Evolution of lung segmentectomy at our department

Ph.D. Thesis

TIBOR GÉCZI MD

Supervisors:

József Furák MD, PhD

Tamás Zombori MD, PhD

Department of Surgery

Faculty of Medicine

University of Szeged

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CONTENTS

List of papers:

This doctoral thesis is based on the following publications:

I. Géczi, Tibor, Csada, Edit, Tiszlavicz, László, Lázár, György, Furák, József A műtétileg kezelt tüdőrák klinikopatológiai jellemzőinek változása az ezredfordulónkon [Changes in the clinicopathological features of surgically treated lung cancer around the millennium] ORVOSI HETILAP 159 : 10 pp. 391-396. 6 p. (2018) DOI WoS Scopus PubMed Matarka MOB SZTE Publicatio IF:0.564

II. Tamás Zombori, Tibor Nyári, László Tiszlavicz, Regina Pálföldi, Edit Csada, Tibor Géczi, Aurél Ottlakán, Balázs Pécsy, Gábor Cserni, József Furák. The more the micropapillary pattern in stage I lung adenocarcinoma, the worse the prognosis-a retrospective study on digitalized slides Wirchows Archives 472, pages949–958 (2018) DOI: 10.1007/s00428-018-2337-x IF:2.868

III. Tibor Géczi, Zsolt Simonka, Judit Lantos, Melinda Wetzel, Zsolt Szabó, György Lázár, József Furák. Near-infrared fluorescence guided surgery: State of the evidence from a health technology assessment perspective Front. Surg. 9:919739. DOI: 10.3389/fsurg.2022.919739 IF:2.568

Total impact factor of original papers directly related to the thesis: 6.0

List of abbreviations:

CT	Computer Tomography
COVID	COronaVirus Induced Disease
TNM	Tumor Node Metastasis
OS	Overall Survival
DFS	Disease-Free Survival
VATS	Video-Assisted Thoracic Surgery
NIR	Near-InfraRed
ICG	IndoCyanine Green
FDA	Food and Drug Administration
PET-CT	Positron Emission Tomography- CT
ACOSOG	American College of Surgeons Oncology Group
NSCLC	Non-Small Cell Lung Cancer
FEV1	Forced Expiratory Volume in 1 second
DLCO	Diffusing Capacity for Carbon Monoxide
GGO	Ground Glass Opacity
TTF-1	Thyroid Transcription Factor 1
KRAS	Kirsten RAt Sarcoma virus (oncogene)
EGFR	Epidermal Growth FactoR
WHO	World Health Organization
IASLC	International Association for the Study of Lung Cancer
ATS	American Thoracic Society
ERS	European Respiratory Society
STAS	Spread Through Air Spaces
NITS	Non-Intubated Thoracic Surgery

1. Introduction

Cancer-related mortality is on the second place following cardiovascularis mortality in developed countries. Lung cancer is the most common malignant tumor among men, while it is on the third place after breast and colorectal malignancies among women. Smoking plays significant role in the developement of lung cancer, 80-85% of lung cancer patients have more than 5 years of smoking history.

Unfortunately, diagnosis and the treatment of lung cancer is far away from being good. According to the current data, the screening rate by chest X-ray of the hungarian population was around 25%. Thanks to this fact and the frequently poor functional status, only 30% of these patients are candidates for radical lung surgery.

Smoking has been pushed back a bit in developed countries, therefore the increase of lung cancer incidence looks like to be stopped rising, but this process also lead to the decrease of squamous cell carcinomas and the increase of adenocarcinomas. At the same time, attention is paid on different screening programmes, so much more early stage lung cancers are diagnosed than earlier. In Hungary, the Hunchest programme has been introduced providing effective screening with low dose chest CT for the endangered smoking population. Furthermore, the widespread use of CT in the investigation of patients with different type of chest problems, in the use of follow-up after any type cancer therapy leads to much more newly discovered solitary pulmonary nodule. This process has been amplified by the latest big human catastrophy, the COVID recently, with the widespread us of CT. On the other hand, human population is getting older, there is more chance to develop further tumors, for example lung cancer. Surgery should be performed in an older population with impaired lung function and often with severe comorbodities. So the surgeons' demand to perform more parenchyma preserving lung resections using less invasive way from surgical and anaesthesiological point of view as well is natural.

Since 'radical lobectomy' was published by Cahan in 1960, the standard surgical care for lung cancer has been lobectomy. Atypical wedge resection and segmentectomy are known as sublobar resections. These limited resections were recognized as 'compromise' procedures, mostly performed for benign diseases, although some investigators stated that it could be the standard treatment for T1N0 lung cancer patients.

Pastorino et al. published a retrospective study of comparison of lobectomy and sublobar resection, with no significant differences in 5-year survival and recurrences groups. Thanks to this retrospective study, Ginsberg et al. conducted a randomized controlled trial in which limited resection and lobectomy for stage I lung cancer were compared and found that sublobar resection is not recommended for healthy patients with stage IA lung cancer. Thanks to these contoversial results, sublobar resection for lung cancer has been, and still is, a controversial issue. Sublobar resections were associated with a significant increase in local recurrence compared with lobectomies, but cancer-related and overall death rates were similar, did not show significant differences. The main weaknesses of these retrospective and prospective studies were the confusion of wedge resections and segmentectomies in the same group as sublobar resections and question of the extent of lymphadenectomies. A meta-analysis by Nakamura et al. on survival following lobectomy and limited resection for stage I lung cancer confirmed the results of the randomised trial: there were no statistically significant differences between the two groups, but there was a small benefit in the lobectomy group. By now, most thoracic surgeons accept that segmentectomy is an option for patients otherwise inoperable from functional point of view and it is equal to lobectomy for T1N0 lung cancer patients after careful patient selection.

