods.

Type of study, permission of ethics committee

The study was accepted by State stock-holder company Pauls Stradiņš Clinical University Hospital Cardiology Institute Ethics Committee, conclusion Nr. 260504-82.

The type of study: prospective cohort study.

Study population

In total the data of all patients, who had undergone lobectomy, bilobectomy or pneumonectomy due to a primary lung cancer at P.Stradiņš CUH Centre of Thoracic Surgery within 5 years were analyzed (i.e. from January 1, 2000 till December 31, 2004). In total 449 patient data were analyzed, from them 390 were males and 59 females.

Methods of patient examination

Case history

The most common complaints were: cough – 321 patients or 71.5%, pain in the chest – 157 patients or 35%, and blood spitting – 116 patients or 26.8%. 13% patients mentioned elevated body temperature, but 45 patients (10%) did not have any complaints. Tumour in these patients was diagnosed in the prophylactic screening.

Additional examination methods

Prior to the operation the patients were examined according to a unified scheme. They were performed chest X-ray, computed tomography, lung ventilation functions by bronchodilatation examination, as well as electrocardiogram by 12 standard leads, fibrobronchoscopy and abdominal organ ultrasonoscopy. All patients were made coagulogram – prothrombin index, APTL, INR, fibrinogen.

All patients prior to the prospective operation were calculated the planned postoperative functions by using various methods.

Morphological verification of diagnosis

96% patients already before the operation were verified the diagnosis of malignant lung neoplasm.

Data collection and methods of statistical processing

We registered maximum of available preoperative examination, intraoperative data, as well as postoperative complications.

Postoperative complications were considered to be those which were diagnosed within 30 days after the operation, or during the hospitalization time, if the patient was staying in hospital longer than 30 postoperative days.

We compared the prospective function with the real postoperative function which was determined one month after the operation.

Preoperative 42 parameters: sex, age, BMI, lung ventilation function (FEV1, FVC, TLC, RV, DLCO, VA), expectant lung ventilation function (according to Juhl, Nakahara, Wernly, Kopeika), smoking history in a package per year, SaO₂, size of tumor, central or peripheral tumor, tumor localization in the upper lobe or middle lobe towards the lower lobe, tumor localization in the right or left side, lymph node involvement in the process, tumour morphology, scope of the operation, cardiac history, arterial hypertension, angina of effort, myocardial infarction, heart disease, cardiac arrhythmia, impulse conduction disorders, heart disease, chronic heart failure, cardiac output fraction, physical load tolerance in Wats, obturated segments in fibrobronchoscopy, vascular diseases, liver and bile duct diseases, renal diseases, diabetes mellitus, connective tissue diseases,

CNS diseases, gastrointestinal tract diseases, other oncology in the history.

Three intraoperative parameters: the length of the operation, necessity to do freshly frozen plasma transfusion, necessity to do erythrocyte mass transfusion.

Postoperative 32 parameters or complications: the death within 30 days after the operation, or in a longer period of the same hospitalization time, lung ventilation function (FEV1, FVC, TLC, RV, DLCO, VA), oxygen dependency, acute coronary syndrome, cardiac arrhythmias, cardiac impulse conduction disorders, bleeding, repeated operation, insertion of repeated pleural drainage, pneumonia, sputum retence, necessity to do sanation fibroscopies, acute respiratory distress syndrome, lung ventilation failure, vomiting, increase of uroamilase, acute ulcer, lung thrombemboly, leg vascular thrombosis, cerebrovascular disorders, renal failure, hypoxic encephalopathy, bronchial trunk fistula, residual cavity, residual cavity empyema, wound infection, sepsis and as an extra factor – any of the above-mentioned complications.

Results

General characteristics of patients.

In total 449 patients were included into the study, pneumonectomies were performed on 173 (38.5%) and lobectomies on 276 (61.5%) patients.

Histology and stage.

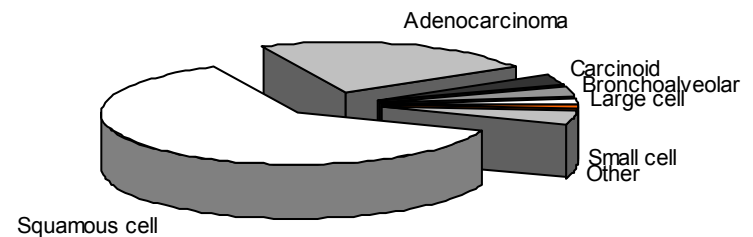


Fig.1. Morphological distribution of tumors.

In 281 cases (62.6%) we diagnosed flat cell cancer, in 106 cases (23.6%) adenocarcinoma, in 15 cases (3.35%) carcinoid, in 13 cases (2.9%) bronchoalveolar cancer, in 8 cases (1.8%) large cell cancer, in 5 cases (1.1%) cases – localized small cell cancer. In the remaining 21 case (4.7%) we detected other, rare malignant tumor forms.

Stage. Examining the operation material histological, we found IA stage in 31 patients (6.8%), IB stage – 132 patients (29.1%), IIA stage – 5 patients (1.1%), IIB stage – 92 patients (20.3%), IIIA stage – 138 patients (30.5%), IIIB stage – 17 patients (3.7%), and also IV stage – 14 patients (3.1%). In the rest of 20 patients (5.3%) with small cell cancer or rare tumor forms, the cancer stage was not specified. The stage was classified by taking into account amendment of 1997 (Mountain, 1997).

Staging according to the type of the operation

Lobectomies were performed mainly in stage I case, pneumonectomies – mainly in stage III case.

Table 1. Complications after lobectomies.

