SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3398.

JÁNVÁRY ZSOLT LEVENTE

Klinikai onkológia és sugárterápia

című program

Program- és témavezető: Dr. Polgár Csaba, egyetemi tanár

STEREOTACTIC BODY RADIOTHERAPY OF PRIMARY AND SECONDARY LUNG TUMORS USING CYBERKNIFE AND LINEAR ACCELERATOR: ANALYSIS OF CLINICAL RESULTS, PROGNOSTIC FACTORS AND TOXICITY

PhD thesis

Zsolt Levente Jánváry, MD.

Semmelweis University Doctoral School

Pathological and Oncological Division

Supervisor: Csaba Polgár, MD, DSc

Official reviewers: Péter Radeczky, MD, PhD

Anikó Maráz, MD, PhD

Head of the Complex Examination Committee: Veronika Müller, MD, DSc

Members of the Complex Examination Committee: Gergő Papp, PhD

Csilla Katona, MD, PhD

Budapest

2025

Table of contents

List of abbreviations:

18F-FDG PET/CT: Fluorine-18-fluorodeoxyglucose positron emission tomography-computer tomography

4D-CT: four-dimensional CT

AE: adverse event

ASTRO: American Society for Radiation Oncology

BED: biologically equivalent dose

BED_{10}: biologically effective dose using $\alpha/\beta=10$ Gy

CBCT: cone-beam CT

CI: confidence interval

CK: CyberKnife

COPD: chronic obstructive pulmonary disease

CT: computer tomography

CTCAE: common terminology criteria for adverse events

CTV: clinical target volume

DRR: digitally reconstructed radiograph

DVH: dose volume histogram

ECOG: Eastern Cooperative Oncology Group Performance Status

EORTC: European Organisation for Research and Treatment of Cancer

ETT TUKEB: Hungarian Ethical Review Board (Egészségügyi Tudományos Tanács Tudományos és Kutatásetikai Bizottság)

ESTRO: European Society for Radiotherapy and Oncology

FEV1: forced expiratory volume in one second

FEV1 (%): forced expiratory volume in one second, % of predicted

FFF: flattening filter-free

GTV: gross tumor volume

Gy: Gray

HR: hazard ratio

IGRT: image-guided radiotherapy

ITV: internal target volume

LC: local control

LF: local failure

LINAC: linear accelerator

LPFS: local progression-free survival

LQ-model: linear quadratic model

MLC: multi-leaf collimator

MLD: mean lung dose

NA: not applicable

NS: not stipulated

NSCLC: non-small cell lung cancer

OAR: organ at risk

OS: overall survival

PFS: progression-free survival

PTV: planning target volume

PTX: pneumothorax

RECIST: response evaluation criteria in solid tumors

RTOG: Radiation Therapy Oncology Group

SBRT: stereotactic body radiotherapy

SRT: stereotactic radiotherapy

SRS: stereotactic radiosurgery

TPS: treatment planning system

VMAT: volumetric modulated arc therapy

1. Introduction

Stereotactic radiotherapy (SRT) is a special type of external beam radiotherapy, delivering high doses on relatively small targets, with high accuracy, while maximizing the protection of surrounding organs. The principle of SRT is the application of a large number of beams, aiming onto the same point (either by static beams or rotating arcs), resulting a dose concentration in the intersection, and the dilution of the dose in the neighbouring tissues due to rapid dose fall-off **(Figure 1)**.

Nowadays, modern SRT is widely used in medically inoperable early-stage lung cancer and in patients with limited number of lung metastases. The aim of this thesis is to evaluate clinical outcomes, prognostic factors and side effects of primary and secondary lung tumors treated with stereotactic radiotherapy.

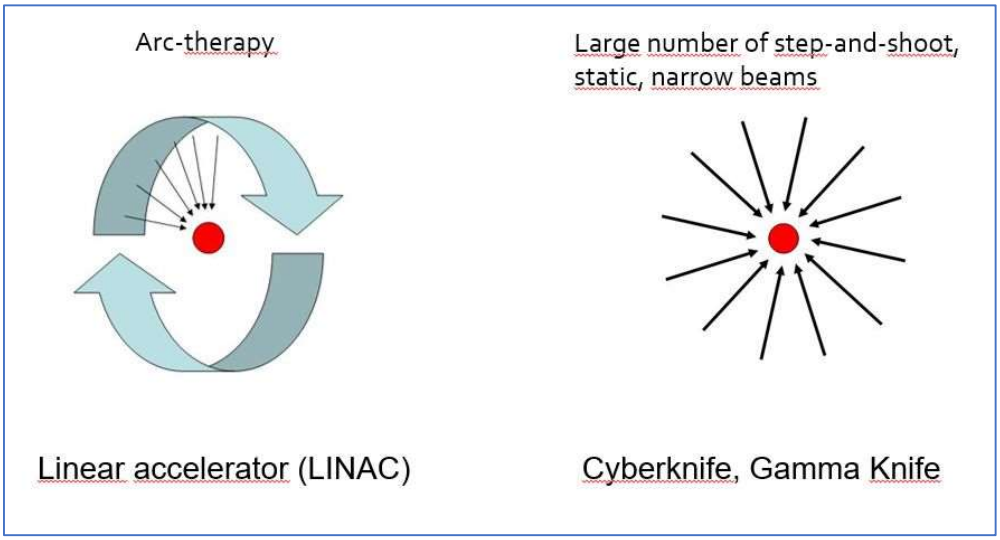


Figure 1. Principles of stereotactic radiotherapy

1.1. Principles of stereotactic radiotherapy

The introduction of stereotactic radiotherapy dates back in the 1960s, when the method was first applied in intracranial targets. Originally, the treatment was delivered in one, high-dose fraction, with ablative effect, which was called stereotactic radiosurgery (SRS).

The first dedicated machine, the Gamma Knife, was developed by Lars Leksell neurosurgeon and his coworkers, having the first patient treated in 1968 in Sophiahemmet Hospital in Stockholm, Sweden [1]. This machine contained multiple, non-opposed cobalt-60 sources positioned in a hemisphere and the method required the use of a rigid, external fixation frame, attached to the skull bone to provide precise, three-dimensional coordinates for targeting radiation to a specific area. For long decades, brain SRS was successfully performed for thousands of patients with Gamma Knife or later with gantry-based linear accelerators, using invasive stereotactic head-frames.

The concept was only able to be transferred to extracranial tumors (SBRT=Stereotactic body radiotherapy) in the 1990s, thanks to newer developments on radiation delivery, imaging, patient immobilisation, and position verification. [2]. For SBRT, gantry-based linear accelerators were applied, using photon beams. Challenges linked to uncertainties of external skin markers, organ and tumor motion, led to invention of stereotactic body frame immobilisation systems equipped with vacuum bed, abdominal compression devices to reduce diaphragm movement, and high-quality, 3D position verification imaging, like cone-beam CT (CBCT). Besides the gantry-based machines, from the late 1990s - early 2000s a dedicated SBRT/SRT system was also introduced, with robotic technology, intrafraction position-verification, and the possibility of real-time tumor tracking: it was called CyberKnife. In addition to these, there are further technologies to implement SBRT, using helical tomotherapy or protontherapy.

In contrast to conventional radiotherapy, stereotactic treatments are performed in an extremely hypofractionated way, ranging from 1 to 8 fractions of high doses. The linear-quadratic (LQ) model is a radiobiological formula to predict the effect of irradiation. This formalism is commonly used to compare the biological effect of different fractionation schemes.

Biologically Effective Dose (BED) = $n \times d (1+ d / \alpha/\beta)$,

where n is the number of treatment fractions, d is the dose per fraction in Gray (Gy) and α/β is a tissue-specific ratio, generally ≥ 10 for most tumors.

Though there are uncertainties, whether the abovementioned equation can be used for high single fractions, it is generally applied for the comparison of different SBRT regimens.

The radiobiological aspects of SBRT are described in detail in the work of Macià I Garau [3].

1.2. Technical aspects of thoracic SBRT

Treating intrapulmonary lesions is especially affected by organ movement due to breathing. Therefore, the actual position of intrapulmonary targets relative to bony landmarks or skin markers is not only affected by intraabdominal/intrathoracic pressure, but also by the cyclic movement of respiration. The uncertainties introduced by these phenomena require the application of elaborated preparational procedures and robust quality assurance in terms of CT-simulation, tumor-position verification during patient setup and responsible delivery of high dose/fraction radiotherapy. The summarizing name of the strategies aimed to overcome the uncertainties mentioned above, is *respiratory movement management*. A schematic comparison of the different strategies is depicted in **Figure 2.** For gantry-based LINAC machines there are several concepts available: During respiratory gated technique, irradiation is only given in a certain narrow range of the respiratory cycle, typically near to exhale position, allowing a few millimetres of movement. This method is performed in free breathing, but uses surrogates to detect the actual breathing phase. Deep inspiration breath hold (DIBH) technique requires voluntary holding of the breath in deep end-inspiration phase, and irradiation is only given when the target is motionless. Obvious advantage of these two techniques is smaller irradiated volume, but fundamentally longer treatment times and the need for special devices imply considerable limitations. Internal target volume (ITV) method is one of the most widespread ways for LINAC-based SBRT. During this method, the target volume covers the whole range of movement between the two end phases in free-breathing, resulting in a larger treated volume, but also better patient comfort, and a relatively simple feasibility with the most of modern linear accelerators equipped with CBCT. Additionally, very

short treatment times can be observed with the application of volumetric modulated arc therapy (VMAT) rotational delivery technique.

In terms of respiratory motion management, the main advantage of the CyberKnife robotic system is the capability of real-time tumor tracking. Due to specific parts of the system as the orthogonal 2D X-ray pair, internal- (gold fiducials of tumor contour), and external markers (LED lights on the body surface) a complex algorithm can follow the tumor movement during free-breathing. This leads to better patient comfort and reduced target volumes, but also longer treatment times compared to VMAT-ITV treatments.

Figure 3. shows the construction of a gantry-based LINAC and the robotic CyberKnife system. Despite the many differences, between the two technologies, both produce rapid dose fall-off in the target region using similar photon beams, as the CyberKnife uses a compact, lightweight 6 MV linear accelerator.