During the preoperative evaluation we have to identify the so-called „high risk” patients, who are not candidates for lobectomy, but can undergo sublobar resections. Furthermore we have to identify those early-stage lung cancer patients, who can have sublobar resections with the same expected survival as with lobectomy. There are be many factors to be considered during decision making, like tumor size, localization, histological type etc. Tumor histology is one of the most important questions.

Adenocarcinoma is the most frequent histological subtype among non-small cell carcinomas. Most cases of adenocarcinoma are neoplasms with mixed architecture. They should be subclassified according to the predominant growth pattern. Most studies have focused on predominant growth patterns and their impact on survival. It is well documented that lepidic predominant carcinomas have better outcome, while solid and micropapillary predominant carcinomas have an unfavourable prognosis. However, many lung adenocarcinomas show mixed-subtype patterns, the impact of non-predominant growth patterns on survival is controversial. Three growth patterns of invasive adenocarcinomas have been investigated recently, namely the lepidic, the solid and micropapillary patterns. Higher proportion of lepidic component is usually associated with better prognosis. Pure lepidic carcinoma is defined as in situ adenocarcinoma with 100% overall survival and disease-free survival. A higher proportion of solid or micropapillary pattern refers to worse prognosis. Some authors have found that even 1% or 5% of these components may cause an unfavourable outcome. Similarly, Sumiyoshi et al. found that the mean percentages of micropapillary pattern showed no significant differences in the recurrent (20.4%) and non-recurrent (18.3%) groups. Predominant and secondary predominant growth patterns can be investigated, as well. Zhao and coworkers have found that acinar/papillary carcinomas having secondary predominant solid or micropapillary patterns show worse prognosis than acinary/papillary carcinomas without secondary solid or micropapillary components.

Performing sublobar lung resections, mainly segmentectomy might be challenging. There are a few techniques developed for intersegmental plane identification. Traditionally, the inflation and deflation technique has been used for intersegmental plane identification, but obstruction of the surgical view during VATS procedures is still an issue. To avoid this problem, many other techniques have been developed, while in 2009, Misaki et al. demonstrated the feasibility of intersegmental plain identification using near-infrared imaging after intravenous administration of indocyanine green (ICG). NIR fluorescence imaging systems use a special camera to detect the infrared light emitted by a fluorescent dye after excitation by a specified infrared light. There are several advantages to using NIR light-imaging systems. While visible light can travel to the tissue only a few microns, NIR light (700–900 nm) can penetrate even up to centimeters through different tissues. As the tissue shows minimal autofluorescence in the infared spectrum, the so called signal-to-background ratio can be maximized, achieving optimal contrast during imaging**.** Furthermore, as NIR light is not visible to the human eye, it does not affect the surgeon’s vision. ICG) is the dye that is used most frequently for NIR guidancen. When administered systemically the liver takes up and excretes more than 80% of the available ICG into the bile within 18 h of administration. ICG is safe at systemic doses as high as 5 mg/kg. Wavelengths of excitation and emission are approximately 805 and 830 nm, when ICG is dissolved in blood. However, ICG also has some disadvantages, such as moderate photostability, a relatively narrow fluorescence quantum yield, a high propensity to bind plasma proteins and aggregation in water solutions.

2. Objectives:

Our main goal was to study the changes of the lung cancer and the impact of this change on the surgical treatment, its possible effect on the surgical trends and techniques.

I.: In our retrospective study we studied the changes in the clinicopathological features of surgically treated lung cancer around the millenium. In our work, the data of lung cancer patients of the last 15 years were retrospectively analyzed, we examined the demographic characteristics, the histological type, the stage of the lung cancer, the type of the surgical procedure used, other supplemental treatment and survival.

II.: We aimed to identify the parameters for proper patient selection for sublobar resection. Our aim was to analyse the predominant and the secondary predominant components and the proportions of different growth patterns, in stage I lung adenocarcinoma and their influence on overall and disease-free survival in our second study.

III.: Thirdly, in our mini-review, we intended to overlook the use of near-infrared fluorescence guided surgery during thoracic procedures, emphasizing the usefulness of ICG, which is very effective for intersegmental plane identification in difficult cases.

3. Study I.:

Géczi, Tibor, Csada, Edit, Tiszlavicz, László, Lázár, György, Furák, József. A műtétileg kezelt tüdőrák klinikopatológiai jellemzőinek változása az ezredfordulónkon [Changes in the clinicopathological features of surgically treated lung cancer around the millennium] ORVOSI HETILAP 159 : 10 pp. 391-396. , 6 p. (2018) DOI WoS Scopus PubMed Matarka MOB SZTE Publicatio (33)

3.1. Materials and methods I.

I.: We compared the clinicopathological features of lung resection cases carried out in our department of 2 different 5-year periods. The earlier period was defined as operations performed between 01.01.1998 and 31.12.2002, while the later one was between 01.01.2008 and 31.12.2012. Patient age, sex, change of cancer histological type and the evolution of different surgical methods were studied. During the first period TNM staging was determined by the 6th TNM classification of lung tumors, but the 7th TNM classification has been used since january 2010, This change might distort the data of the non-early lung cancer cases, but it has no effect on the I/A stage. Statistical analysis was performed by the SPSS (Statistical Package for the Social Sciences, 19.0, SPSS Inc. Chicago, IL, USA) programe using $\chi 2$ and Kaplan-Meier probe.