Complication	Number of cases	Percentage
FB sanations	50	18.12
ARDS	8	2.90
Thoracostomy	25	9
Repeated operation	11	3.99
Stress ulcer	2	0.72
Thromboses	3	1.09
Uroamilase increase	19	6.88
Bronchial fistula	2	0.72
Residual cavity	11	3.99
Infection	23	8.33
Remaining lobe pneumonia	21	7.6
Cardiac rhythm disorders	49	17.75

Atrial fibrillation	19	6.88
Acute coronary syndrome	12	4.3
Exitus letalis	6	2.17
Other complications	8	2.90
Number of patients with complications	125	45.29

Table 2. Complications after pneumonectomies.

Complication	Number of cases	Percentage
FB sanations	37	21.39
ARDS	7	4.04
Thoracostomy	5	2.89
Repeated operation	9	5.2
Stress ulcer	2	1.16
Thromboses	2	1.16
Uroamilase increase	7	4.05
Bronchial fistula	5	2.89
Infection	18	10.4
Cardiac rhythm disorders	41	23.7
Atrial fibrillation	13	7.51
Acute coronary syndrome	10	5.7
Encelopathy	4	2.31
Exitus letalis	8	4.62
Other complications	2	1.16
Number of patients with complications	86	49.71

The total number of severe complications, which could be objectively documented, was as follows: 125 patients (45.29%) in lobectomy group, and 86 patients (49.71%) in pneumonectomy group. Some patients were seen to have several complications at the same time, therefore the total number of registered complications is bigger than the number of patients who had complications.

Among the operation groups, statistically differed 2 complication rates. In pneumonectomy group bronchial fistulas ($p=0.0811$), and in lobectomy group more common is the need for a repeated making of thoracostomy ($p=0.0108$).

Surgical complications

The most significant surgical complications were as follows: bleeding, where in order to stop it, we had to perform a repeated operation (3.99% patients after lobectomy and 5.2% after pneumonectomy). They were usually performed by means of rethoracotomy, in single cases after pneumonectomy – also videothoracoscopically. Another most significant complication – bronchial stem fistula was more common after pneumonectomy (5 patients, or 2.89%) rather than after lobectomy – (2 patients, or 0.72%). In 1 case after pneumonectomy the fistula was due to central tumor rupture during the intubation. One should mention also residual cavity after lobectomy which was seen in 3.99% patients.

Cardiac complication

Cardiac complications were the biggest complication group. Most commonly were seen cardiac rhythm disorders: 17.75% patients after lobectomy and 23.7% patients after pneumonectomy. Atrial fibrillation, which is documented in ECG record, was seen in 19 patients (6.88%) after lobectomy and 13 patients (7.51%) after pneumonectomy. Acute coronary syndrome was seen respectively 4.3% cases after lobectomies and 5.7% cases after pneumonectomies.

Thrombembolic complications

These complications were seen in 1.09% cases after lobectomies and 1.16% cases after pneumonectomies. Besides, in 2.31% cases after pneumonectomies were seen also cerebrovascular disorders.

Pulmonary complications

Acute respiratory distress syndrome was seen in 2.90% cases after lobectomies and 4.04% cases after pneumonectomies. Sputum retence or atelectasis of part of the lung, when sever repeated fibroscopies and bronchial sataion were needed, we observed in 18.2% and 21.39% cases respectively. In the lobectomy group, the inflammation of the remaining lung was 7.6% patients.

Gastrointestinal complications

Acute gastric ulcer with bleeding was seen in 2 patients (1.16%) after pneumonectomies and 2 patients (0.72%) after lobectomies. Despite a very active therapy, including also the operation on the stomach, 1 patient died. 7 patients (4.05%) were seen to have vomiting and increased uroamilase after pneumonectomies, the same signs were seen also in 19 patients (6.88%) after lobectomies.

Surgical treatment of complications

Surgical treatment was done due to acute bleeding gastric ulcer after pneumonectomy in 2 patients (1.16%), as well as in all patients with fistula after pneumonectomy (5 patients, or 2.9%) were performed a repeated thoracostomy. Repeated thoracostomy was done due to various reasons: residual cavity, collection of fluid in the pleural space, had to be performed also in 9% patients after lobectomies. 1 patient after lobectomy (0.36%) and 1 patient after pneumonectomy (0.58%), due to bradiarrhythmia after the operation were implanted a permanent electrocardiostimulator.

Mortality rate

Total mortality rate after the operations was 3.12% (14 patients). Mortality rate in pneumonectomy group was bigger, however, the difference did not reach statistically confident level $RR=2.13$ ($0.75 < RR < 6.03$, $p=0.1459$).

Making data analysis, we compared the mortality indices according to the years; the data are seen in Fig.1. Making data analysis with

Chi-square method, we found that the confidence ($p=0.0679$) of mortality rate in the last years tended to decrease.

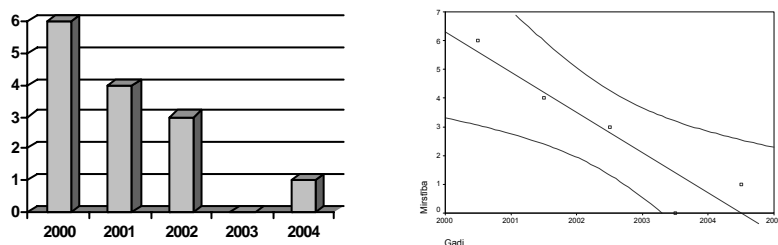


Fig.2. A and B. Decrease of postoperative mortality rate per years.

Linear regression model was chosen to see the correlation between mortality rate for 5 years to the calculated ones and we found that there is a close correlation ($r=0.927$, $n=14$) between the studied values, model determination coefficient $r^2=0.860$. During these 5 years the mortality rate on average has decreased by 1.4 cases per year.