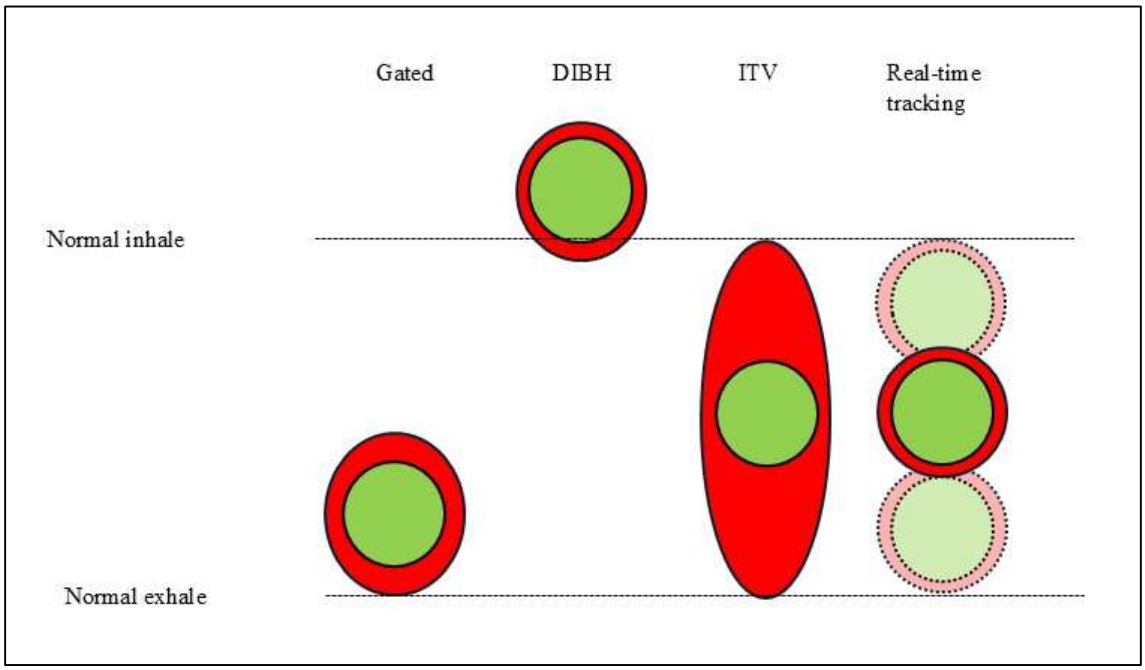
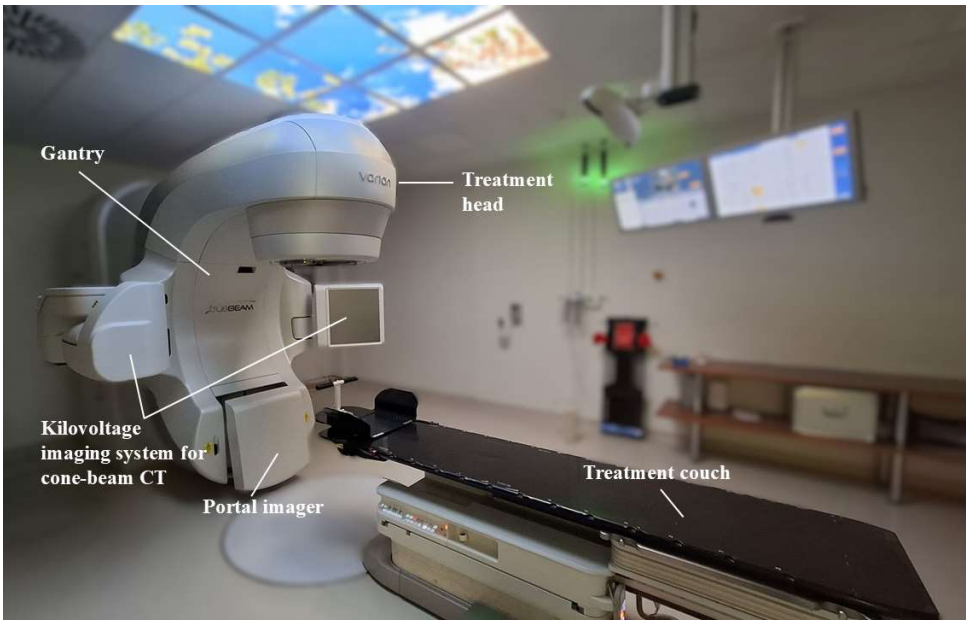


Figure 2. Illustration of different respiratory movement management techniques

a)



b)

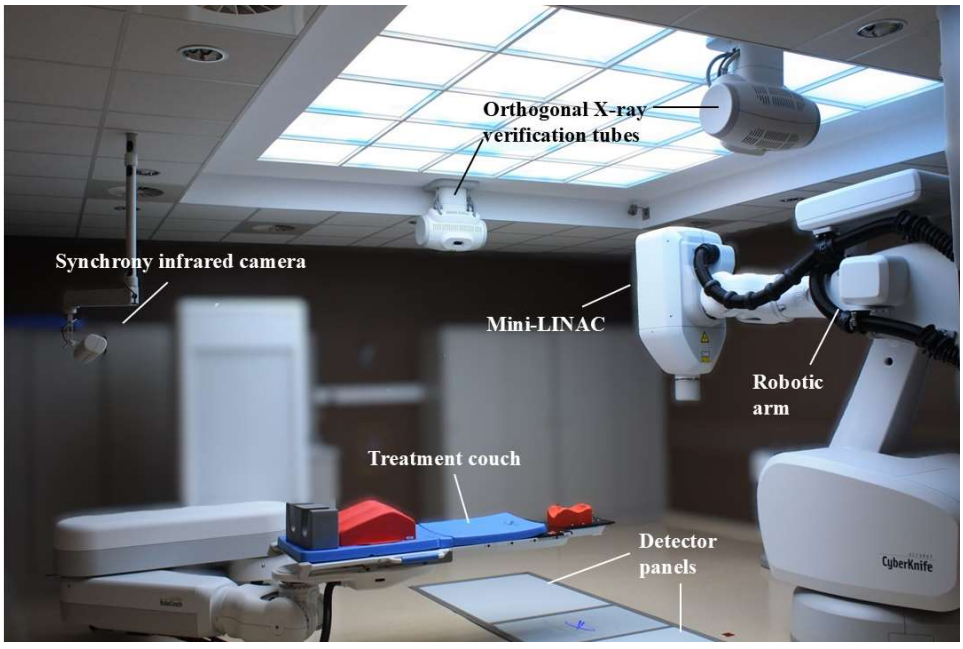


Figure 3. Gantry-based and robotic devices for SBRT: **a)** TrueBeam LINAC by Varian **b**) CyberKnife VSI robotic radiosurgery unit (generation 5) by Accuray

1.3. The place of SBRT in the management of lung tumors

The gold standard treatment for early-stage non-small cell lung cancer is surgical removal, however in case of medical inoperability, non-surgical alternatives are needed. Currently, there are several technologies available to perform non-surgical local treatment in the lung, including microwave ablation, radiofrequency ablation or cryoablation, using either extreme heat or cold to cause tumor-tissue necrosis. While the methods listed above are invasive, with the necessity of insertion of a special tool near/inside the tumor, stereotactic radiotherapy can be performed in a completely non-invasive way.

The phase II. trial of Timmermann et al. (RTOG 0236, = Radiation Therapy Oncology Group) was one of the first studies establishing the extremely high local control rates (97%) of SBRT, with 3-year OS of 56%, after the application of 3x18 Gy regimen [4].

Results from the study of Lagerwaard et al. underlined the importance of differentiation of dose schemes during lung SBRT in function of the localization of the target lesion, with more caution, and more modest biological doses on central lesions. In this study 3 dose regimens were used (3 x 20 Gy, 5 x 12 Gy, and 8 x7.5 Gy), and authors emphasised the need for risk-adapted fractionation in lung SBRT [5].

By now, SBRT has become the treatment of choice in many countries for medically inoperable early-stage non-small cell lung cancer, supported by guidelines from ESTRO (European Society for Radiotherapy and Oncology), ASTRO (American Society for Radiation Oncology), and EORTC (European Organisation for Research and Treatment of Cancer) [6-8].

Obviously, histological confirmation is the basis of all cancer therapies, even for inoperable cases. This could be achieved via bronchoscopy for centrally located tumors, but often, peripheral lesions are only accessible by percutaneous transthoracic biopsy. However, a significant proportion of medically inoperable patients present poor lung functions or other comorbidities contraindicating percutaneous needle biopsy. Provided that 18F-FDG PET/CT (Fluorine-18-fluorodeoxyglucose positron emission tomography-computer tomography) supports a strong suspicion of malignancy, nowadays these conditions are considered eligible for SBRT in many centers, in the absence of other alternative, effective therapy.

The precise techniques of SBRT are not limited to primary lung cancer but can be performed in lung metastases as well. With the era of modern systemic anticancer therapies, patients with solitary-, or oligometastases in the lung can be long survivors, therefore aggressive local treatments can be justified.

Over time, several dose and fractionation schemes has been tested by different workgroups using 1-8 fractions of SBRT with wide ranges of biological effective doses, however, the results concerning optimal lung SBRT doses are controversial.

This thesis is based on two clinical studies with focus on optimal dose, clinical results, predictive factors and toxicities. Both benchmarking researches investigated the implementation of a special technique, being novelty in the given institutions. Question was raised whether clinical results of a large cohort of the first consecutive patients would reflect high rate of success, as had been shown in the literature. Furthermore, our results make contribution in defining the optimal, individualized dose/fraction regimens in lung SBRT.

2. Objectives

1. Evaluation of clinical results of primary and recurrent lung tumors and lung metastases treated with CyberKnife stereotactic radiotherapy (SBRT) .

2. Evaluation of long-term clinical results focusing on a large-scale, consecutive patient cohort of early-stage primary lung cancer treated with gantry-based LINAC or CyberKnife SBRT.

3. Analysis of predictive factors influencing local control (LC), local progression free survival (LPFS), progression free survival (PFS) and overall survival (OS) in patients treated with lung SBRT.

4. Validation of use of SBRT in patients of high risk of invasive biopsy (unknown histology).

5. Investigation of early-, and late toxicities after pulmonary SBRT.

6. Validation of use of risk-adapted SBRT dose-schemes in a real-life cohort.

3. Methods

The thesis is principally based on two large-cohort, retrospective studies. The first one was based on patients treated for either primary, recurrent or metastatic lung tumors in the University Hospital of Liège (CHU de Liège), Belgium between 2010 and 2012, using Cyberknife robotic fractionated SBRT (results published in 2017, in Radiology and Oncology, Jánváry et al. [9]). The second study was conducted in the National Institute of Oncology (NIO), Budapest between 2015 and 2023, on a larger, and more homogenous patient cohort of exclusively early-stage primary lung cancer treated predominantly with LINAC or with CyberKnife to a lesser extent (results published in 2025, in Strahlentherapie und Onkologie, Jánváry et al. [10]).

3.1. Methods of Study I.: Cyberknife SBRT of primary, recurrent, and secondary lung tumors (Belgium)

Patients of Study I.

A CyberKnife robotic stereotactic system was installed in the University Hospital of Liège, Belgium in 2010, enabling the implementation of intra-, and extracranial SRT treatments. This retrospective analysis focused on clinical results and toxicities of patients treated for intrapulmonary malignancies. In total we identified 130 patients treated between April 2010 and June 2012, including medically inoperable patients presenting 62% primary (n=81), 18% (n=23) recurrent lung cancer, and 20 % (n=26) with solitary or oligometastatic lung lesions from other primary malignancies. Most of the patients were elderly, with a median age of 71 years (range 40–93), and treatment decisions were made in multidisciplinary tumor boards. The presence of histological confirmation was needed, mostly for primary tumors either by bronchoscopy or percutaneous biopsy, or in case of contraindications for invasive verification (due to poor lung function, comorbidities, or technical ineligibility) strong clinical diagnosis based on high FDG-18 uptake on PET/CT was also accepted for SBRT.

For the one hundred and thirty patients, 160 lesions were treated in total, with 53% (n = 86) primary, 22% (n = 35) recurrent tumors/intrapulmonary metastasis of an earlier lung tumor and 25% (n = 39) of metastatic origin from other malignancies.

For the 86 metastases the primary cancer was colorectal in 49% (n = 19), salivary gland in 13% (n = 5), breast in 10% (n = 4), melanoma and kidney in 5-5% (n = 2-2), neuroendocrine tumor in 3% (n = 1), multiple primaries in 13% (n = 5), and unknown in 2% (n = 1). In the primary cancer subgroup, there were 62 cases with histology proven disease, with 47% adenocarcinoma, 33% squamous cell carcinoma, 15% NSCLC and 5% undifferentiated cancer. In the whole study group, the rate of histological confirmation was 62% (n=81) in terms of patients, and 54% (n=86) in terms of lesions. The distribution of peripheral vs central location of the target lesions was 71% vs 29%. Lesions were classified central, if located within 2 cm from great vessels, heart, hilar structures, oesophagus or trachea. Detailed patient, tumor and treatment characteristics are shown in **Table 1.** As presented in the table, T3 tumors and T1N1, lymph node positive cases were also represented in smaller numbers. For this latter subgroup, the primary tumor and the positive hilar lymph node were irradiated at the same time, both with SBRT technique.