3.2. Results I.

I. There were 497 patients (27% women and 73% men) operated during the first period, their age varied between 30 and 80 years (mean age:58,5 years) and 63,1% of them were smokers. During the second period much more, 799 patients had thoracic surgery for primary lung cancer, only 43% of them were women and 57% men. Their mean age was 61,5 years (23-85 years) and 68% of them were smokers (*Table 1.*).

	1st period (1998-2003)	**2nd period** (2008-2012)
Operations	497	799
Sex (women/men)	27%/73%	43%/57%
Average age (years)	58.5 years (30-80)	61.5years (23-85)
Smokers (%)	63.1%	68%

Table 1. Age and sex distribution of resected lung cancer cases

During the second period there were quite many, 126 patients (16%) presenting with lung cancer as second primary malignant tumor. In 42 cases (33%) this lung cancer developed after a succesfully treated first, but different lung tumor, it is 5.2% of all the lung cancer cases. The histology of these surgically resected lung cancers are shown in *Table 2*. We would like to emphasize that occurance of the adenocarcinoma, squamous cell and large cell carcinoma cases changed significantly.

	1st period (1998-2002)	**2nd period** (2008-2012)	***p*-value**
Addenocarcinoma	**199 (40%)**	**499 (62.5%)**	0.001
Squamous cell carcinoma	**203 (40.8%)**	**205 (25.7%)**	0.001
Large cell carcinoma	23/497	3/799	0.001
Small cell carcinoma	14/497	32/799	0.352
Carcinoid	29/497	28/799	0.162

Table 2. Histology of resected lung cancer cases

Analyzing the different surgical methods, we can see that the rate of pneumonectomies decreased from 27.1% to 9.4% (*Table 3*.). Parallel to this fact, the rate of lobectomies and sleeve lobectomies increased from 58% to 75.2%. During the second period thoracoscopy became the method of choice for lobectomies too. In the first period only minor resections, atypical wedge resections were carried out via thoracoscopy. There was no anatomical segmentectomy performed during the first period, while 3.2% of patients had segmentectomy in the second one.

	1st period (1998-2002) (497 patients)	**2nd period** (2008-2012) (799 patients)	***p*-value**
Pneumonectomy	27.1%	9.4%	0.001
Lobectomy	58%	75.2%	0.001
Bilobectomy	2.2%	3.3%	0.149
Pneumonectomy/ sleeve lobectomy	104/13	78/76	
Segmentectomy	**0%**	**3,2%**	0.051
Atypical wedge resection	7.8%	7.2%	0.134
Exploratory thoracotomy	4.3%	2.8%	0.139

Table 3. Distribution of different surgical types for lung cancer

Distribution of lung cancer cases according to staging is shown in *Table 4*. Due to the change of TNM classification, comparison of advanced cases might be distorted, but the early cases are unchanged. 30 day mortality after neoadjuvant chemo/radiotherapy was 5.7% (3/53) in the second period, while there was no preoperative treatment in the first one.

	1st period (1998-2002)	**2nd period** (2008-2012)	***p*-value**
I/A	87 (17.5%)	261 (32.7%)	0.001
I/B	145/497	202 (25.3%)	0.029
II/A	7/497	46/799	0.001
II/B	91 (18.3%)	48/799	0.001
III/A	83 (16.7%)	169 (21.2%)	0.142
III/B	29/497	15/799	0.001
IV	26/497	39/799	0.6

Table 4. TNM staging of the resected lung cancer cases

5-year survival was similar in both periods, 52% in the first period and 50% in the second one. Median survival was 27 months after lung resections following neoadjuvant treatment. Less than half of the patients (45.2%) were able to tolerate adjuvant chemo- or radiotherapy after pneumonectomy. This ratio was significantly (p=0.016) higher (82.6%) after sleeve lobectomies. This difference is clearly visible in overall survival as well, patients being able to receive complete adjuvant therapy survived significantly (p=0.009) longer (44 months) compared those, who could not (20 months).

3.3. Discussion I.

From our article No. I. it is clearly visible, that the ratio of women is continuously rising among the lung cancer cases. Analyzing the histological results we can see that nowadays thoracic surgeons meet lung adenocarcinomas most often. Viewing the distribution of tumor stages, it is clear that the proportion of early, I/A stage lung cancers has significantly increased, from 17.5% to 32.7 % (p = 0.001). It can be partially thanked to the improving quality of digitalized radiographycal technique and low-dose CT screening and partially to the fact, that the routine follow-up of patients treated with cancer is performed with CT. The ratio of pneumonectomies decreased from 27.1% in the first period to 9.4% in the second one, paralell to this the amount of lobectomies and sleeve lobectomies increased from 58% to 75.2%. After pneumonectomy only 45.2% of the patients were able to undergo and receive the whole adjuvant chemotherapy. This ratio is significantly higher (82.6%) after sleeve lobectomy. There was no neoadjuvant therapy in the first period, but 53 patients (11.9%) received oncological treatment in the second period. Currently, minimally invasive surgery, VATS is the gold standard. During the first period only the „minor procedures" were performed by VATS, there was no VATS lobectomy. The first VATS lobectomy was carried out in 2006 in our department and 70% of the lobectomies were performed by VATS in 2015.

Most importantly, sublobar resections, primarily segmentectomy is used more and more often with curative intent in the literature and in our practice as well. There was no segmentectomy during the first period, while 3,2% of the operations was anatomical segmentectomy in the second period. This ratio is continuously rising in our practice, according to the european data 6,5 % of resections for tumor is segmentectomy.

Originally, sublobar resections were considered for only high-risk patients with compromised lung function. One of the most frequently used definitions for high-risk patients comes from the American College of Surgeons Oncology Group (ACOSOG) Z4032.