Table 3. Exact causes of patients' death:

Cause	Number of cases	% of lethal outcome	% of all patients
Bronchial trunk fistula	3	21.4%	0.6%
Massive lung artery thrombemboly	3	21.4%	0.6%
ARDS	2	14.3%	0.46%
Acute bleeding Posoperative ulcer which was operated on	1	7.1%	0.22%
Stroke a.cerebri Posterior sinistra	1	7.1%	0.22%
Both leg artery Thrombosis	1	7.1%	0.22%
Acute heart failure	1	7.1%	0.22%

Ventricular fibrillation	1	7.1%	0.22%
Postoperative bleeding with subsequent rethoracotomy	1	7.1%	0.22%
Total	14	100%	3.12%

Lung ventilation function early after the operation

Either lobectomy, or pneumonectomy group patients with TEA on the first postoperative day had better statistically confident lung ventilatory parameters in comparison to patients who were given opiates intravenously. Only those patients' data were analyzed, who had participated to take part in the study. 39 patients who were performed TEA, were divided into groups, depending on the operation performed – pneumonectomy or lobectomy. In the control group 40 patients were included who were operated on the lungs, not using TEA.

In the **lobectomy group** 24 hours after the operation FVC was more statistically confident in TEA patient group - $61 \pm 12\%$ against $45 \pm 13\%$ in the control group ($p=0.0152$). FEV1 was also bigger that was statistically confident $-56 \pm 11\%$ and $41 \pm 11\%$ ($p=0.0308$) respectively. Lung ventilatory function changes in the first 7 days after lobectomy, depending on analgesia method, are shown in Fig. 3 and 4.

Fig.3

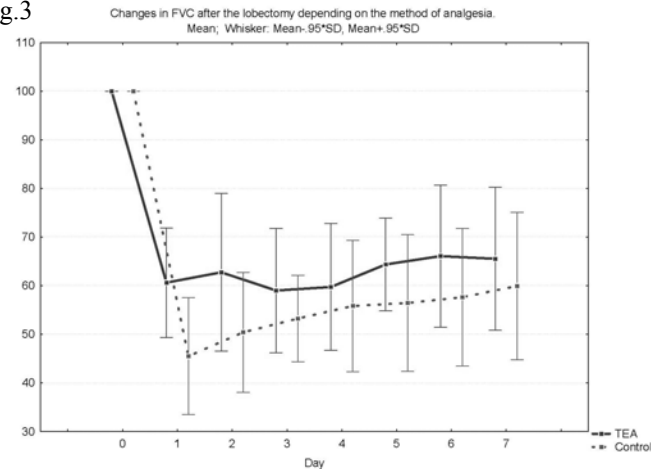
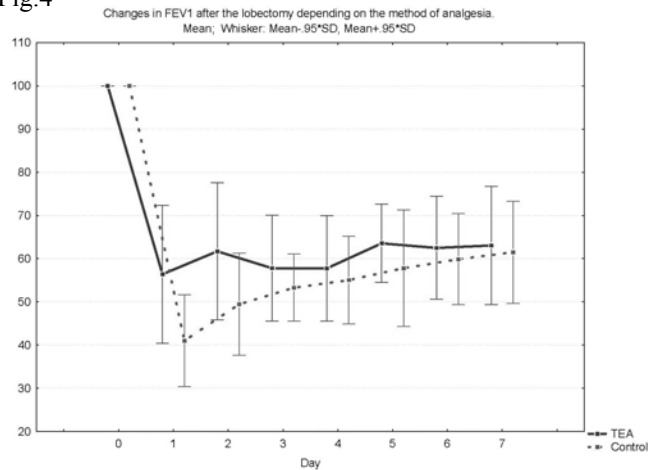


Fig.4



In the **pneumonectomy group** 24 hours after the operation FVC was bigger that was statistically confident in TEA patient group - $47 \pm 16\%$ against $35 \pm 11\%$ in control patient group ($p=0.080$). FEV1 was also bigger that was statistically confident $-47 \pm 7\%$ and $36 \pm 7\%$ ($p=0.0449$) respectively. Lung ventilation function changes in the first 7 days after pneumonectomy, depending on analgesia method, are shown in Fig.5 and 6.

Fig. 5

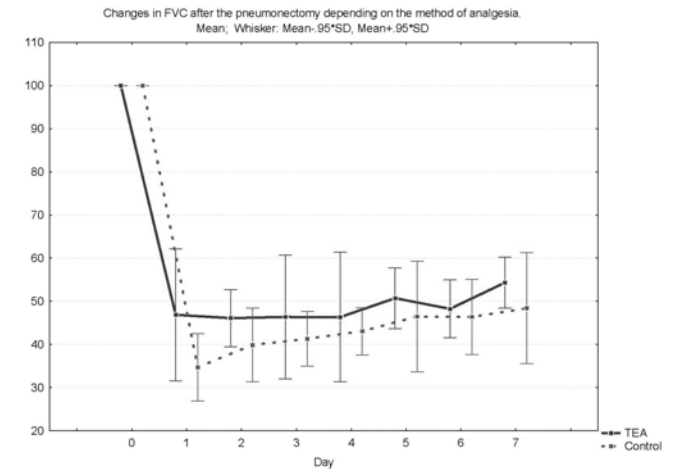
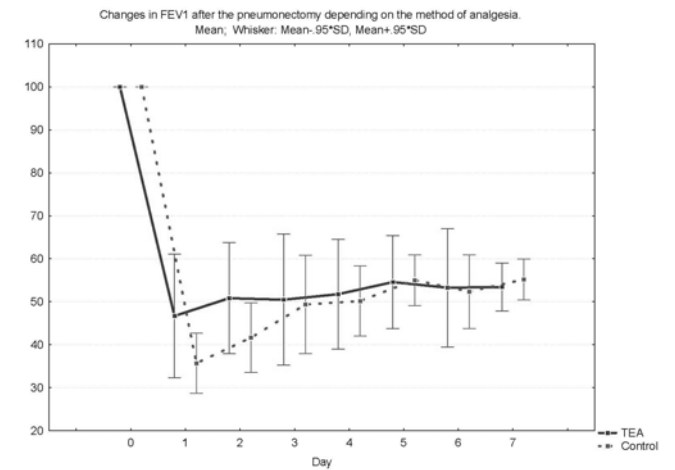


Fig.6



Pain intensity according to VAS, depending on the type of analgesia.