Table 1. Patient, tumor and treatment characteristics for Study I. (table from: Jánváry, 2017 [9])

Characteristic	n (%)
Total number of patients/lesions	130 (100%)/160 (100%)
Mean age in years	71 (range: 40–92)
Male/female ratio	77 (59%) / 53 (41%)
No. with COPD	45 (35%)
Mean FEV1 (%)	65 (range: 24–139)
Mean FEV1 (L)	2 (range: 0.53–3.65)
Histological confirmation	79 (61%)
Primary cancer patients/lesions	81 (62%) / 86 (54%)
T1N0	53
T2N0	19
T3N0	5
T1N1	4
Recurrent tumor patients /lesions (n)	23 (18%) / 35 (22%)
Lung metastasis patients /lesions (n)	26 (20%) / 39 (24%)
Mean GTV volume (ml)	11.5 (range: 0.6–86.5)
Mean PTV volume (ml)	33.2 (range: 5.8–118.1)
Location of lesions: peripheral/central	113 (71%) /47 (29%)
Mean total dose (Gy)/Mean no. of fractions	60/3 fx (range: 40–60 / 3–5 fx)
Mean/median BED_{10Gy} (Gy)	151/180 Gy

Abbreviations for Table 1: COPD = chronic obstructive pulmonary disease; FEV1 =forced expiratory volume in 1 second; fx = fractions; GTV = gross tumour volume; PTV = planning target volume, BED10Gy= biologically effective dose using α/β=10 Gy

SBRT treatment of Study I.

The CyberKnife system offered three different treatment methods for respiratory motion management, requiring specific treatment preparation.

1. Fiducial based real-time tumor tracking (Synchrony algorithm) required CT guided placement of gold markers around the target (2-6 fiducial markers implanted), followed by the planning CT in 10-14 days. This method was limited to patients without contraindication of percutaneous puncture. (44/130 pts)
2. Direct tumor tracking (Xsight Lung algorithm) was applicable for selected cases when 2D tumor contours were detectable on the verification kilovoltage X-ray images during treatment. The prerequisite for this method is a tumor size greater than 15 mm, and peripheral location (13/130 pts). The two subtype of Xsight Lung is 2-view if both camera is able to detect tumor position, and 1-view if only one of them.
3. For cases, where neither the two abovementioned respiratory movement tracking method were possible, Xsight Spine algorithm was used. This means the definition of a larger target volume, covering the complete amplitude of tumor movement during the breathing cycle (=ITV method, internal target volume). (73/130pts)

Patient immobilisation was performed using an individual vacuum bag in supine position, with arms next to the body. During CT simulation, planning CT images with a slice thickness of 1 mm were acquired for all cases, to achieve high-resolution images for the planning and for the verification digitally reconstructed radiograph images (DRR). CT simulation was followed by an 18F-FDG PET/CT using the same immobilisation vacuum bag for 96 % of patients to improve target definition. Gross tumor volume (GTV) was contoured to cover the macroscopic tumor, in lung windowing. Then a safety margin of 3 mm was added, to achieve clinical target volume (CTV), which was manually modified

in case on conflict with ribs, or mediastinal organs. In case of Xsight spine method, CTVs in both exhale and inhale position were delineated, and a larger volume between the two end phases was defined (ITV method). The planning target volume (PTV) was defined as CTV +2 mm additional margin.

Radiotherapy plans were performed with Multiplan treatment planning system (TPS), which operated with Ray-Tracing dose calculation algorithm. The main preferred dose/fractions were 3x20 Gy and 3x15 Gy, but dose reduction, or using of 5 fraction was also allowed to decrease risk of toxicities, especially in central localization. We used 3 or 5 fraction dose schemes, to a total dose of 40 to 60 Gy, with respect to nearby organs at risk (OAR) dose limits. The dose was prescribed to 75-82 % PTV-encompassing isodoses. The OAR dose constraints and applied doses are shown in **Table 2. and Table 3.** Mean GTV and PTV volumes were 11.5 cc (range 0.6-86.5) and 33.2 cc (range 5.8-118.1).

Table 2. Dose constraints for organs at risks for Study I. (table from: Jánváry, 2017 [9])

Organ	Type of constraint	Dose (Gy) for 3 fractions SBRT	Dose (Gy) for 5 fractions SBRT
Spinal cord	D_{max}	22 (7.33 Gy/fx)	30 (6 Gy/fx)
Esophagus	D_{max}	27 (9 Gy/fx)	35 (7 Gy/fx)
Trachea and main bronchi	D_{max}	30 (10 Gy/fx)	32 (6.4 Gy/fx)
Heart	D_{max}	30 (10 Gy/fx)	38 (7.6 Gy/fx)
Plexus brachialis	D_{max}	24 (8 Gy/fx)	32 (6.4 Gy/fx)
Ribs	D_{max}	37 (12.3/fx)	43 (8.6/fx)
Skin	D_{max}	32 (10.6/fx)	24 (4.8/fx)
Lung (both lungs)	Volumetric	$V_{10.5Gy}$ < 1500 cc $V_{11.4Gy}$ < 1000 cc	$V_{12.5Gy}$ < 1500 cc $V_{13.5Gy}$ < 1000 cc
Liver	Volumetric	$V_{17.1Gy}$ < 700 cc	V_{21Gy} < 700 cc

Abbreviations: Dmax= maximum point dose, fx=fraction, V_{xGy} = volume of tissue receiving x Gy (constraints were based on Timmerman RD et al and AAPM Taskgroup 101 guidelines [11-12])

SBRT treatments were performed with the CyberKnife VSI robotic radiosurgery unit - generation 5- (Accuray, Madison, WI, USA) **(see Figure 3.b)**, using Iris collimator of 15-60 mm apertures, 6 MV flattening filter-free (FFF) photon beams with 600 min/MU dose rate. Real-time position verification was ensured by the orthogonal kilovoltage imaging of the CK system. Three-fraction treatments were delivered every other day, and 5-fraction treatments on consecutive working days.

Tabe 3. Applied dose schemes for study I. (table from: Jánváry, 2017 [9])

Radiotherapy scheme	BED_{10Gy} (Gy)	n (%)
3x20 Gy	180	96 (60%)
3x18 Gy	151.2	7 (4%)
3x17 Gy	137.7	4 (2.5%)
5x12 Gy	132	1 (0,6%)
3x15 Gy	112.5	24 (15%)
5x10 Gy	100	4 (2.5%)
5x9 Gy	85.5	11 (7%)
5x8 Gy	72	13 (8%)

Abbreviations: BED10 =biologically effective dose with α/β= 10 Gy, Gy= Gray

Patients were followed up with regular CT scans or PET/CT, and acute and late toxicities were classified according to the Common Terminology Criteria for Adverse Events (CTC-AE v4.0). Follow up time was defined as the interval between first day of SBRT and last visit or death. During follow-up imaging examinations, lesions were classified as "locally controlled" in case of the absence of progression.

Statistics for Study I.

Descriptive analysis was applied for patient and treatment characteristics, acute and late toxicities. For enabling comparison of different dose—fractionation regimens, biologically effective doses using α/β=10 Gy (BED_{10}) were calculated for each treatment. Analysis of LC, OS and CSS (cause specific survival) was performed using the Kaplan-Meier method. Uni-, and multivariate Cox-regression analysis was used for investigation of prognostic factors influencing local control. P-values ≤ 0.05 were considered statistically significant. Software: SAS ver.9.3 was used for statistical analysis.

3.2. Methods of Study II.: LINAC and Cyberknife SBRT of early-stage primary lung tumors (Hungary)

Patients of Study II.

Gantry-based LINAC lung SBRT was implemented in the National Institute of Oncology in 2015. CyberKnife lung SBRT has become available from 2018. In this retrospective study we focused on a homogenous patient population of early-stage (T1-2 N0 M0) primary lung cancer with or without histological confirmation treated with either SBRT technique. Study ethical clearance number: ETT TUKEB: BM/1754-2/2024. The overwhelming reason for selection of SBRT was medical / functional inoperability. All cases were discussed in multidisciplinary tumor board, and for patients with high risk for invasive biopsy, 18F-FDG PET/CT was obligatory for SBRT decision. Local recurrences, tumors with satellites, metastatic lesions and patients with previous lung irradiation were excluded. Altogether we identified 401 patients, 53% males, 47% females. Median age was 70 years (range 44-90). Classification by tumor size was T1a (≤1 cm) in 8 % (n=32), T1b (>1cm to ≤2 cm) in 44.6% (n=179), T1c (> 2cm ≤ 3cm) in 27.9% (n=112), T2a (>3cm to ≤4 cm) in 16.7% (n=67) and T2b (>4cm to ≤5 cm) in 2.7% (n=11).

Histology was adenocarcinoma in 23% (n=92), squamous cell carcinoma in 12% (n=48), other in 2.5 % (n=10) and unknown in 62.5% (n=251). The clinical diagnoses were supported with 18-FDG-PT/CT positivity in all cases without proven histology and the rate of PET/CT was high (96.3%) in the total cohort as well. The general condition of

patients was good, with 84% (n=338) classified as ECOG 1 (Eastern Cooperative Oncology Group Performance Status), meaning *"Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work"*.

Patient and tumor characteristics are shown in **Table 4.**

Table 4. Patient and tumor characteristics of Study II. (n=401) (table from: Jánváry, 2025 [10])

Characteristic		Number (%/ range)
Age, median (years, range)	–	70 (44–90)
Gender	Male	211 (53%)
	Female	190 (47%)
Tumor stage	T1a (≤ 1 cm)	32 (8%)
	T1b (> 1 to ≤ 2 cm)	179 (44.6%)
	T1c (> 2 to ≤ 3 cm)	112 (27.9%)
	T2a (> 3 to ≤ 4 cm)	67 (16.7%)
	T2b (> 4 to ≤ 5 cm)	11 (2.7%)
Histology	Adenocarcinoma	92 (23%)
	Squamous cell	48 (12%)
	Other	10 (2.5%)
	Unknown*	251 (62.5%)
Location	Left upper lobe	89 (22%)
	Left lower lobe	64 (16%)
	Right upper lobe	153 (38%)
	Right middle lobe	20 (5%)
	Right lower lobe	75 (19%)
ECOG	0	39 (10%)
	1	338 (84%)
	2	24 (6%)

Abbreviations: ECOG=Eastern Cooperative Oncology Group Performance Status

SBRT treatment of Study II.

Treatment preparation was adapted to the chosen SBRT technique. For lesions more likely suitable for CyberKnife Xsight Lung direct tumor tracking 1.25 mm slice thickness planning CT was acquired in exhale and inhale phases, in supine position, on simple, thin comfort mattress with arms next to the body. The application of gold fiducial-based tracking was omitted to minimise risk of side effects (pneumothorax, pulmonary haemorrhage) in a patient population already affected with comorbidities. The Xsight Spine CK method was also omitted. The reason for it was, that CBCT-based LINAC IGRT was considered more reliable for targeting ITV, than tracking of the spine, if the tumor itself was not identifiable on the CK 2D kilovoltage imaging. (For detailed description of CK tracking methods see chapter 3.1.2.).

For tumors planned to be treated with LINAC, a 4-dimensional CT-simulation was carried out in supine position, with arms above the head using wingboard immobilisation system, acquiring in 7-10 respiratory phases, with 2 mm slice thickness, which served as a basis of covering the complete range of the lesion's movement linked to breathing. For LINAC CT simulation, permanent tattoo skin marks were performed for initial patient setup during the treatment, and additional abdominal compression device was used for lower-lobe tumors, to reduce diaphragm motion (and consequential tumor motion) during treatment.

GTV -representing the macroscopic tumor extension- was contoured in lung windowing. For 2-view CK cases GTV was defined in exhale phase, for in 1-view CK cases in both exhale and inhale phase, and for LINAC treatments in all 7-10 respiratory phases.

GTV to CTV margin was 3 mm, which could be manually corrected in case of interference with adjacent bones or mediastinal organs. The CTV was defined solely on exhale phase for CK cases, where the tumor was visible for both kV imaging camera (2-view), and on both exhale and inhale phases when preparing for 1-view. For 1-view cases, an asymmetrical CTV-to-PTV expansion was added in a next step which still resulted a smaller PTV volume compared to classic ITV. For LINAC cases, GTV was contoured in each respiratory phases, then unified in an accumulated volume (GTV_Acc = representing ITV), expanded also with 3mm to achieve CTV.