It is very important to emphysize, that nowadays, sublobar resections, especially segmentectomy can be curative surgical operations with the same radicality for otherwise fit patients, who would be candidates for lobectomy as well. There are various clinicopathological, radiological and surgical criterias we should take into consideration to achieve this goal. Mery et al. in their sudy examined the overall survival after lobectomy or sublobar resection and patients' age in 3 different age groups. They found that over 75 years the difference has vanished. Further statistical analysis showed the age of 71 year to be the burning point.

Pulmonary function-preserving limited resection for lung cancer has gradually become more prevalent in the late 20th century. Ginsberg et al.conducted in their randomized conttolled trial in which limited lung resection and lobectomy for stage I lung cancer were compared and reported that limited resection should not be applied to healthy patients. In contrary to this, other studies showed that segmentectomy can provide the same overall and tumor-free survival than lobectomy in selected patients. Nakamura et al. in their meta-analysis found that in the examined 13 retrospective studies the survival after limited resection for stage I lung cancer is comparable to lobectomy, there is no significant difference. Miller et al. examined the survival of 1cm or smaller non-small cell lung cancer cases treated with lobectomy and sublobar resections. There was no difference in tumor recurrence rate between lobectomy and sublobar resections, but wedge resection had higher recurrency rate. El-Sherif et al. found similar survival in patients with IA stage lung cancer between the lobectomy and sublobar resection group and Okumura et al showed the same. 2 cm tumor size was the cut-off value in other studies as well. Aokage et al. in their review of the recently finished and ongoing studies of the Japan Clinical Oncology Group showed satisfactory results after segmentectomy and hilar lymph node dissection in patients with predominantly GGO with I/A tumors. According to the results of JCOG0802/WJOG4607L study, Saji et al. published segmentectomy to be equal to lobectomy with regards to overall survival.

4. Study II.

Tamás Zombori, Tibor Nyári, László Tiszlavicz, Regina Pálföldi, Edit Csada, Tibor Géczi, Aurél Ottlakán, Balázs Pécsy, Gábor Cserni, József Furák. The more the micropapillary pattern in stage I lung adenocarcinoma, the worse the prognosis-a retrospective study on digitalized slides Wirchows Archives 472, pages949–958 (2018) DOI: 10.1007/s00428-018-2337-x

4.1. Materials and methods II.

Haematoxylin-eosin slides of consecutive patients having pulmonary adenocarcinoma in stage I according the 8th Edition of TNM Classification were analysed in our retrospective cohort study II. The patients were operated on between 2004 and 2013 at the Department of Surgery, University of Szeged. For all cases included, mucin staining and immunohistochemistry were applied in the routine diagnostic process. Clinical and follow-up data were obtained from medical charts. Stage I was defined by the combination of tumour size and nodal status in addition to clinical data about the lack of distant metastasis. The follow-up period ended on the 31th August 2017. All available tumour containing slides were digitalized by a Panoramic 250 scanner (3DHistec, Budapest). In the present study, we used digitalized slides. In the first step, the proportions of growth patterns were estimated in 5% increments, and the predominant, secondly and thirdly predominant components were determined with naked eye evaluation. In the second step, the different patterns of the entire tumour were annotated and their areas were measured in square millimetre. The proportions of each component were calculated from the measured areas. In the third step, the predominant and secondly predominant patterns were reevaluated in one third of the cases after a time period of minimum 2 weeks. The patterns were re-annotated for assessing intra-observer variability. All available tumour slides were used for all the listed evaluations. Statistical models were based on the calculated proportions of the components (second step evaluation mentioned above). Spearman’s rank correlation was used to investigate intraobserver variability. Five-year overall and disease-free survival estimates and mean survival times with their 95% confidence intervals (95% CI) for overall and disease-free survival were assessed using Kaplan-Meier estimates. The log rank test was used for pairwise comparisons. All statistical tests were two-sided, and $p<0.05$ values were considered statistically significant. We utilised the SPSS Statistics software (IBM, SSPS 22.0, Armonk, NY, USA)

4.2. Results II.

Altogether, 327 patients matched the inclusion criteria described in the materials and methods' section in our histopathological study. After exclusion of patients with missing data or slides, 243 cases remained for this retrospective analysis, with 141 cases in stage IA1–3 and 102 cases in stage IB. Median age of the patients was 62.3 years (range 33–85). No gender predominance was observed (female 50.7% vs. male 49.3%) in stage I. Most patients had complete lobectomy (lobectomy 90.1% vs. sublobar resection 9.9%). *Table 5* displays the most important clinicopathological data.

Clinicopathological data	
Gender	**n (%)**
Female	123 (50.7%)
Male	120 (49.3%)
Age	**years**
mean	61.6
median	62.3
Localisation	**n (%)**
Left	144 (59.2%)
Right	99 (40.8%)
Type of surgery	**n (%)**
Lobar resection	219 (90.1%)
Sublobar resection	24 (9.9%)
Smoking habits	**n (%)**
Active smoker	170 (70%)
Not anymore > 1year	21 (8.6%)
Never	52 (21.4%)
pT (pN0, pM0)	**n (%)**
T1a	13 (5.5%)
T1b	64 (26.3%)
T1c	64 (26.3%)
T2a	102 (41.9%)
Stage	
IA1-3	141 (58.1%)
IB	102 (41.9%)
Immunophenotype/Histochemistry	**n (%)**
TTF-1 positive	188 (77.3%)
CK-7 positive	243 (100%)
Alcian-blue positive	198 (81.4%)

Table 5. Clinicopathological characteristics of patients

With all available haematoxylin-eosin-stained slides digitalized and evaluated, the median number of slides per patient was 3 (range 2–5). Although the statistical results described below were based on the calculated proportions of the components, the results were similar if the proportions were determined with naked eye. In *Table 6*, the different growth patterns were recorded in all cases as predominant, secondly predominant, thirdly predominant or absent and associated with 5-year overall and disease-free survival estimates. The median follow-up was 61.5 months (range 1.5– 175.3 months). Significant differences in survival rates were found in association with proportions of lepidic pattern (better survival) and proportions of micropapillary or solid patterns (worse survival).