Effectivity of analgesia.

Analgesia was better in TEA patient group that was statistically confident, 76% patients mentioned analgesia as being good, only some patients needed extra administration of non-steroid analgesics. In the control group about 30% patients evaluated analgesia as being unsatisfactory.

Pain intensity is depicted according to VAS scale for both patient groups in Fig.7.

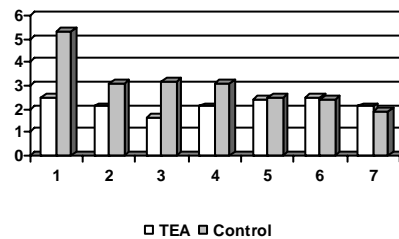


Fig.7. Evaluation of effectivity of analgesia according to VAS scale in TEA and control group patients.

Ventilation function after lobectomy

Considering all 3 methods by linear regression models, one can make a conclusion, that the best method for postoperative FEV1 prognosis is a modified *Juhl* method. Thus, the best conformity (less error, less data dispersion, better correlation coefficient) between the real postoperative FEV1 and the prospective FEV1 can be acquired by using linear regression equation:

$$\text{ppoFEV1 \%} = (30.3 \pm 4.4) + (0.55 \pm 0.06) \times \text{FEV1 Juhl \%}$$

or practically

$$\text{ppoFEV1 \%} = 30 + 0.6 \times \text{FEV1 Juhl \%}$$

Ventilation function after pneumonectomy

Evaluating all 3 methods, we suggest to use modified *Nakahara* method:

$$\text{ppoFEV1 \%} = 30 + 0.6 \times \text{FEV1 Nakahara \%}$$

Complication risk factors

In lobectomy group.

The following factors increase all complication risk:

1. tumour localization in the upper lobe or middle lobe;
2. heart disease history;
3. our suggested formula for predicting postoperative lung ventilation function was statistically confident to predict an increased complication risk ($p=0.0085$), however, up to now, *Nakahara* formula used, turned out to be wrong – in 21 patients with an estimated prospective postoperative $\text{FEV1} < 40\%$ the complication relative risk was not statistically bigger than in the rest ($\text{RR}=1.63$, borders $0.97 < \text{RR} < 2.77$, $p=0.1998$);
4. thoracic epidural analgesia, on the other hand, decreased the complication risk that was statistically confident.

The following factors increase the mortality risk:

Tumour T3 or T4, tumour distribution to N1 or N2 lymph nodes, the tumour localization in the upper lobe or middle lobe, the patient's age > 65 years, heart disease history, liver disease history. Cardiac history was a very significant ($p=0.043$) mortality risk factor – all the deceased had had cardiac problems. One should mention, that 21 patients were operated on with estimated prospective postoperative $\text{FEV1} < 40\%$, these patients' mortality relative risk was not bigger, that was statistically confident in comparison to the rest ($\text{RR}=5.93$, borders $0.77 < \text{RR} < 45.71$, $p=0.1818$). On the other hand, our suggested formula for predicting postoperative ventilation function predicted an increased mortality risk ($p=0.0021$), that was statistically confident.

Pneumonectomy group

The following factors increase all complication risk:

Difficult cardiac history, squamous cell tumor, necessity to make transfusion of erythrocyte mass and freshly frozen plasma during the operation. Our suggested formula for predicting postoperative ventilatory function predicted an increased complication risk that was statistically confident (p=0.0063).

Mortality risk is increased by the following factors:

BMI>25, heart disease, as well as severe operation, that is >240 min, with erythrocyte mass and freshly frozen plasma transfusion. Our suggested formula predicted an increased mortality risk that was statistically confident (p=0.0320).

Logistic regression

Logistic regression model was used in the study to prognose all possible kind of complications after operations. The acquired equations are shown below.

Lobectomies.

Logit(probability of postoperative complications) = -0.814 + 0.502 x Tumour localization - 1.443 x Thoracic epidural anaesthesia + 0.611 x Heart history + 0.904 x ppoFEV1 Kopeika <60%

Logit(for mortality after lobectomy) = -11.1 + 2.934 x T3 or T4 tumour + 2.932 x N1 or N2 lymph nodes + 3.315 x Age > 65 years + 4.113 x ppoFEV1 Kopeika <60%

Pneumonectomies.

Logit (for complications after pneumonectomy) = -1.468 + 0.921 x cardiac history + 0.986 x N1 or N2 lymph nodes + 0.780 x ppoFEV1 Kopeika <60%

Logit (for mortality after pneumonectomy = -5.135 + 1.51 x BMI > 25 + 2.054 x ppoFEV1 Kopeika <60%

Interactive input form for calculating of predicted postoperative complications and mortality rate after lung cancer surgery is published on web site www.dakteris.lv/risks .

Discussion.

Preoperative findings.

Concomitant diseases.

We found out that 78% patients were having at least one concomitant disease, for many patients – several diseases. The most common concomitant diseases were cardiac – angina of effort, arterial hypertension; ventilation failure, ulcer. Other authors also admit that lung cancer operations have to be performed on more elderly patients, who have more and more concomitant diseases (Lopez-Encuentra, 2002; Ambrogi, Pompeo et al., 2003; Jeremic, 2003; Ploeg, Kappetein et al., 2003; Aguilo and Minguella, 2005; Birim, Kappetein et al., 2005; Fukuse, Satoda et al., 2005; Sekine, Chiyo et al., 2005; Birim, kappetein et al., 2006).