CTV to PTV margin was generally 2 mm for both LINAC and CK cases, except for 1-view CK cases, where it was asymmetrically 4 mm, only in the direction of lack of tracking.

For LINAC treatments radiotherapy planning was performed with Eclipse TPS (Varian), using Acuros XB dose calculation algorithm, and SBRTs were performed with volumetric modulated arc therapy (VMAT), 6MV, FFF photon beams on either Varian VitalBeam or TrueBeam linear accelerators (Varian, Palo Alto, CA, USA) **(see Figure 3.)**. These LINACs are equipped with either 4 or 6 degrees of freedom treatment tables, enabling rotational and translational position corrections of the body. Image verification was carried out with kilovoltage built-in CBCT of the LINAC before each treatment fraction.

For Cyberknife treatments planning was performed with Precision TPS (Accuray), using VOLO^{TM} dose calculation algorithm, followed by Monte Carlo recalculation. Treatments were done with Cyberknife M6 generation device **(Figure 4.)** using the novel MLC (multileaf collimator) for beam shaping. Step-and-shoot IMRT was carried out using 6MV, FFF photon beams, with real-time tumor tracking ensured by the orthogonal 2D kilovoltage imaging system and the Synchrony camera.

Figure 4. CyberKnife M6 generation robotic radiosurgery unit by Accuray

Institutional protocol defined 3 preferred dose levels for both LINAC and CK SBRT treatments: 3 x 18 Gy (BED_{10}=151.2 Gy), 5 x 12 Gy (BED_{10}=132.2 Gy) and 8 x 7.5 Gy (BED_{10}=105 Gy) in function of tumor location, with lower BED doses forseen for tumors adjacent to the chest wall, or more particularly to mediastinal organs or pulmonary hilum. Further dose reduction was allowed in case of conflict with OAR constraints (constraints defined in institutional protocol, based mainly on AAPM Task Group 101 report [12], with some modifications). Organs at risk constraints and treatment characteristics are shown in **Table 5.** and **Table 6.** The median prescribed dose was 60 Gy in 5 fractions.

Table 5. Dose constraints for organs at risk for Study II.

Organ	**Type of constraint**	**Dose (Gy) for 3-fraction SBRT**	**Dose (Gy) for 5-fraction SBRT**	**Dose (Gy) for 8-fraction SBRT**
Spinal cord	D_{max}	CK: 21.9 Gy L: 21.9 Gy	CK: 30 Gy L: 30 Gy	CK: 30 Gy L: 30 Gy
Esophagus	D_{max} $D_{0.1cc}$	CK: 25.2 Gy L: 21 Gy	CK: 35 L: 30	CK: 40 L: 40
Trachea and main bronchi	D_{max} $D_{0.1cc}$	CK: 23.1 Gy L: 30 Gy	CK: 33 L: 35	CK: 40 L: 40
Heart	D_{max} $D_{0.1cc}$	CK: 30 Gy L: 30 Gy	CK: 38 Gy L: 35 Gy	CK: 50 Gy L: 50 Gy
Great vessels	D_{max} $D_{0.1cc}$	CK: 45 Gy L: 45 Gy	CK: 53 Gy L: 50 Gy	CK: 60 Gy L: 60 Gy
Plexus brachialis	D_{max}	CK: 24 Gy	CK: 30.5 Gy	CK: 30.5 Gy
Ribs	D_{max}	CK: 36.9 Gy L: 36 Gy	CK: 43 Gy L: 43 Gy	CK: 60 Gy L: 60 Gy
Lungs	volumetric	CK: $V_{tüdő}$-$V_{12.4}$>1000 cc L: $V_{tüdő}$-V10.5>1000 cc	CK: $V_{tüdő}$-$V_{13.5}$>1000 cc L: $V_{tüdő}$-12.5>1500 cc	CK: $V_{tüdő}$-12.5>1500 cc L: $V_{tüdő}$-12.5>1500 cc
Liver	volumetric	as low as possible	as low as possible	as low as possible

Abbreviations: Dmax= maximum point dose, fx=fraction, V_{xGy} = volume of tissue receiving x Gy, $D_{0.1cc}$= highest dose on 0.1 cc volume, CK= CyberKnife, L= LINAC

Table 6. Treatment characteristics for Study II. (n=401) (table from: Jánváry, 2025 [10])

Dose scheme	*Number (%)*	*BED (Gy)*
3 × 15 Gy	1 (<1%)	112.5
3 × 17 Gy	2 (<1%)	137.7
3 × 18 Gy	34 (8.5%)	151.2
5 × 10 Gy	30 (7.5%)	100
5 × 11 Gy	38 (9.5%)	115.5
5 × 12 Gy	172 (43%)	132
8 × 6.5 Gy	3 (<1%)	85.8
8 × 7 Gy	4 (1%)	95.2
8 × 7.5 Gy	117 (29%)	105
BED_{10}		
≥ 132 Gy	208 (52%)	
< 132 Gy	193 (48%)	
Technique	*Number (%)*	
LINAC	362 (90%)	
CK	39 (10%)	
Target Volume characteristics	*Median*	*Mean (range)*
GTV volume (cc)	3.9	7.4 (0.3–85.1)
CTV volume (cc)	12.4	18 (1.5–144.7)
PTV volume (cc)	26.2	34.7 (5–195.9)
PTV D98% (Gy)	58.4	56.9 (43.6–63.8)
PTV coverage (V95) %	99.7	99.4 (91–100)
PTV coverage (V100) %	95	94.9 (72.7–100)

Abbreviations: BED10 =biologically effective dose with α/β= 10 Gy, GTV= gross tumor volume, CTV=clinical target volume, PTV=planning target volume, PTV D98% =dose covering 98% of the PTV

As presented in **Table 6.**, most patients were treated with LINAC (90%, n= 362), and only 10 % (n=39) with CyberKnife. Mean GTV and PTV volumes were 7.4 cc (range 0.3-85.1) and 34.7 cc (range 5-195.9).

The maximum dose criteria inside the PTV was 120-130 % of the prescribed dose. Dose prescription for PTV for both techniques were identical:

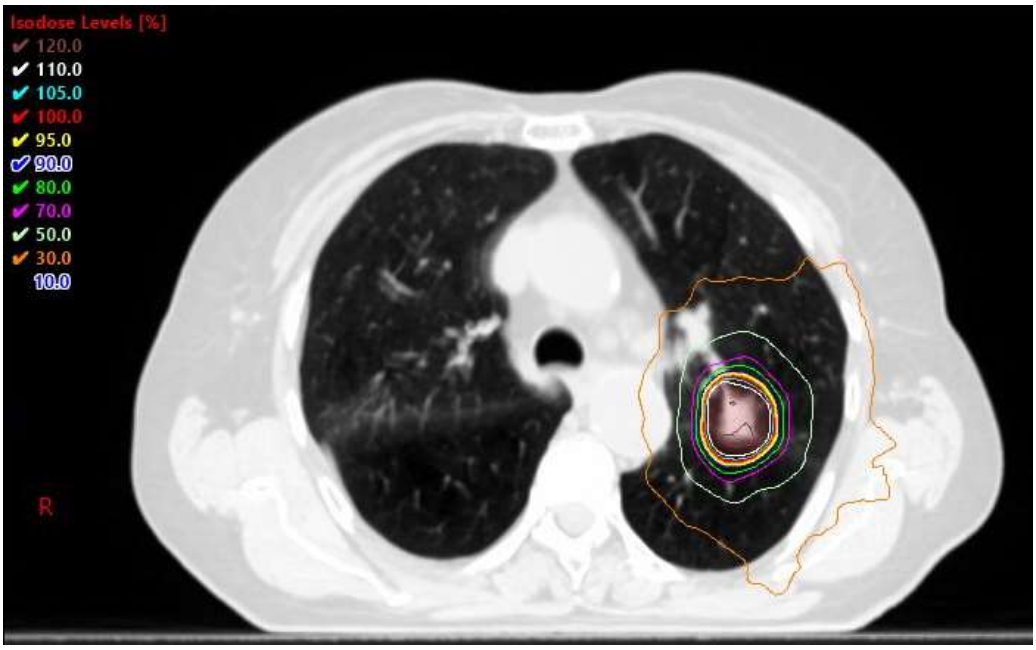
95% of the prescribed dose should cover the 99% of PTV (V95%>99)

100% of the prescribed dose should cover the 90% of PTV (`V100%>90%)

3-fraction treatments were performed every other day, while 5- and 8 fraction regimens were given on consecutive working days. **Figure 5.** shows illustrative cases of similarly highly conformal dose distribution of LINAC and CK treatment plans.

After the completion of SBRT treatment, patients were followed up regularly with CT scans every 3-6 months, supplemented with 18F-FDG PET/CT in case of dubious CT result (e.g: differentiation between fibrosis and recurrent tumor tissue). Toxicities (acute and late) were classified according to CTCAE v4.0. Follow up time was defined as the interval between first day of SBRT and last visit or death. During follow-up imaging examinations, lesions were classified as “locally controlled” in case of the absence of progression.

a)



b)

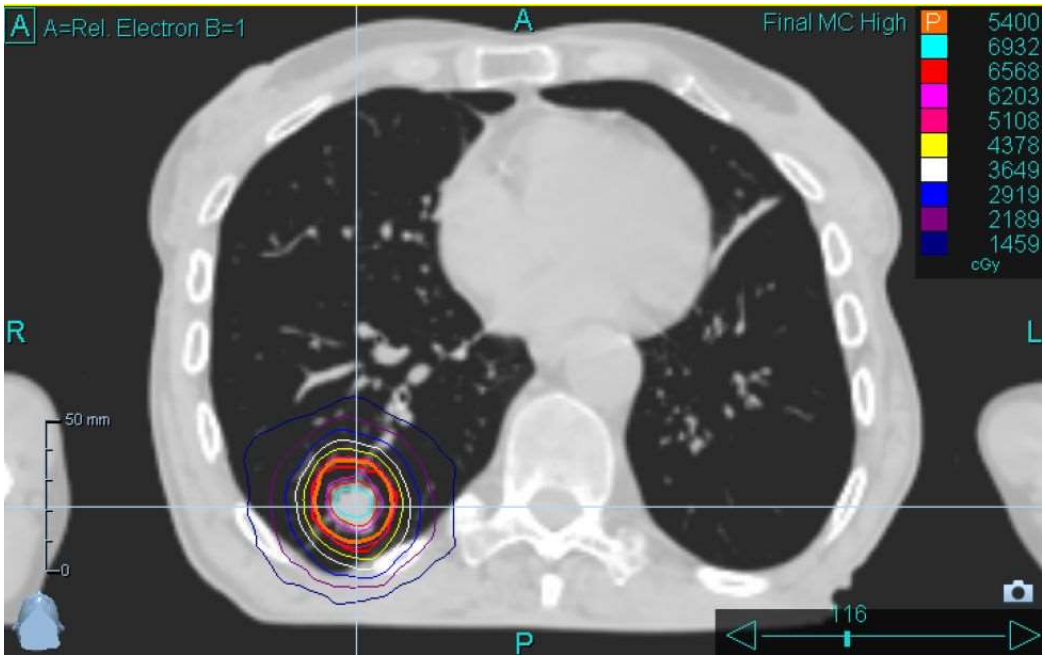


Figure 5. Similarly highly conformal dose distributions of a LINAC **(a)** and a CK **(b)** SBRT plan (illustrative cases, isodose colours are not identical for the two plans)

Statistics for Study II.

Descriptive analysis was applied for patient and treatment characteristics, acute and late toxicities. For enabling comparison of different dose—fractionation regimens, biologically effective doses using α/β=10 Gy (BED_{10}) were calculated for each treatment. Analysis of LC, LPFS, PFS and OS was performed using Kaplan-Meier method. Univariate (Cox-Mantel test)-, and multivariate (Cox regression test) analysis were performed in order to identify prognostic factors influencing local control, local progression free survival, progression free survival and overall survival. P-values < 0.05 were considered statistically significant. Software: Statistica (ver10) was used for statistical analysis.