Growth pattern	**·dominant (1)**			**Secondly predominant (2)**			**Thirdly predominant (3)**			**Absent (0)**			
	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)	p
													(log rank test)
Lepidic	48 (20)	90.5	89.4	25 (10)	67.2	54	34 (14)	75	75	136 (56)	69.4	60.3	p1-0=0.005 (OS)
													p1-0=0.004 (DFS)
													p1-2=0.019 (OS)
													p1-2<0.001 (DFS)
Acinar	36 (15)	83.3	61.,5	45 (19)	84.4	76.3	17 (7)	58.4	63.5	145 (59)	70.9	66.7	
Papillary	35 (15)	85.2	72.4	44 (19)	72.4	73.9	31 (13)	91.4	82.,5	133 (53)	66.,8	56.1	
Solid	100 (41)	64.1	56.3	10 (4)	69.5	60	26 (11)	73.1	72.1	107 (44)	82.9	73.2	p1-0<0.001 (OS)
													p1-0=0.023 (DFS)
Micropapillary	16 (7)	28.1	28.1	20 (8)	51.1	57.8	26 (11)	65.7	63.4	181 (73)	74.9	67.8	p1-0<0.001 (OS)
													p1-0=0.004 (DFS)
													p2-0=0.002 (OS)
													p2-0=0.05 (DFS)
													p1-2=0.02 (OS)
													p1-2=0.004 (DFS)
Cribriform	8 (4)	75	75	9 (4)	88	88	7 (3)	68.6	71.4	219 (89)	73.3	64.2	

Table 6. Kaplan-Meier estimates of 5-year overall survival (OS) and disease-free survival (DFS) rates, and mean values of OS and DFS associated with predominant, secondly and thirdly predominant or absent growth patterns and the log rank p values found significant are displayed

Growth pattern	>75%			51-75%			25-50%			<25%			0%		
	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)
Lepidic	25 (10)	88	91.4	14 (6)	70.3	76.2	4 (2)	75	75	21 (9)	75.2	60	179 (73)	70.5	61
Acinar	20 (8)	90	68.7	15 (6)	93.3	79.4	21 (9)	72.5	66.3	51 (21)	78.3	72.8	136 (56)	67.8	60
Papillary	24 (10)	82.9	70	14 (6)	92.9	77.9	13 (5)	84.6	76.9	63 (26)	78.3	74.9	129 (53)	65.1	56.8
Solid	81 (34)	58.2	52.2	15 (6)	68	65.2	13 (5)	50	53.8	29 (12)	80	78.1	105 (43)	82.5	72.7
Micropapillary	15 (6)	25	25	18 (7)	38.9	37	12 (5)	55	57.80	37 (15)	70.6	68.4	161 (67)	74.1	68
Cribriform	6 (2)	66.7	66.7	7 (3)	100	100	5 (2)	100	100	18 (7)	82.5	63.2	207 (86)	72.4	73.1

Table 7. Kaplan-Meier estimates of 5-year overall survival (OS) and disease-free survival (DFS) and mean values of OS and DFS associated with different proportions of growth patterns

Table 7. demonstrates the overall and disease-free estimates of growth patterns grouped into five groups, namely 0,≤ 25, 26–50, 51–75 and ≥ 75%. Significant differences were observed between various subgroups of lepidic, solid and micropapillary patterns.

Growth pattern	≥5%			<5%			log rank	
	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)	p (OS)	p (DFS)
Lepidic	61 (25)	81.4	77.8	182 (75)	72.1	61.6	**0.04**	**0.021**
Acinar	100 (42)	72.6	61.2	143 (58)	68.5	59.8	0.23	0.28
Papillary	104 (43)	78.6	71.4	139 (57)	73.4	67.4	0.54	0.12
Solid	127 (52)	67.5	58.7	116 (48)	80.2	71.7	**0.012**	**0.005**
Micropapillary	56 (23)	61.2	53	187 (77)	75.6	68.7	**0.045**	**0.041**
Cribriform	24 (10)	86.3	72	219 (90)	82	64.3	0.31	0.56
Growth pattern	≥1%			<1%			log rank	
	n (%)	OS (%)	DFS (%)	n (%)	OS (%)	DFS (%)	p (OS)	p (DFS)
Lepidic	64 (27)	82.2	78.9	179 (73)	71.7	61	**0.037**	**0.008**
Acinar	107 (44)	75.8	71	167 (56)	67.8	60	0.33	0.58
Papillary	114 (47)	80.3	74.1	129 (53)	71.5	65.2	0.27	0.078
Solid	138 (57)	66.7	60.2	105 (43)	82.5	72.7	**0.045**	**0.005**
Micropapillary	72 (30)	69.4	56.6	171 (70)	74.1	68,6	0.95	0.11
Cribriform	31 (13)	82.5	71.9	212 (87)	72.4	64	0.42	0.49

Table 8. Five-year overall survival (OS) and disease-free survival estimates and mean values of ≥5% or less and ≥1% or less component with log rank model results

The overall and disease-free survival rates of growth patterns classified as ≥ 5 and < 5% and ≥ 1 and < 1% are displayed in Table 8. With the 5% cut-off point, significant differences in survival were observed in lepidic, solid and micropapillary patterns, and with the 1% cut-off point in lepidic and solid patterns.