Postoperative mortality

We observed a tendency that mortality after pneumonectomies was higher (4.62%) than after lobectomies (2.17%). The observed fact that lethality was higher after pneumonectomies concided, in fact, with the data of other authors (Myrdal, Gustafsson et al., 2001; Fujiu, Kanno et al., 2003; Stoelben, Sauerbrei et al., 2003; Villani, De Maria et al., 2003; Watanabe, Asamura et al., 2004; Damhuis, Coonar et al., 2006; Rostad, Strand et al., 2006). There are also publications showing even a higher postoperative mortality rate – even 9.3% after pneumonectomies (Licker, Spiliopoulos et al., 2002).

We are of the opinion that a comparatively low mortality is provided by a very careful preoperative examination, the use of the above-mentioned algorithm in the preoperative selection of patients. Great importance in reducing the operation risk is attributed to the possibilities offered by the University Clinic (Bach, Cramer et al., 2001) – in case of cardiac concomitant diseases to introduce veloergometry, coronarography, and in case of need to do percutaneous coronary angioplasty before the operation, or even aortocoronary bypassing.

Postoperative complications

45% patients had complications after lobectomy and 49% patients after pneumonectomy, which, in fact, coincides with the other authors' data (Licker, Spiliopoulos et al., 2002; Ayed, Bazerbashi et al., 2006).

There are authors who show a lesser complication rate after the operation – 25-30% (Villani, De Maria et al., 2003), however, it is often problematic to state the exact complication rate because many of them are interrelated. Slighter complications, which often do not call for extra treatment, e.g., subcutaneous emphysema, are sometimes not documented, therefore their precise recording quite often is not done (Kopeika, Bukovskis et al., 2004., Kopeika, Taivans et al., 2005; Kopeika, Taivans et al., 2005). We, on the other hand, registered at maximum all postoperative problems, even the slightest ones. Consequently, it is difficult to compare the total number of complications, it is better and more precise if complications are compared according to groups.

Cardiac complications

We found that in the postoperative period most commonly developed cardiac complications. Various kind of cardiac rhythm disorders were seen in 23% patients after pneumonectomies and 17% after lobectomies. Other authors have also mentioned a great number of cardiac complications (Licker, Spiliopoulos et al., 2002).

The most common complication has been atrial fibrillation and that coincides with other authors' data (el Hammami, Djilani-Horchani et al., 2001; Sekine, Kesler et al., 2001). Majority of rhythm disorders complied with medicamental therapy, according to other authors' data, up to 95%. In our case 1 patient with ventricular fibrillation

died, and two patients with refractory bradiarrhythmia had to be implanted a cardiostimulator. The development of cardiac rhythm disorders may be due to increase of acute pressure in the lesser circulatory system and in the overload of the right heart. Indirect evidence to it might be more common episodes of atrial fibrillation after pneumonectomies, in comparison to lobectomies, as well as in COPD patients (Sekine, Kesler et al., 2001).

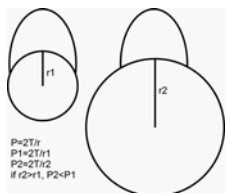
Pulmonary and infectious complications

We found that insufficient analgesia in the postoperative period was a significant risk factor for the development of infectious complications (pneumonia, residual cavity empyema). While other authors (Belda, Cavalcanti et al., 2005) have found infectious complications in 31% patients, we, on the other hand, about 10%, in which we have succeeded to identify the causative agent in culture. About 20% patients had to be performed sanation bronchoscopy due to hypoventilation and sputum stasis. As a result, we have to conclude that the total number of the above-mentioned complications is approximately similar (30%). Many authors have found pulmonary complications – 15-27% patients (Stephan, Boucheseiche et al., 2000; Algar, Alvarez et al., 2003; Ayed, Bazerbashi et al., 2006). Others have found hard pulmonary complications only in 12.8% patients after pneumonectomy, while they have registered only massive pneumonias, but slight atelectasis or aspiration were not taken into account (Vaporciyan, Merriman et al., 2002).

Lung ventilation function changes as a result of the operation.

We found out that the current formulae for calculating the lung ventilation function are not precise. They overestimate the loss of function, especially in patients with an initially poor ventilation function. But this patient category is the most significant for prognosing the function. In 27 patients the postoperative function was better than the preoperative one, in a great part of patients it was better for the expected. Our experience also shows that patients with emphysema can be performed lung lobectomy, besides, the ventilation function in the postoperative period usually exceeds the planned (Kopeika, Bashko et al., 2001; Kopeika, Taivans et al., 2003; Kopeika, Taivans et al., 2004) and in the patient group with

ppo FEV1 >40% the postoperative indices corresponded to the estimated ones, but in the group with ppo FEV1 <40%, the indices were on average 10.3% better for the expected ones (Sekine, Iwata et al., 2003; Kopeika, Taivans et al., 2004).



In our opinion, changes of diaphragm cupola radius after lung lobectomy is one of the possible mechanisms that can improve the ventilatory function in patients with initially severe ventilatory failure (Kopeika, Jakušenko et al., 2005).

Fig.8. Explanation of breathh work according Laplass equination.

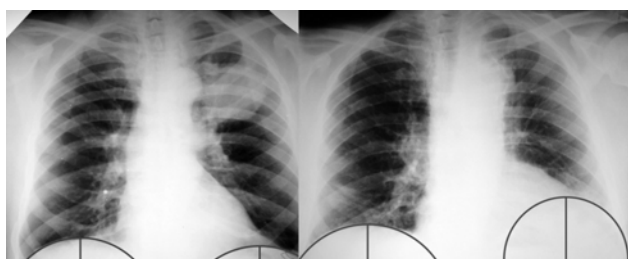


Fig. 9. Patient K.L. Plain chest roentgenograms before and after lobectomy.