The variables tested in Cox-Mantel univariate analysis were: age (<70 vs >70 years), gender, tumor stage (2 groups: T1a,b vs. T1c, T2a,b), histological verification (proven vs. unknown), biologically effective dose with α/β= 10 Gy (BED10), SBRT technique (LINAC vs. CK) and ECOG performance status.

Definitions of survival functions (verbatim quote : Jánváry, 2025 [10]:

"-Local control (LC) was defined as the interval between the first day of radiotherapy and the date of local recurrence of the lung tumor or the most recent follow-up. Patients who died of any cause without local recurrence were censored.

-Local progression-free survival (LPFS) was defined as the interval between the first day of radiotherapy and the date of local recurrence of the lung tumor, death, or the most recent follow-up.

-Progression-free survival (PFS) was defined as the interval between the first day of radiotherapy and the date of disease progression (local recurrence, new lung lesions distant from the PTV, lymph node metastases, distant metastasis), death, or the most recent follow-up.

-Overall survival (OS) was defined as the interval between the first day of radiotherapy and the date of death from any cause or the most recent follow-up. Actuarial LC, LPFS, PFS, and OS rates were calculated using Kaplan–Meier method."

4. Results

4.1 Results of Study I. (Jánváry, 2017 [9])

Clinical effectiveness of Study I.

After a median follow-up time of 21 months (range 2-39) the crude rate of survival was 78 % (102/130 pts). The actuarial LC rates were 86%, 75% and 62% at 1-, 2-, and 3 years **(Figure 6)**. We investigated factors influencing local control, and univariate analysis showed significantly higher probability of LC for treatments using doses >112.5 Gy. **(Figure 7.)**

The corresponding probability of LC at 1, 2 and 3-years were 93%, 80% and 63% for the higher-dose group, and 73%, 61% and 54% for the lower doses. Analysis in function of tumor location, similarly, showed significant advantage for peripheral lesions with 91%, 79% and 60% in contrast to central lesions with 74%, and 63% vs 56%, at 1-, 2 and 3 years **(Figure 8.)**. Smaller GTV and PTV volumes were also associated with better LC probability. The presence or absence of real-time tumor tracking, proven or unknown histology, or origin (namely primary, recurrent or metastasis) were not shown significant correlation with LC in univariate analysis. Interestingly, a separate pairwise analysis, nevertheless, showed a significant advantage for primary tumors compared to recurrent tumors or metastases **(Figure 9.).** The actuarial local control rates at 1-, 2-, and 3-years were 89%, 80%, and 64 % for the primary group, 83%, 83%, 83% for recurrent lesions and 84%, 59% 53% for the metastases.

In multivariate analysis *proven histology*, *larger PTV* and *metastatic origin* were associated with lower probability of local control (HR = 1.03; p < 0.0001).

Actuarial OS and CSS probability at 1-, 2 and 3 years were 85%, 74% and 62%, and 93%, 90%, and 80%, respectively. Kaplan-Meier curve of OS is depicted in **Figure 10.**

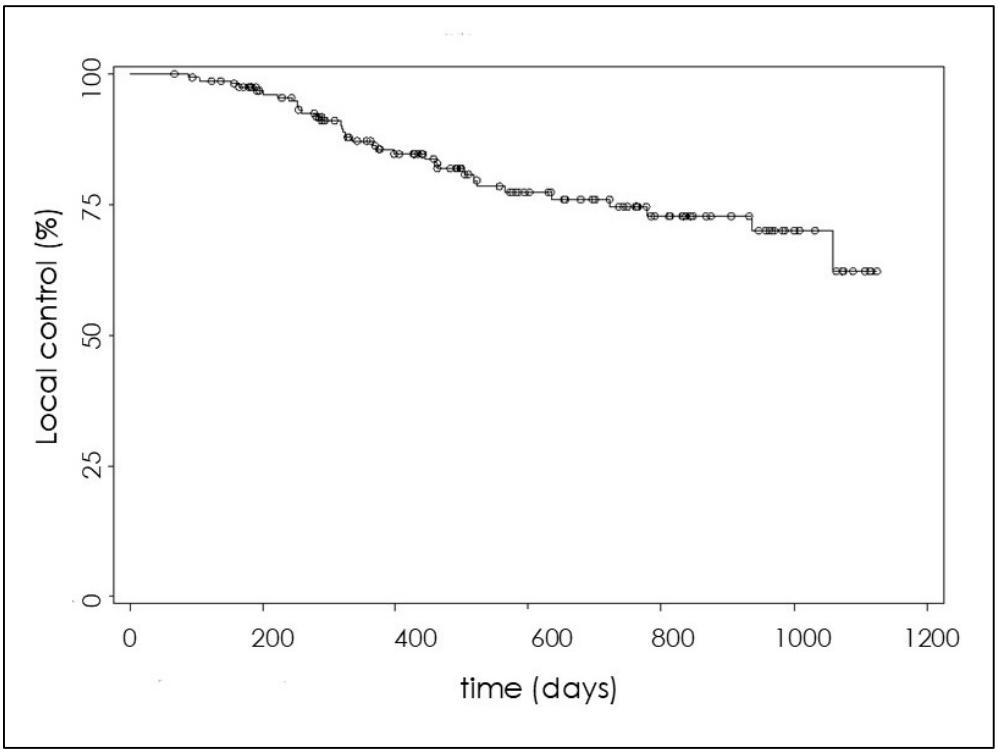


Figure 6. Probability of actuarial local control for the total cohort of Study I. *(Figure not previously published)*

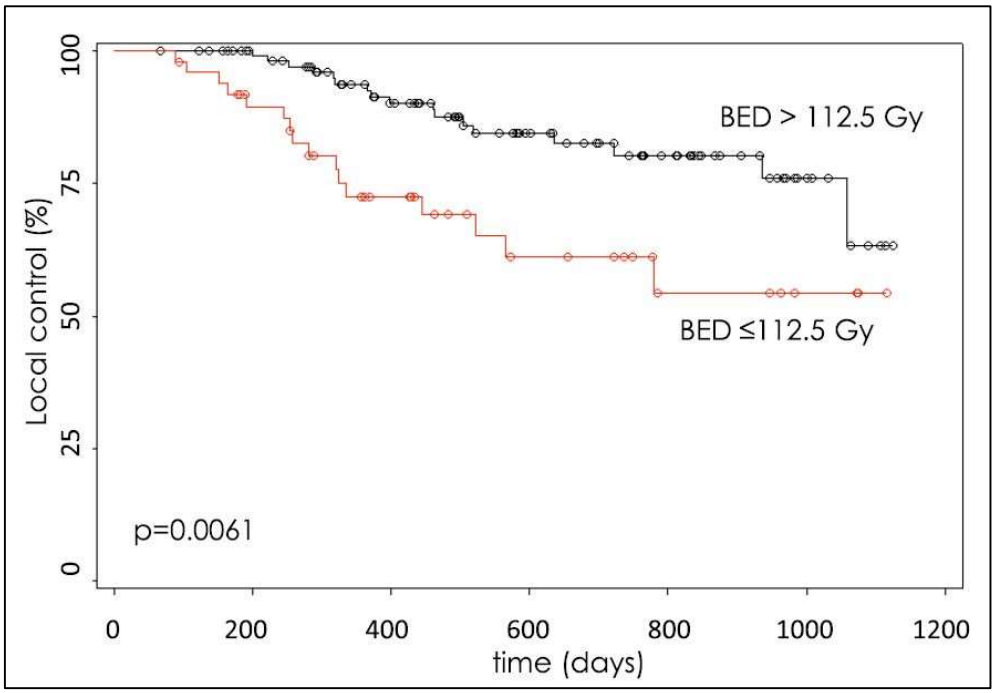


Figure 7. Probability of local control according to dose (BED ≤ 112.5 Gy *vs.* higher) in Study I. (figure from: Jánváry, 2017 [9])

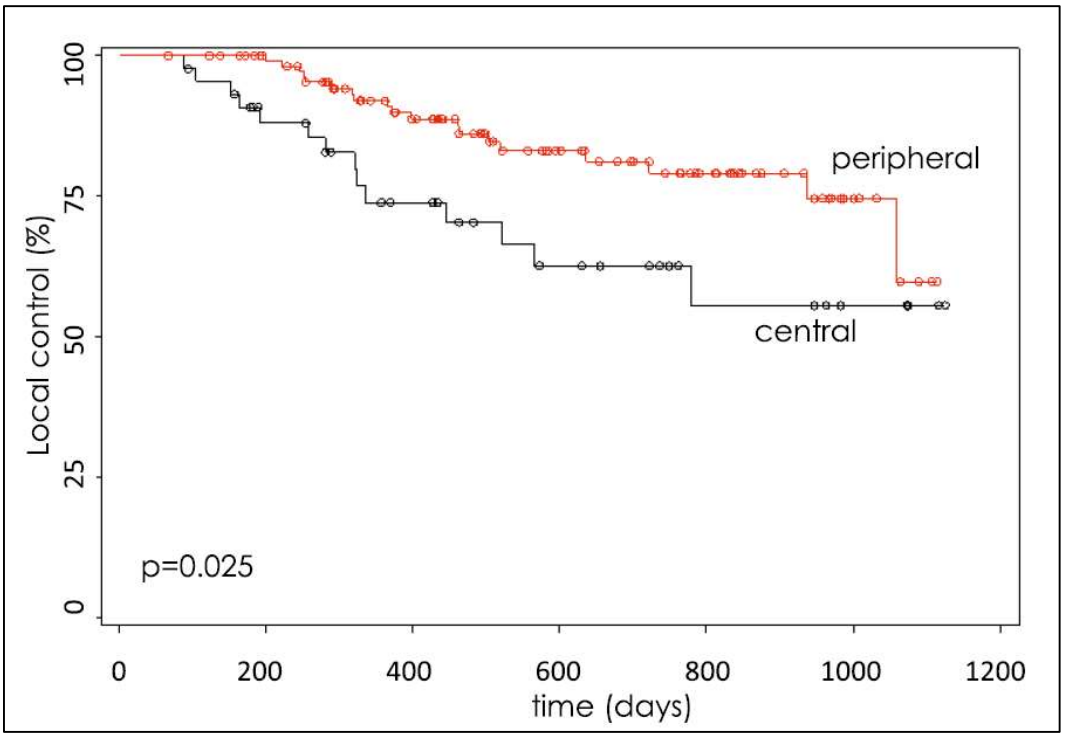


Figure 8. Probability of local control for central vs peripheral lesions. (figure from: Jánváry, 2017 [9])