There was no recurrence in 151 cases (62.1%). Among these cases, the predominant patterns were the following: lepidic (n = 40), acinar (n = 22), papillary (n = 25), solid (n = 54), micropapillary (n = 5) and cribriform (n = 5). Recurrence was diagnosed in 92 cases including lepidic (n = 8), acinar (n = 14), papillary (n = 10), solid (n = 46), micropapillary (n = 11) and cribriform (n = 3) carcinomas. The rate of recurrence was low in lepidic carcinoma (16.6%); intermediate in acinar (38.8%), papillary (28.5%) and cribriform carcinomas (37.5%); and high in solid (46%) and micropapillary carcinomas (68.7%). Systemic dissemination was detected in 59 patients including lepidic (n = 5), acinar (n = 8), papillary (n = 6), solid (n = 30), micropapillary (n = 9) and cribriform (n = 1) carcinomas. In the non-recurrent group, the average proportion of lepidic, solid and micropapillary patterns were 20, 4 and 5%, respectively, whereas in the recurrent group, these rates were 8, 48 and 13%, respectively. The proportions of other patterns were close to equal in the recurrent and non-recurrent groups.

4.3. Discussion II.

During the careful preoperative imaging evaluation, we can get information not only about the details of the planned surgical procedure, but sometimes about the likely histological type of the tumor as well. Tumor histology plays crucial role in OS. Predominance of Groung Glass Opacity (GGO) of a lung nodule on thin-sliced CT has been widely recognized to correlate with less-invasive pathological finding of cancer cells replacing the alveolar epithelial cells (lepidic growth). Many researchers have reported that patients with lung adenocarcinomas of predominantly GGO on CT images achieved very good prognoses following surgical resection. Radiological non-invasive lung adenocarcinoma was initially defined as those with a consolidated maximum tumour diameter to tumour diameter ratio (C/T ratio) of less than 0.5 based on previous reports (Fig.5). On CT consolidation component is defined as an area of increased opacification that completely obscures the underlying vascular structures, while ground-glass opacity is defined as an increased hazy density that does not obscure the underlying vascular structure. In an exploratory analysis, the authors examined several C/T ratio cut-off values and found 0.25 resulted in diagnostic specificity of 98.7%.

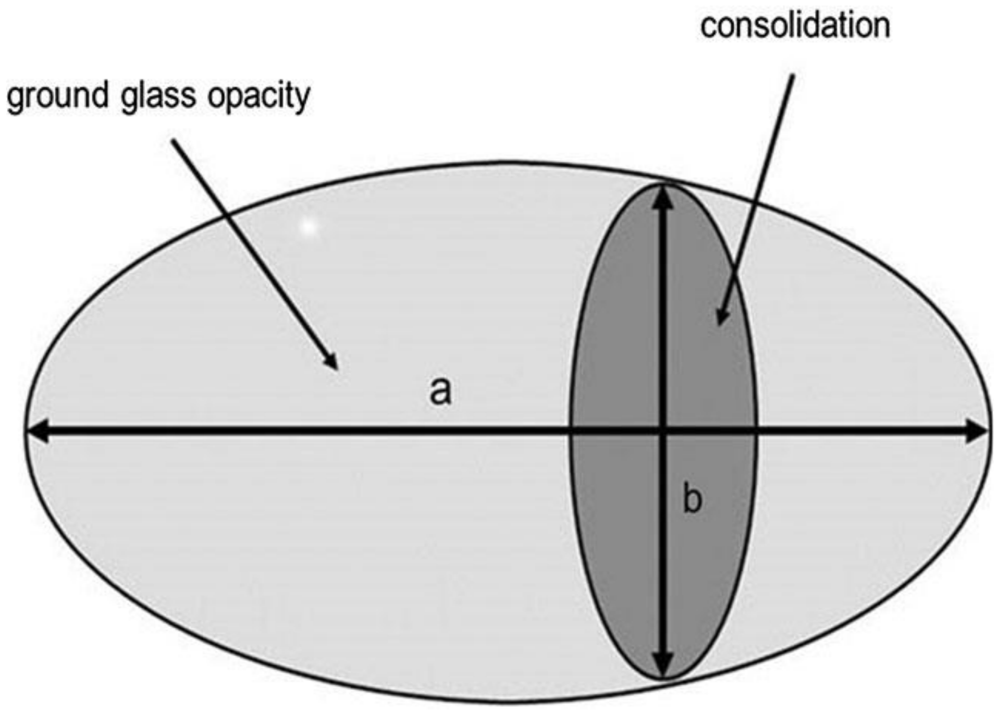

Fig. 5. Schematic of a pulmonary nodule with ground-glass opacity on CT. Length a: the maximum tumour dimension, including the ground glass part, in the lung window. Length b: the maximum consolidation size in the lung window. The consolidation-to-tumour ratio (C/T ratio) was defined as b/a.