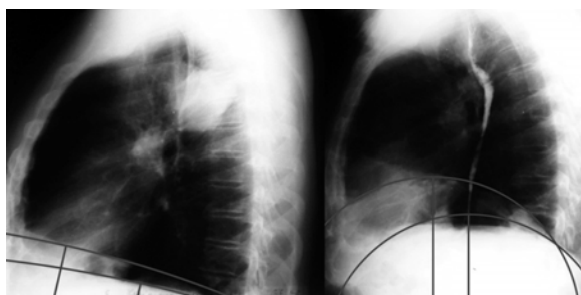


Fig. 10. Patient K.L. Plain chest roentgenograms before and after lobectomy.

As a result, we offer our formula, which is more precise for the existing one, and it is proved by standard error analysis of various formulae described in the chapter on results.

Besides, our newly-formed formulae make it not only better prognose the postoperative lung ventilation function, but it also correlate quite well with postoperative complications.

It allows radically to increase the range of patients to be operated on in nonsmall cell lung cancer cases (Bolliger, Wyser et al., 1996; Kopeika, Bashko et al., 2001).

Operation risk factors

All operations

The main risk factors for increased postoperative mortality or complication risk either after lobectomies, or pneumonectomies and which were statistically confident also by doing binary logistic regression, were as follows:

- ppoFEV1<60% according to our proposed formula;**
- cardiac history;**
- tumor distribution to N1 and N2 lymph nodes.**

This coincides with other authors' data (Harpole, DeCamp et al., 1999; Brutsche, Spiliopoulos et al., 2000; Stephan, Boucheseiche et al., 2000), who have analyzed independent risk factors.

Lung ventilation function. We found out that the expected lung ventilation function <40% calculated by widely used formulae of to day (Juhl and Frost, 1975; Wernly, DeMeester et al., 1980; Nakahara, Fujimoto et al., 1983; Nakahara, Monden et al., 1985; Nakahara, Ohno et al., 1988; Nakahara, Monden et al., 1992) was not statistically confident in connection to a greater mortality rate either after pneumonectomies, or lobectomies (Kopeika, Bashko et al., 2001), despite the fact, that other authors had found the correlation (Ribas, Diaz et al., 1998). At the same time, our worked out formula can well independently prognoses the increased postoperative complication risk, as well as it fits well into the complex binary logistic regression model together with other factors.

Cardiac history. We also agree to other authors' findings that cardiac histories were found as statistically confident postoperative complication risk factor (Eagle, Rihal et al., 1997; Bonde, McManus et al., 2002; Algar, Alvarez et al., 2003; Ambrogi, Pompeo et al., 2003; Licker, de Perrot et al., 2003; Peka, Jirgensons et al., 2004; Birim, Kappetein et al., 2005; Ayed, Bazerbashi et al., 2006; Birim, Kappetein et al., 2006; Gomez-Caro, Moradiellos et al., 2006).

Tumour invasion to N1 or N2 lymph nodes. We found out that the tumour invasion into the lymph nodes is a risk factor not only for a more frequent tumour recurrence after the operation, but also for a more severe operation, more common early complications. Other authors also agree to that (Dalton and Keller, 1994; Cangemi, Volpino et al., 1995; Ueda, Kaneda et al., 2002; Doddoli, Barlesi et al., 2005).

Pneumonectomies.

The main risk factor for increased postoperative mortality or complication risk just after pneumonectomies, additionally to the above-mentioned total risk factors was the patient's obesity – body mass index higher than 25.

We have seen that a big body weight is an essential operation risk factor, although majority of authors acknowledge that just the reduction of the body mass by more than 10% is a risk factor. However, there are reports which coincide with our point of view, that a big weight is a risk factor for postoperative complications after pneumonectomies since the patient has difficulties in breathing (Pierce, Copland et al., 1994; von Ungern-Sternberg, Regli et al., 2005).

Lobectomies.

The main risk factors for increased postoperative mortality or complication risk just after lobectomies, additionally to the above-mentioned total risk factors are:

T3 or T4 tumour;

Age > 65 years;

Tumor in the upper region of the lung;

TEA was found to be a complication risk-decreasing factor.

T3 or T4 tumor. One has to admit that the scope of the operation and the tumor stage are, in fact, connected parameters, because usually the further tumor stage calls for a vaster scope of the operation, however, T3 and T4 tumor lobectomy cases have proved to be an essential risk factor. This assumption has been found also in other authors' studies (Licker, de Perrot et al., 2003; Stoelben, Sauerbrei et al., 2003; Birim, Kappetein et al., 2005).

Patients' age over 65 years was proved to be a risk factor for more common postoperative complications, which has been found in other authors' studies as well (Ginsberg, Hill et al., 1983; Kohman, Meyer et al., 1986; Deslauriers, Ginsberg et al., 1994; Baško, 1995; Wada, Fukuse et al., 1995; Damhuis and Schutte, 1996; Harpole, DeCamp et al., 1999; Sardelli, Lopez et al., 2003). It has been also found that the complication risk is caused not the age itself, but comorbidities which in elderly patients are more common (Dienemann, Hoffmann et al., 2005; Ramesh, Pope et al., 2005). We have to admit, however, that the patient's age and cardiac block diseases in the case history are interrelated parameters. We cannot neglect the fact as well, that even now, more than half of cancer patients at the time of making the diagnosis, are older than 65 years and this age tends to increase (Ramesh, Pope et al., 2005).

Tumor in the upper region of the lung was also mentioned as the factor for more common postoperative complications. In the literature, on the other hand, one can find reports, saying, that after upper lobectomies, the loss of the lung ventilation function is less in comparison to lower lobectomies. We try to explain the higher incidence of complications by specificities of the lung anatomy – the lung artery and the bronchus go into the direction from upwards to downwards, consequently, the operation is more difficult in upper lobectomies, since segmentary artery branches have to be dissected, leaving the main trunk untouched. In lower lobectomy cases one has to dissect the bronchial and artery end branches which is technically much easier.