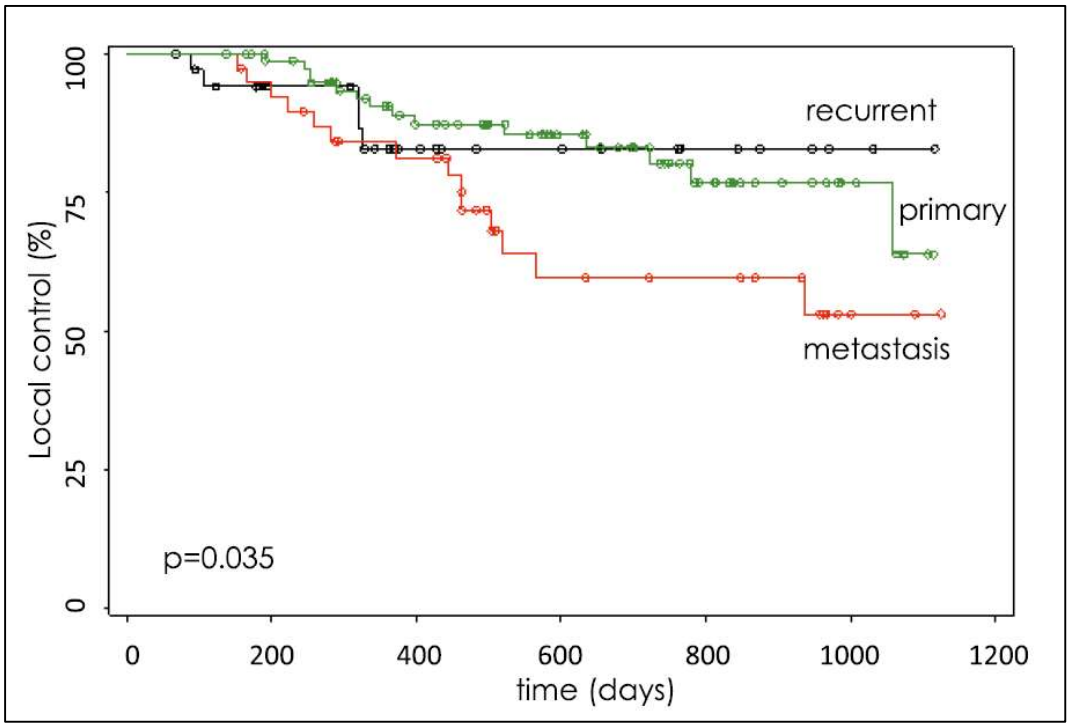


Figure 9. Probability of local control for primary, recurrent and metastatic lesions. (figure from: Jánváry, 2017 [9])

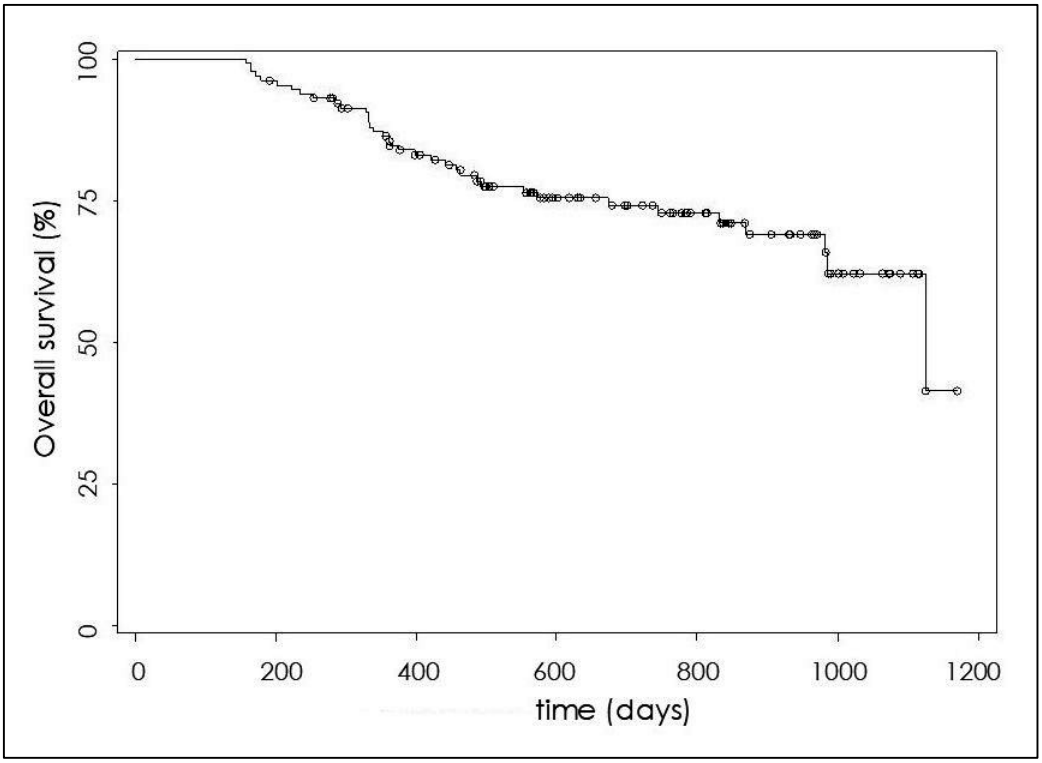


Figure 10. Probability of overall survival for the total cohort of Study I. *(Figure not previously published)*

Toxicities of Study I.

Generally, the CyberKnife-based lung SBRT treatment were well tolerated, with mild cough, fatigue, and chest-wall pain being the most frequent side effects, however severe toxicities have been observed in small proportion of cases. Acute toxicities ≥Grade 3 were observed in 2.3% (n=3) of patients, of which 2 cases of Grade 3 pneumonitis and 1 case of potentially treatment related fatal (Grade 5) pulmonary haemorrhage (applied dose 5x9 Gy, central tumor, event occurred 1 month after irradiation).

Late toxicities of Grade 2 could be identified in the documentations in 20% (n=26), including 5 cases of asymptomatic, or moderately painful rib fractures, 1 case presenting recurrent laryngeal nerve palsy, 14 cases (11%) of symptomatic chronic pulmonary fibrosis and 6 cases (5%) of pneumothorax (PTX) after gold fiducial placement.

Late toxicities ≥Grade 3 were observed in 4.6 % (n=6) as follows:

- 3 cases of Grade 3 dyspnea (each patient suffered from severe COPD (chronic obstructive pulmonary disease) before SBRT.

- 1 Grade 3 case of cardiac arrythmia (sick sinus syndrome) treated with pacemaker implantation (8 months after SBRT).

- 1 case of Grade 3 chest wall pain due to radiogenic rib fracture

- 1 case of (Grade 5) fatal pulmonary haemorrhage, 7 months after treatment (5x8 Gy, central tumor, with large vessel invasion already at time of RT).

It was also investigated whether SBRT treatment was associated with permanent alteration of lung function, using follow up FEV1 (Forced expiratory volume in 1 second) results. Although retrospective data was incomplete, a pattern of detectable decrease in lung function could be shown as demonstrated in **Figure 11.**

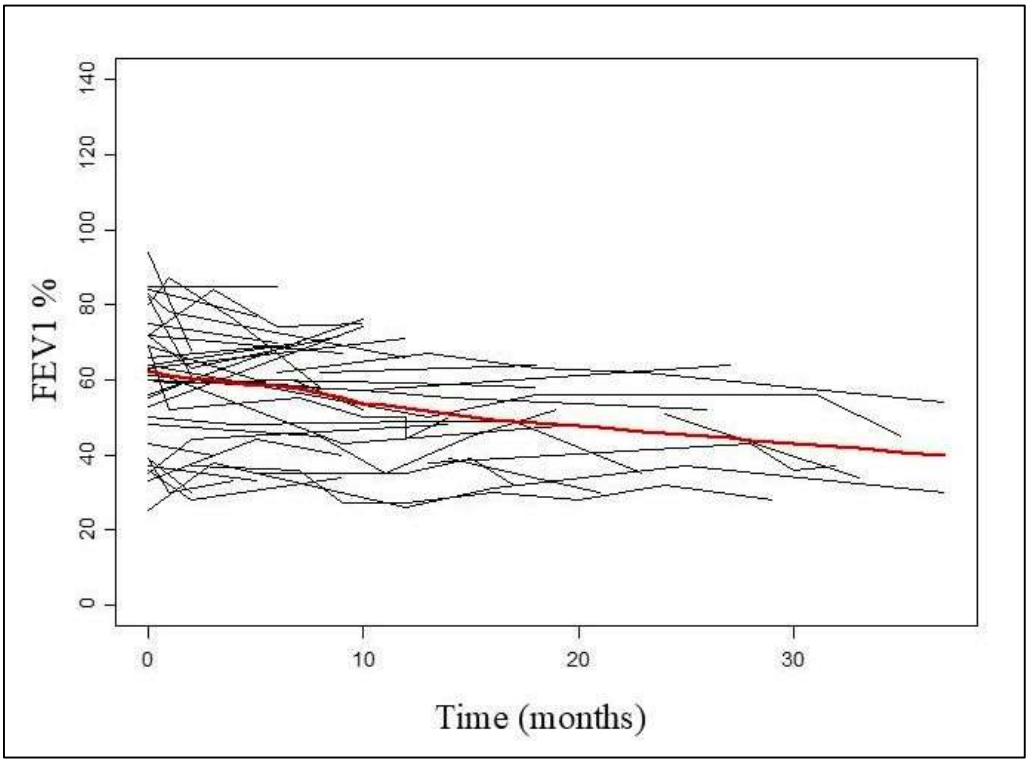


Figure 11. Alteration of lung function using FEV1(%) values (Forced expiratory volume in 1 second as a percentage of expected) in function of FUP time ($p<0.0001$).
(Results not previously published)

4.2. Results of Study II. (Jánváry, 2025 [10])

Clinical effectiveness of Study II.

After a median follow-up time of 32 months (range 2-104) the crude rate of survival was 58 % (233/410 pts). The crude rate of local-, regional- and out-of-field intrapulmonary relapse was 9%, 8.2% and 14.9 %, respectively, while the incidence of distant metastasis was 17.9 %.

In the total cohort, Kaplan-Meier analysis of OS resulted 79, 68 and 56% at 2, 3 and 4 years, and median overall survival was 63 months ((95% CI: 51.1–74.8). Kaplan-Meier LC was 94%, 90% and 87% at 2, 3 and 4 years, and the median LC was not reached.

The calculated Kaplan-Meier local progression free survival and progression free survival rates were 75%, 60%, 51% and 66%, 51%, 42% at 2, 3, and 4 years, respectively. The median values were 49.5 months (95% CI: 42.8–56.3) for LPFS and 37 months (95% CI: 31.2.–42.8) for PFS.

Kaplan– Meier curves of LC, LPFS, PFS, and OS for the entire cohort of Study II. are demonstrated in **Figure 12.**

We performed multivariate analysis using the significant factors identified in univariate test, and found that lower T-stage and better ECOG performance status was associated with better OS ($p < 0.0001$), and BED10 dose ≥ 132Gy was correlated with better LPFS **(see Figure 13. -14. and Table 7.).** Significant difference was found between the median OS of smaller (T1a+T1b) and larger (T1c+T2a+T2b) tumors: 69 *(95% CI: 47.3–90.7)* versus 46 (*95% CI: 37–55)* months, with an advantage of 23 months. Similarly, better 3-year OS was shown for smaller tumors (*73 vs. 61% (p= 0.0044).* Significant OS benefit was observed in favor of better performance status, with 83%, 68%, and 37% at 3 years, regarding EGOG 0,1 and 2 subgroups (p= 0.0005).

Application of doses of BED≥ 132Gy was associated with an advantage of more than 12 months median, and 6 % of 3-year local progression free survival, compared to lower doses-group: 55 vs. 42.4 months (95% CI: 42.8–67.2 and 35.8–49) and 63 vs. 57% (p= 0.0046) respectively.