It is clear that the final histologicy type of small-sized lung cancers has a huge impact on survival. Among the small, early non-small cell lung cancers squamous cell carcinomas are rare, adenocarcinomas ar more common. Okumura et al.in their study showed that segmentectomy resulted in a poor outcome in patients with large cell carcinomas. The new WHO classification of lung adenocarcinomas follows the recommendations of the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS). Although the majority of these carcinomas are mixed, the classification takes only the predominant pattern into consideration. Recent studies have shown that secondly predominant patterns or even a small proportion of some patterns can alter prognosis. Lepidic growth pattern is the first morphologic sign of carcinogenesis, and if the tumour shows only this pattern, it is called in situ carcinoma and has an excellent prognosis. The lepidic pattern may be associated with other patterns in mixed tumours. Lepidic carcinoma is an invasive mixed tumour with lepidic predominant component and is associated with favourable outcome; therefore, it may be proposed that the more lepidic pattern, the better the prognosis. Our results confirm the evidence that lepidic predominant carcinoma has a favourable prognosis, but there was no difference in overall or disease-free survival between tumours with secondly predominant lepidic component and tumours without lepidic component. A difference was found between the mean proportion of lepidic component of tumours with recurrence (8%) and those without recurrence (20%).

Solid pattern lacking glandular differentiation is a feature of high-grade lung adenocarcinomas. Recent studies have shown that solid predominant adenocarcinoma has a poor outcome and secondary predominant solid pattern or even a small amount of solid component (≥ 5 or ≥ 1%) may worsen the prognosis. A significant difference was observed between OS and DFS of tumours having ≥5 or ≥ 1% solid component and those having less. Similarly, significant differences were found in OS and DFS between various comparisons of tumours with solid component of 0, ≤ 25, 26–50, 51–75 and > 75%. Concerning a solid predominant component, significant differences were found between the OS and DFS estimates of solid predominant tumours and neoplasms without solid features. Despite the worsening tendency of OS and DFS with growing proportion of the solid pattern, there were no differences between tumours having secondly or thirdly predominant solid component and tumours without solid pattern. The mean proportion of solid pattern in tumours with recurrence was 48%, contrasting with the 5% in adenocarcinomas without recurrence. The micropapillary pattern has been incorporated in the adenocarcinoma classification since 2015. Although, according to the classification based on predominant pattern, it would seems that only the greatest proportion of this pattern matters, some studies indicated that even a minimal amount of micropapillary area is associated with poor prognosis. Kamiya et al. found that both OS and DFS estimates were worse with the increase in the proportion of the micropapillary component. Zhang et al. have divided their patients into four groups according to the extent of micropapillary component, namely < 1, 1–5, 6–50 and > 51%. Their conclusion was similar to that of Kamiya et al. Our results also parallel these two cited studies. The tumours having more than 25% of micropapillary component formed a uniform group according to OS and DFS estimates and differed from tumours having 0–25% micropapillary area. When using the 5% cut-off for micropapillary component, a significant difference was observed in survival in comparison with tumours with no micropapillary component, while at 1% cut off point, such a difference was not found. In contrast with Sumiyoshi and coworkers, a difference was observed between the groups of patients with and without recurrence: the mean proportions of micropapillary pattern were 13 and 4%, respectively. In the present study, a significant difference in survival was observed between tumours without micropapillary pattern and micropapillary predominant tumours. As our study showed, there is a broad spectrum of morphological intra-tumour heterogenity in lung adenocarcinomas. Interestingly, the invasive tumours having only one component had a more unfavourable prognosis, than neoplasms having mixed pattern. This finding may be explained by the fact that most tumours having one component were solid tumours with poor outcome. Several series have concluded that this morphological heterogeneity is paralleled by a more complex genetic heterogenity, as well.

The prognostic impact of predominant growth pattern was proven on the basis of measuring the area occupied by each pattern on all available (and digitalized) slides, i.e. the most precise way of determining the size of each component from the material available. We think that our study was unique in this respect. Tumours with a secondary predominant micropapillary component demonstrated significant differences in OS and DFS from micropapillary predominant tumours and non-micropapillary tumours. Therefore, we suggested using predominant and secondly predominant patterns particularly in tumours having solid (as suggested by others or micropapillary (as proven by our data) patterns. Our results are in tight correlation with the new proposed grading system of lung adenocarcnomas by the Study of Lung Cancer (IASLC) Pathology Committee, which recommended to state all the adenocarcinomas containing at least 20% of solid, micropapillary or cribriform component to be high grade.

We have confirmed that lepidic predominant stage I adenocarcinomas have a good prognosis and solid or micropapillary predominant ones have the worst prognosis. A secondly predominant component of the bad prognostic patterns also worsen prognosis; therefore, the reporting of all patterns observed beyond the predominant component is recommended. Naked eye estimation of the proportions of each pattern does not seem to be worse than objective measurement on digitalised slides and can be used in routine practice.

Stage I lung cancer are tumors smaller than 3 cm without lymph node or distant metastases. The current TNM staging doesn't take into consideration the newly discovered invasion type of lung adenocacinomas, the so called „Spread Through Air Spaces" (STAS), which has been extensively studied by Kadota et al. It is defined as spread of cells into air spaces in the lung parenchyma adjacent to the main tumor, histologically tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor. In their retrospective study the risk of developing any types (locoregional or distant) of recurrence was significantly higher in patients with STAS-positive tumors than in patients with STAS-negative tumors and STAS-positive tumors was significantly associated with worse overall survival. STAS was proved to be a significant prognostic factor for recurrence in patients undergoing limited resection. It was found in almost 40% of resected lung adenocarcinomas and observed tumor cells over 1 cm away from the edge of the tumor. STAS was found mostly in predominant micropapillary and solid adenocarcinomas, lepidic pattern was less frequently identified in SATS positive tumors. STAS is an insidious pattern of invasion, because it is not detectable by pathologists on macroscopic examination and by surgeons during surgery, and there is no radiological sign of it.