TEA. We found out that regional anesthesia decreases the risk for the development of complications after lobectomies, and, similarly to

other authors, we advise to use them the more, the better (Bonde, McManus et al., 2002). As a result of TEA, we observed the decrease of sputum retence by 4 times, which coincides with the data of other authors, who have found that as a result of TEA, the pulmonary complication rate decreases by 2-5 times (Cuschieri, Morran et al., 1985; Licker, Spiliopoulos et al., 2002), as well as also decreases the risk for atelactases after lung operations by twofold (Ballantyne, Carr et al., 1998; Boisseau, Rabary et al., 2001). The data that the lung ventilation function in the first opstoperative days is dramatically low and very much depends on adequate analgesia coincide with the data of other authors (39-50% from the preoperative level) (Bigler, 2003; Cui, Zhang et al., 2003; Matot, Drenger et al., 2004). Some authors who have found that TEA does not improve the lung ventilation function, in comparison to other analgesia methods, have analyzed either some other operations but not the lung cancer (Ballantyne, Carr et al., 1998; Groeben, Schafer et al., 2002), or have compared almost equivalent methods (Miguel and Hubbell, 1993; Ballantyne, Carr et al., 1998).

Binary logistic regression.

It was possible to find only 3 studies in the data base, where authors have used binary logistics for determination of lung cancer operation risk – 2 in English (Hollaus, Wilfing et al., 2003; Dyszkiewicz, Piwkowski et al., 2004) and 1 in Spanish (Varela, Jimenez et al., 2003). Besides, the authors do not use binary logistics to a full extent – either at a small number of patients – 37 patients (Dyszkiewicz, Piwkowski et al., 2004) and 108 patients (Hollaus, Wilfing et al., 2003), finding only separate risk factors and not seeing their interrelationship and their potential influence, or, even at a larger number of patients - 515 patients (Varela, Jimenez et al., 2003), include all possible risk factors in the analysis and make a conclusion that the model does not work. It is understandable because one cannot include in the model completely independent risk factors, where each of them is statistically confident risk factor. In the mentioned case (Varela, Jimenez et al., 2003) these preconditions were not taken into account.

We, in difference to other authors, succeeded to find the correlation between several, mutually independent risk factors and postoperative

complications. These, previously mentioned factors, are connected with increased postoperative complication and mortality risk, either each one itself, or they have a cumulative effect – the predicted complication risk of several factors is higher than the arithmetic sum of separate risks.

Contrary to the generally accepted recommendations (BTS guidelines., 2001), patients with low preoperative lung ventilation parameters usually can endure lung lobectomy, besides, the lung ventilation function not only does not deteriorate, but even improves (Kopeika, Bashko et al., 2001).

Conclusions.

#Lung cancer surgery is characterized by high complication rate. Higher complication rate and mortality are after pneumonectomies, in comparison to lobectomies.

#After the operation one can observe the reduction of lung ventilation function. On the first postoperative day it is markedly dependent on adequate analgesia. In the longer period, the loss of function is up to 30% after pneumonectomies, and less than 10% after lobectomies. In separate cases the lung ventilation function after lobectomies was seen even to improve, in comparison to preoperative examination.

#Prognosing the lung postoperative function by perfusion scintigraphy method is simple, non-invasive procedure and Wernly formula can be accepted as sufficiently precise for prognosing lung ventilation function after pneumonectomies.

If lung scintigraphy data are not available, we recommend to use a modified *Nakahara* formula :

ppoFEV1 % = 30+ 0.6 x FEV1 Nakahara %

After lobectomies one should take into account the reduction effect of the lung volume and prognosis of the lung ventilation function. We advise to make it after lobectomy by means of the following formula:

ppoFEV1 % = 30 + 0.6 x FEV1 Juhl %.

#We found many parameters of case history and objective examination data being as risk factors for more common postoperative complication, but mutually unrelated risk factors for postoperative complications and increased mortality risk were the following:

1. T3 and T4 tumor;
2. tumor invasion to N1 and N2 lymph nodes;
3. tumor localization in upper region of the lung;
4. cardiac history;
5. ppo FEV1 by Kopeika < 60%;
6. age > 65 years;
7. BMI > 25;
8. We found the introduction of TEA as a risk-reducing factor.

Our advice to all thoracic surgeons is to apply our worked-out operation risk prognosing algorithm in practice, since its use makes reduce early postoperative mortality which is statistically significant fact.

Novelty of research

1. New formulae have been made for calculating postoperative lung ventilation function after lobectomies and pneumonectomies. Formulae is also published on web site www.dakteris.lv/formula .

2. Risk factor analysis has been done by using all 449 patient data operated on within 5 years at the Centre of Thoracic Surgery, as well as binary logistic regression model.

3. Formulae have been worked out to calculate prospective postoperative complication and mortality rates, which take into account a simultaneous, cumulative effect of several risk factors.

4. Interactive input form for calculating of predicted postoperative complications and mortality rate after lung cancer surgery is also published on web site www.dakteris.lv/risks .

5. The use of the above-mentioned, evidence-based methods has allowed to reduce postoperative mortality quite significantly at the Centre of Thoracic Surgery.

Practical importance of research

The preoperative examination algorithm and postoperative complication prediction algorithm have been worked out and introduced into practice. The above-mentioned algorithms are being used in daily practice at Pauls Stradiņš Clinical University Hospital Centre of Thoracic Surgery. It has made it possible within the last years to essentially decrease postoperative mortality at the Centre of Thoracic Surgery.

All colleagues of the hospital have been introduced to the results of algorithm use, by announcing about it at the scientific morning conferences of Pauls Stradiņš Clinical University Hospital.

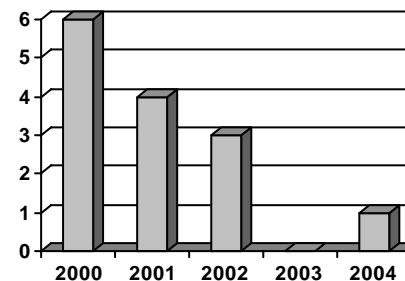


Fig. 11. Decrease of mortality by years.