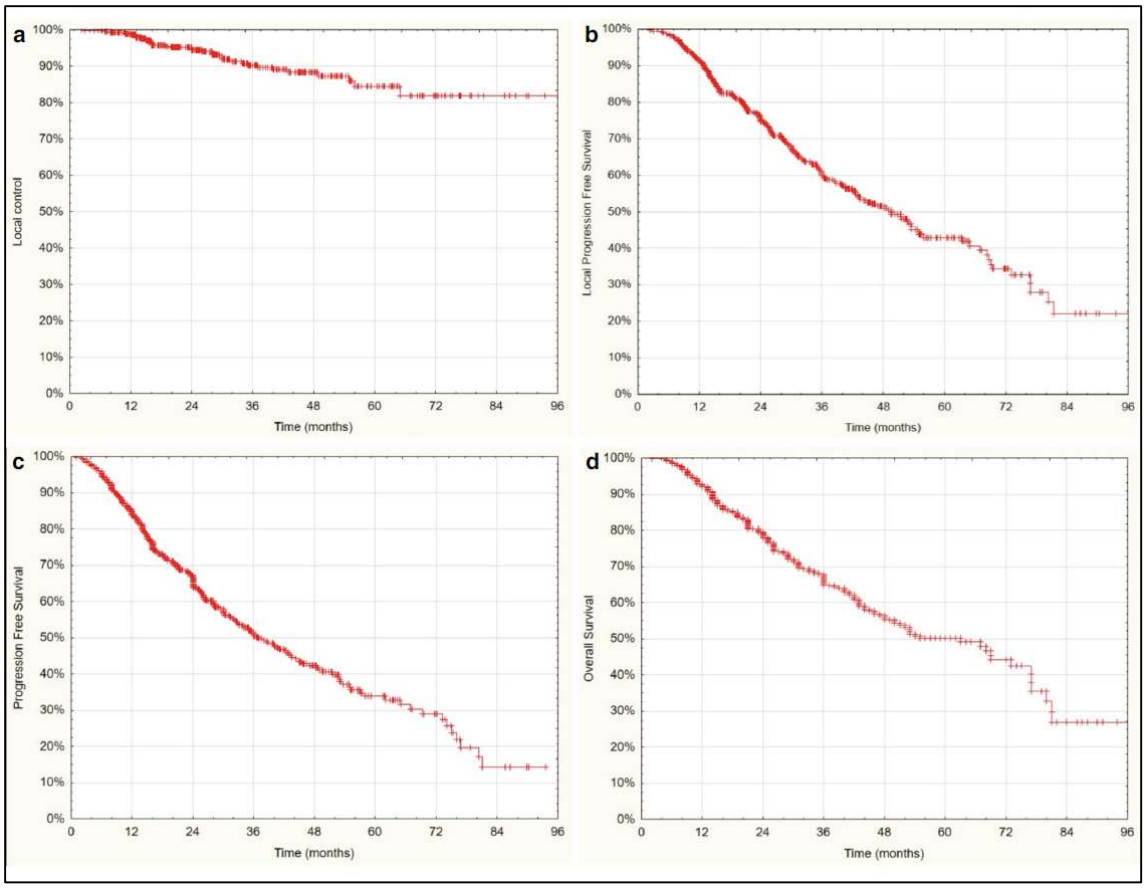


Figure 12. a–d Kaplan–Meier curves of the entire cohort of Study II. (*n*= 401 patients) treated with SBRT **a)** Local control, **b)** local progression-free survival, **c)** progression-free survival, **d)** overall survival (figure from: Jánváry, 2025 [10])

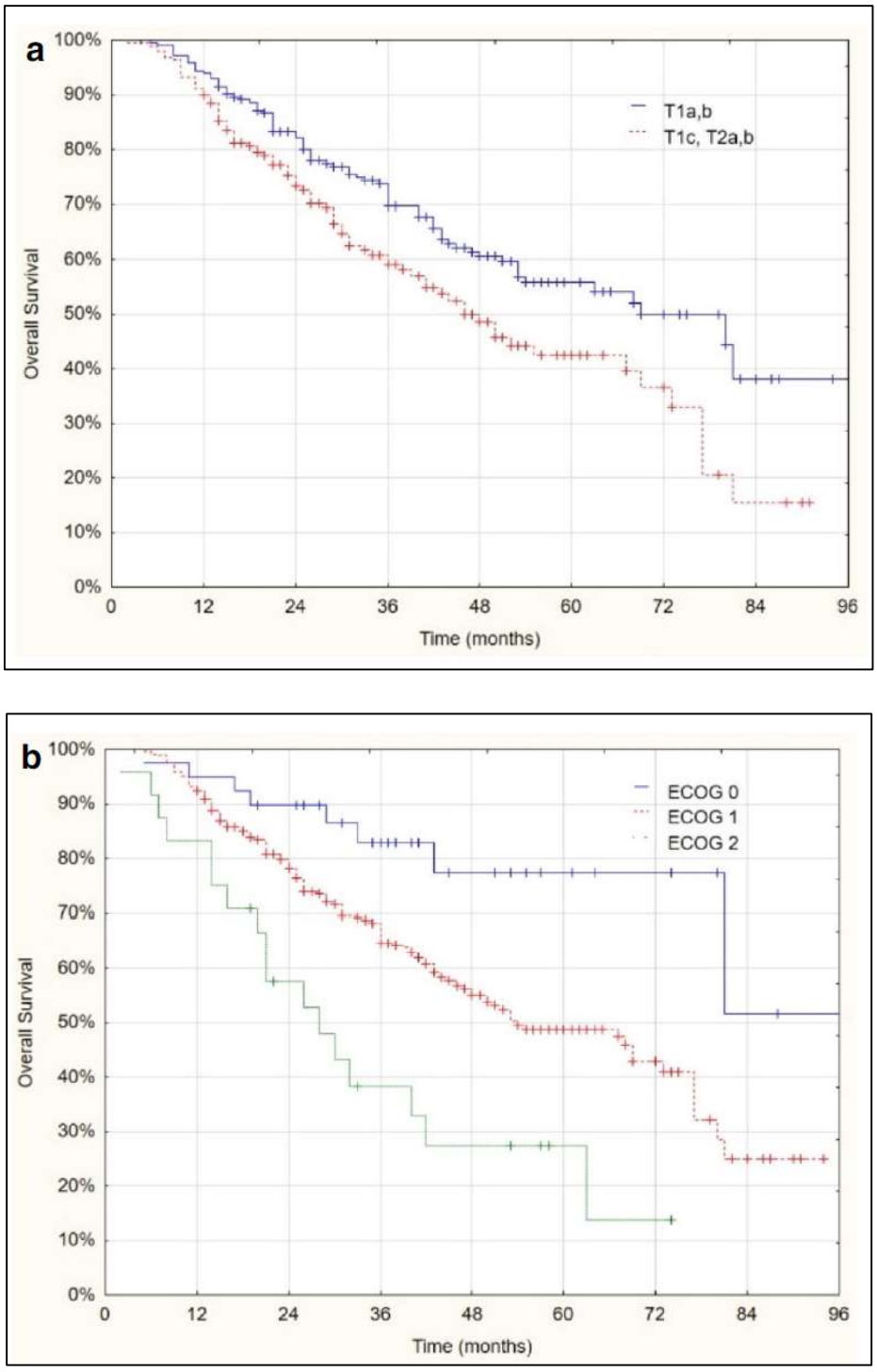


Figure 13. Study II. Kaplan–Meier curves of overall survival, **a)** T stage 1a,b vs. T1c, T2a,b (p= 0.0044) and **b)** ECOG performance status (p= 0.0005) (figures from: Jánváry, 2025[10])

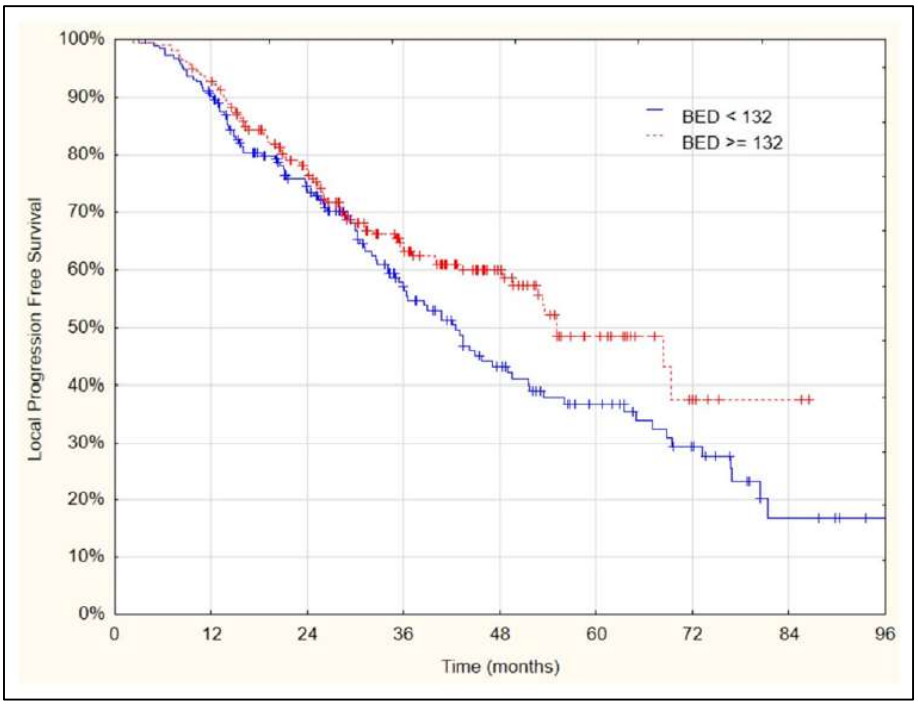


Figure 14. Study II. Kaplan–Meier curves of local progression-free survival as a function of biologically effective dose (*BED*) <132Gy vs. ≥132Gy (*p*= 0.046) (figure from: Jánváry, 2025 [10]

Table 7. Results of univariate Cox-Mantel test, investigating the potential factors influencing LC, LPFS, PFS and OS in Study II. (Jánváry 2025, supplementary material [10])

	LC	**LPFS**	**PFS**	**OS**
Age (<70 vs >70 years)	NS	NS	NS	NS
Sex (male vs female)	**p=0.005**	**p=0.001**	**p=0.0008**	**p=0.0087**
T-stage (T1a,b vs T1c,T2a,b)	NS	**p=0.018**	NS	**p=0.0044**
Histology (proven vs unkown)	NS	NS	NS	NS
BED_{10} (<132 Gy vs ≥ 132 Gy	NS	**p=0.0457**	NS	**p=0.03**
Technique (LINAC vs CK)	NS	NS	NS	NS
ECOG (0 vs 1 vs 2)	NS	**p=0.0044**	NS	**p=0.0005**

Abbreviations: NS: non-significant, p-values below 0.05 were considered to be significant

Toxicities of Study II.

Generally, treatments were well tolerated, without interruption due to adverse event. Acute toxicities associated to lung SBRT was generally mild cough, general fatigue and local chest wall pain in the treated region, without the appearance of any Grade 3 or higher toxicities in the first 3 months. Concerning late toxicities, retrospective data collection revealed 32% (n=130) Grade 1-2, and 0.7 %, (n=3) Grade 3 lung fibrosis. We identified 1 patient (0.2%) with a grade 3 PTX at 19 months follow-up, which was classified as potentially-treatment-related toxicity. PTX was successfully treated with transient chest tube placement. There were not late adverse events higher than Grade 3.

Frequency of late rib fracture was 3% (n=14), with a mean time to appearance of 21 months (range 6-50).

Investigation concerning the prescribed dose and the onset of rib fracture did not show any correlation in the cohort.

5. Discussion

Lung cancer is one of the most frequent types of cancer, with high mortality rates, correlated to approximately 25% of all cancer deaths. The estimated worldwide incidence is approximately 2.4 million new cases annually, worldwide [13], and the proportion of early diagnosis (lymph node negative stage) is around 16-23 % [14]. Unfortunately, Hungary presents particularly high incidences of lung cancer in European comparison, with approximately 9500 newly diagnosed cases, annually [15].

The standard treatment for early-stage NSCLC is surgical removal: lobectomy or anatomical segmentectomy alongside with simultaneous removal of hilar and mediastinal lymph nodes. Conventional open thoracotomy approaches are more frequently replaced with minimally invasive video-assisted lobectomy (VATS) or robot-assisted thoracoscopy (RATS). However, approximately 25% of early-stage lung cancer will not undergo surgery because of comorbidities or more rarely of patient refusal [16].

During the last decades, stereotactic body radiotherapy became one of the most important treatment alternatives for inoperable patients. After the first reports in the late 1990s on the application of SBRT technique on lung malignancies, further studies on clinical results appeared in early 2000s [17-18], and as the technology became more widespread, from 2005 on, the annual number of lung SBRT publications raised steeply [19].

Before the era of SBRT, conventional radiotherapy could be offered for those inoperable patients, usually delivered to a total dose of 60–70 Gy in 2.0 Gy daily fractions, however a meta-analysis by Grutters et al. (2010) revealed a significant 5-year OS advantage for SBRT (42%) compared to conventional radiotherapy (20 %) [20]. Interestingly, in this study, authors also found that survival rates for photon SBRT were similar to particle therapy in stage I inoperable NSCLC.