5. Study III.

Tibor Géczi, Zsolt Simonka, Judit Lantos, Melinda Wetzel, Zsolt Szabó, György Lázár, József Furák. Near-infrared fluorescence guided surgery: State of the evidence from a health technology assessment perspective Front. Surg. 9:919739. DOI: 10.3389/fsurg.2022.919739

5.1. Materials and methods III.

In our mini-review, we summarized the use of near-infrared guided fluorescence surgery, focusing on the indocyanine green after careful evaluation of the current literature on this topic (*Table 9*).

LUNG						
	Study	**Year**	**Dose**	**Administration route**	**Interval**	**Number of patients**
Intersegmental plane	Misaki (77)	2009	25mg	iv.	30-90s	dogs
	Mun (78)	2017	0.25mg/kg		30-90s	22
	Guigard (79)	2017	25mg			24
	Meacci (80)	2018	12.5-17.5mg			
	Pschlik (81)	2018	0.15mg/kg			86
	Bedat (82)	2018	1.,5mg			67
	Chen (83)	2019	25mg			19
	Jin (84)	2019	0.5mg/kg			21
	Motono (85)	2019	5mg			22
	Yotsukura (86)	2021	0.25mg/kg			209
	Sun (87)	2021	5mg			198
	Oh (88)	2013	25mg	intrabronchial		40
	Wada (89)	2020	10-15mg	intrabronchial		15
	Sekine (90)	2012	10mg	iv.		10
Pulmonary nodule identification	Doo (91)	2015	0.2ml	intratumoral inj.		34
	Ujie (92)	2017	0.15ml	intratumoral inj.		20
	Wen (93)	2018	0.5ml	intratumoral inj.		26
	Wu (94)	2021	1-2.5mg	intratumoral inj.		32
	Jiang (95)	2015	0,7-10mg/kg	iv.	1min-72h	mice
	Okusanya (96)	2014	5mg/kg	iv.	24h	16
	Predina (97)	2017	OTL38:0,025mg/kg iv.		3-6h	20
	Kim (98)	2016	1mg/kg		24h	11
	Hamaji (99)	2019	0.25mg/kg	iv.	12-24h	22
	Predina (97)	2019	5mg/kg	iv.	24h	30
Sentinel lymph node	Yamashita (100)	2011	10mg	peritumoral	10min	31
	Gilmore (101)	2021		peritumoral	before surgery	29
	Hachey (102)	2017	0.5ml	peritumoral (bronchoscopy)	before surgery	20
	Digesu (103)	2018	0.5ml	peritumoral		42
Thoracic duct	Kamiya (104)	2009	7.5mg	bilateral inguinal	14min	1 (case report)
	Matsutani (105)	2014	7.5mg	bilateral inguinal	10min	1 (case report)
	Vecchiato (106)	2020	1.5mg/kg	bilateral inguinal lymph nodes	10.5min	19

Table 9. Literature review of the use of ICG in near-infrared fluorescence guided thoracic surgery

5.2. Results III.

Performing segmentectomy can be very difficult, mainly by thoracoscopy. As mentioned previously, traditionally, the inflation and deflation technique has been used for intersegmental plane identification, owing to difficulties in emphysematous lungs and obstruction of the surgical view mainly during VATS procedures. To avoid these problems, other techniques have been developed, such as selective bronchoscopic ventilation of the affected bronchus, inflation of the selected bronchus by instilling oxygen through a butterfly needle, slip-knot ligation of the bronchus, or selective dye administration into the segmental pulmonary bronchus or artery. In 2009, Misaki et al. conducted an experimental study on dogs and demonstrated the feasibility of intersegmental plain identification using near-infrared imaging after intravenous administration of ICG. During the surgery, immediately after the identification and division of the segmental arteries, ICG was injected through a peripheral vein (Fig. 6.).

5.3. Discussion III.

As we could see, after careful and proper patient selection segmentectomy can provide sufficient radicality and lung parenchyma preservation at the same time. Surgical trauma can be further minimalized by VATS, which reduces the surgical trauma coming from surgical access and moreover non-intubated thoracic surgery (NITS) is able to lower the anaesthetic trauma coming from securing airway and arteficial ventillation. When perfroming segmentectomy, proper intersegmental plane identification is important. During near-infrared fluorescence surgery, immediately after the identification and division of the segmental arteries, ICG is injected through a peripheral vein. Thanks to this, the lung segment having no circulation will not show fluorescence and the border between this area and the lung parenchyma with normal circulation will be clearly visible. In conclusion, NIR angiography is a safe, easy-to-reproduce, effective, and inexpensive method to improve the quality of VATS segmentectomy.

6. Summary of our 3 studies

1. In summary, we can say, that in our first study we ascertained that the proportion and number of small-sized, early-stage lung cancers, mostly adenocarcinomas are continuosly increasing in an older population with poorer lung function and general status.
2. At the same time the proportion of women is also rising in this population
3. The surgical practice accomodated to this tendency, there are more and more sublobar resections (and importantly segmentectomies) performed in this population
4. According to our second study, we showed that lepidic predominant carcinoma has a favourable prognosis, while predominant micropapillary and solid pattern suggests worse survival
5. We also suggested using predominant and secondly predominant patterns particularly in tumours having solid or micropapillary patterns, because these have their own individual effect on survival
6. In our third article we showed the usefulness of ICG and NIR fluorescence imaging in thoracic surgery, mainly in identification of intersegmental plane during segmentectomies

In our practice, after careful preoperative evaluation of the patient and images, we perform lung segmentectomy for patients with lymph node negative non-small cell lung cancer smaller than 2 cm, when the minimum 1 cm tumor-free margin can be achieved. If necessery, ICG and near-infrared fluorescence guidance is used for intersegmental plane identification.

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