The worked-out formula for prognosing postoperative complications are adapted to simple and easy use. In order not to make daily calculations with logarithms, 4 tables have been prepared, where all the possible complication risk and lethal outcome values in % have been already calculated.

Publications on the research theme.

Full articles in reviewed editions.

1. Kopeika U, Taivans I., Ūdre S., Jakušenko, N., Strazda G., Mihelšons M., Effects of prolonged epidural analgesia on ventilation function and complication rate after the lung operations. Medicina 2006, Lithuania, accepted for publication.
2. Isajevs S, Taivans I, Kopeika U, Strazda G. Influence of cigarette smoking history on HDAC2 expression in central and peripheral airways in smokers with and without COPD. Accepted for publication in LU collected articles.
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4. Kopeika U, Jakushenko N, Taivans I, Baško J, Pirtnieks A, Demidovs G. Changes of the diaphragmatic radius after the lung lobectomy. Latvijas Ķirurģijas žurnāls 2005;5:6-9. [Latvian Journal of Surgery]
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8. Kopeika U, Jakushenko N, Udre S, Baško J. Changes in pulmonary ventilation function after thoracal operation depending on anesthesia method. Education and Health, Turkey 2003:128-130
9. Kopeika U, Taivans I, Mihelšons M, Baško J. Change in pulmonary ventilation function after lung resection. Education and Health, Turkey 2003:125-128.

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1. Kopeika U, Baško J, Lange A, Pirtnieks A, Pēka M, Ambalovs G. Plaušu vēža funkcionālās operējamības kritēriji. Latvijas Ārsts 2005;4:79-82. [Criteria of lung cancer functional operability. Latvian Physician]
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International conferences.

European Respiratory Society (ERS) congress in Munich . 2-6 September,2006

Kopeika U., Taivans I., Udre S., Baško J., Pirtnieks A. Effects of the epidural analgesia on the complication rate after the lung cancer surgery. ERJ 2006

Peka M., Kopeika U., Erglis A., Kumsars I., Zakke I., Basko J. Coronary artery disease and lung cancer surgery. ERJ 2006

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Report: "Relationship between COPD and complications rate after lung cancer surgery" Uldis Kopeika, Immanuels Taivans, Ainis Pirtnieks, Aija Lange and Jazeps Basko.

Report: "Full completed stress test as good predictor for postoperative complications rate after lung cancer surgery" Mara Peka, Uldis Kopeika, Mara Sauka, Aija Lange and Immanuels Taivans.

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Report "New formula for prediction of postoperative lung function.", U.Kopeika, I.Taivans, J. Basko, G. Demidovs. tēžu publikācija European Respiratory Journal Volume 24, Suppl. 48, 2004 S.11 [publication of theses]

Report: "Risk factors for cardiac complications after lung cancer surgery", M. Peka, J.Jirgensons, U. Kopeika, J. Basko, tēžu publikācija European Respiratory Journal Volume 24, Suppl. 48, 2004 S.172 [publication of theses]

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Report : "Is the lung emphysema contraindication to radical NSCLC surgery?", U. Kopeika, J. Baško I. Taivans. , tēžu publikācija European Respiratory Journal Volume 18, Suppl. 33, 2001 S.94-95 [publication of theses]

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LU 64th scientific conference in Riga, Latvia. 2006

Report: Kopeika, U.; Taivans, I.; Strazda, G.; Mihelons, M.; Baško, J. " Jauna formula pēcoperācijas plaušu funkcijas prognozēšanai" [New formula in prognosing postoperative lung function]

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Appendix.

By marking risk presence or absence in the first column, in the last column we found the probable mortality or complication risk after the operation expressed in %.

Prognosing of postoperative mortality

Table 4. Prognosing mortality risk after pneumonectomies

BMI>25	FEV1<60% ppo Kopeika	Complications %
+	+	17.28 %
+	-	2.61 %
-	+	4.39 %
-	-	0.59 %

Table 5. Prognosing mortality risk after lobectomies.

T3 or T4 tumour	N1 or N2 Lymph nodes	Age > 65 years	FEV1<60% ppo Kopeika	Complications %
+	+	+	+	88.66 %
+	+	+	-	11.33 %
+	+	-	+	25.37 %
+	+	-	-	0.55 %
+	-	+	+	29.40 %
+	-	+	-	0.68 %
+	-	-	+	1.78 %
+	-	-	-	0.03 %
-	+	+	+	29.36 %
-	+	+	-	0.68 %
-	+	-	+	1.78 %
-	+	-	-	0.03 %
-	-	+	+	2.17 %
-	-	+	-	0.04 %
-	-	-	+	0.10 %
-	-	-	-	0 %

Prognosing postoperative complications

Table 6. Prognosing complication risk after pneumonectomies.

N1 or N2 Lymph nodes	Cardiac history	FEV1<60% ppo Kopeika	Complications %
+	+	+	77.17 %
+	+	-	60.78 %
+	-	+	57.73 %
+	-	-	38.15 %
-	+	+	55.77 %
-	+	-	36.63 %
-	-	+	33.43 %
-	-	-	18.71 %

Table 7. Prognosing complication risk after lobectomies.

Tumour in upper region	TEA	Cardiac history	FEV1<60% ppo Kopeika	Complications %
+	+	+	+	44.03 %
+	+	+	-	24.16 %
+	+	-	+	29.92 %
+	+	-	-	14.74 %
+	-	+	+	76.91 %
+	-	+	-	57.42 %
+	-	-	+	64.38 %
+	-	-	-	42.26 %
-	+	+	+	32.26 %
-	+	+	-	16.17 %
-	+	-	+	20.54 %
-	+	-	-	9.47 %
-	-	+	+	66.84 %
-	-	+	-	44.94 %
-	-	-	+	52.25 %
-	-	-	-	30.70 %