After experiencing outstanding local control rates (above 90%) after lung SBRT in prospective and multicentric retrospective trials [5, 21-23] efforts have been made to directly compare SBRT and surgery in operable patients in prospective, phase III randomized trials. Although those trials *(STARS, using CyberKnife [NCT00840749] and ROSEL, using LINAC [NCT00687986], both registered on ClinicalTrials.gov)* were terminated prematurely, some years later a pooled analysis has been performed by

Chang et al., showing significant 3-year OS benefit in favour of radiotherapy: 95% in the SBRT group and 79% in the surgical group after a median follow-up of 35 months [24]. Despite those positive experiences with SBRT of operable lung cancer cases, this radiotherapy technique remained much more in the focus for patients being ineligible for surgery. By the results of several workgroups, it became clear, that risk-adapted dose-fractionation protocols are more advantageous, than utilization of a uniform SBRT dose scheme for all cases [25-28]. It should be noted, that single fraction SRS has also been investigated for lung cancer in a limited number of randomized trials [29-31] showing promising results of 89.4 to 95% LC rates and favorable toxicity profile. Despite encouraging results with single fraction SRS, this „alternative" fractionation has not reached such popularity, and most centres established hypofractinated protocols using 3 to 8 fractions to a total dose of 45-60 Gy. Published results, however, remains controversial concerning the minimum effective threshold dose or „optimal" fractionation schedule.

5.1. Principal findings of Study I.

Study I. was fundamentally addressed on the investigation of clinical effectiveness, and adverse events of a novel technology, the CyberKnife-based lung SBRT at Belgium. As we principally focused on local control, the study cohort consisted of a mixed population of cases with primary, recurrent and secondary (metastases from other cancer) lesions. As another goal of the work was to validate SBRT protocols on real-life population, we selected data of the first consecutively treated 130 patients /160 lesions. SBRT was delivered in 3 or 5 fractions, with significantly larger contribution of 3 fraction treatments, with 60 Gy in 3 fractions being the most frequent schedule. After 21 months of median FUP, we observed promising results showing local control rates of 86%, 75% and 62%, and overall survival rates of 85%, 74% and 62%, at 1-, 2- and 3 years, respectively. Our results are fully consistent with those of other published series, where 2-year LC rates range between 59,7 - 96%, and 2-year OS rates has been reported between 47 to 87% **(Table 8.).**

Table 8. Comparative table with results from series of purely primary / purely metastatic or mixed-group target lesions. Lowermost row represents results from Study I. (table from: Jánváry, 2017 [9])

Study	Technic	Histological confirmation %	No. of pts/ lesions	dose (Gy)/fx	BED_{10Gy} (Gray)	Median FUP (month)	Local Control	Overall Survival
PRIMARY								
Chen VJ (22)	CK	100	40	median 48 (42-60)/3 fx	124.8	44	91%@3y	75%@3y
van der Voort van Zyp (23)	CK	51	70	60/3fx (Peripheral) 45/3fx (Central)	180 (Peripheral) 112.5 (Central)	15	96%@2y for 60 Gy 78%@2y for 45 Gy	62%@2y
Factor (24)	CK	95	78	60/3 fx (Peripheral) 48/4 fx (Central)	75-180	14.4	87%@2y	68%@2y
Bahig (4)	CK	84	150	median 60/3 fx 40- 60/3-5 fx	72-180 (Peripheral) 106-180 (Central)	22	96%@2y	87%@2y
Shen (25)	CK	84	50	57 (48-60)/3fx	104-150	35	crude 96%@2y	86%@1y 74%@2y
Davis, RSS REGISTRY (5)	CK, LINAC	100	723/741	median 54 (10-80)/3 fx	151.2	12	88%@1y 76%@2y	T1: 85/63%@1/2y T2: 76/52@1y/2y
Fakiris (26)	LINAC	100	70	60-66/3fx	180-211.2	50.2	88.1%@3y	42.7%@3y
METASTASES								
Nuyttens (7)	CK	12	30/57	30/1 fx; 60/3-5 fx; 56/7 fx		36	79%@1y	63%@2y 38%@4y
Inoue (8)	LINAC		87/189	48/3fx; 50/5 fx; 52-60/10 fx;	30-168		80%@2y 80%@3y	47%@2y 32%%@3y
MIXED:PRIMARY+METASTASES								
Guckenberger (27)	LINAC	19	124/159	26/1 fx; 37.5/3; 48/8 fx		14	83%@3y	37%@3y (Primary) 16%@3y (Met)
Ernst-Stecken (9)	LINAC	100	21/39	35-40/5 fx	59.5-72	6.3	crude: 87%	crude: 86%
Duncker-Rohr (28)	LINAC	55	39/45	37.5/3 fx; 30/5 fx	84 (Peripheral) 60 (Central)	17	80.5%@2y 95% @2y Prim 59.7%@2y Met	52.7%@2y 45.9% (Primary) 66.7% (Met)
Current study	CK	total 61% primary 77%	130/160	median 60/3 fx (Peripheral) median 45/5 fx (Central)	median 180 (Peripheral) median 112.5 (Central)	21	86%@1y 75%@2y 62 %@3y	85%@1y 74%@2y 62%@3y

Multivariate analysis of Study I. cohort revealed predictive factors associated with significantly lower local control rates after SBRT: metastatic origin (HR=7.3, p<0.0001), proven histology (HR=4.1, p=0.0052 and larger PTV (HR=1.03, p<0001).

Concerning the potential difference of local control effect of SBRT between primary and metastatic tumors the literature is controversial. While one German study observed LC advantage for primary tumors [32], another series from the same country reported comparable results for these two groups [33].
Again, similarly to our results, a Japanese group identified metastatic origin and larger tumor size as negative factors for LC [34].

The negative effect of proven histology on LC in our findings could be consequence of potential statistical bias, as other studies, specifically focusing on this subject, mostly report similar results with or without biopsy for lesions treated with lung SBRT [27-28, 35-36]

Although larger PTV is not necessarily equivalent of larger tumor size, as the tumor movement and the applied respiratory motion management influences the final RT target volume, larger tumors have higher probability to be associated with larger PTV. In this regard, with this generalization, our results can be paralleled with findings of other authors, reporting worse LC rates related to higher T-stage. Parker et al. in a series of SBRT on primary and metastatic lung lesion found, that larger tumor size and larger PTV volume were associated with better LC, but they did not find difference between primary and metastatic groups [37].

5.2. Principal findings of Study II.

Experiences from Study I. turned out to be useful in several ways during the implementation and maintaining of lung SBRT treatments in the National Institute of Oncology, Budapest, as well as on conceptualization of Study II. This study focused on a more homogenous patient population, enrolling solely early-stage (T1-2 0 M0) primary lung cancer patients with or without histological confirmation. Keeping the 3-fraction schemes as well, the range of applied doses moved towards slightly more fractionated regimens, using 3 preferred dose prescriptions: 3 x 18 Gy, 5 x 12 Gy and 8 x 7.5 Gy.

Similarly to our previous study, our goal was the investigation of clinical effectiveness of SBRT using a wider technical platform (Varian VitalBeams, Truebeams and newest generation CyberKnife M6 with MLC collimator), the analysis of toxicities as well as to validate our dose protocols on a large-scale of consecutively treated patients. Taking into account, that the applied doses, target volume safety margins and OAR constraints were similar, we decided to analyse the total cohort as a whole.

After a median follow-up of 32 months, our retrospective analysis of 401 patients revealed important findings. To our knowledge, this represented the largest cohort of primary lung cancer SBRT published so far in Hungary.

We observed outstanding local effect, with only 9% (n=36/401) of local failure and 94%, 90% and 87% of actuarial 2-, 3-and 4-year LC rates. 2-, 3-and 4-year OS rates were 79%, 68% and 56%. When compared to results of series reporting experiences with more than 100 patients, our findings are coherent with the relevant literature **(Table 9.)**

Multivariate analysis of Study II. cohort revealed predictive factors associated with significantly better overall survival rates after SBRT: smaller tumor size (T1a, b vs T1c, T2a,b) (p= 0.002), lower ECOG score (better ECOG status) (p= 0.002). Prescribed doses ≥BED_{10}132 was predictive for better LPFS (p<0.0001)

Firstly, we observed significant 3-year overall survival advantage (73 vs 61%) for smaller tumors (T1a, b vs T1c, T2a,b). In terms of median OS values this advantage was 23 months (69 vs 46 months). Fisher-Valuck et al. has reported similar correlation after comparing tumors below and above 30 mm [38]. Likewise, a registry-trial of Davis et al. on >400 early-stage NSCLC reported 2-year OS rate of 63% for T1 in contrast to 52% for T2 tumors, though the advantage in median OS values was only 4 months (30 vs 26 months) [39]. The likely interpretation on this phenomenon is that larger tumors had more chance of metastasising already before treatment, but also the potentially worse effect of SBRT on larger tumor tissue volume. These findings again draw attention to the importance of early diagnosis.

Secondly, our findings concerning the positive predictive value of better ECOG performance status to OS is obvious in a certain sense, but they also highlight that this elderly, medically inoperable population need a well tolerable, still locally highly

effective treatment, like SBRT. Similarly to our findings, Klement et al showed ECOG status to be a strong predictor for survival in the 6 months interval following SBRT [40].

The third important finding of our multivariate analysis, was the local progression free survival advantage, related to the treatment dose. Patients treated with BED_{10} doses ≥132 Gy had an advantage of 13 months median LPFS (55 vs 42 months), and of 6% in 3-year LPFS rates, though we could not observe advantage in OS. The literature concerning the optimal SBRT dose is controversial. Some of the workgroups found that application of 100-105 Gy BED dose was already associated with improved LC rates and OS [41-43], while a study of more than 600 cases of lung SBRT found that 150-180 Gy was associated with higher LC rates, however, without further advantage in OS [44]. On the other hand, there were studies concluding that optimal dose is more like a wider range between 100-140 Gy of 83-146 Gy [45-46]. Naturally, tumor size and its proximity to certain organ at risks affect the safely deliverable maximum dose.

The extent to which SBRT can be applied to patients with unknown histology is a recurring debate in the relevant literature. It should be noted that stereotactic radiotherapy in lung cancer is an alternative treatment method for surgery, developed for inoperable, elderly patients, with severe comorbidities and poor lung function. In this context, SBRT is often the only effective treatment to be offered, for patients with very high suspicion for malignancy. Studies reporting results with comparison of biopsy proven vs not proven groups, with rate of unknown histology of 26-65%, conclude the lack of significant difference of LC, OS rates and low incidences of adverse events [27-28, 35-36, 38, 47-49]. Similarly, our analysis of Study II. did not show any significant difference between biopsy proven group, and that with unknown histology with regard to LC, LPFS, PFS and OS, validating the widely used, and guideline-recommended clinical routine of offering SBRT to patients with 18F-FDG PET/CT positive lung tumors, in case of high risk for invasive biopsy.

Table 9. Series with n>100, reporting results for early-stage primary lung cancer SBRT. Lowermost row represents results from Study II. (table from: Jánváry 2025 [10])

Authors	Year	LINAC/CK	No. patients	Dose	LC (%)	OS (%)	Prospective/ retrospective (P/R)	Single/ multicentric (S/M)
Onishi et al. [14]	2007	LINAC	257	30–84 Gy (at isocenter) in 1–14 fx, median BED 111 Gy	LF*: 14%	3-year: 56.8 5-year: 46.2	R	M
Bahig et al. [15]	2014	CK	150	40–60 Gy in 3–5 fx, median BED 180 Gy	2-year: 96	87	R	M
Davis et al. [39]	2015	LINAC/CK	723	10–80 Gy in 1–5 fx, median BED 151.2 Gy	1-year: 88 2-year: 76	1-year: T1: 85, T2: 76 2-year: T1: 63, T2: 52	R	M
Resova et al. [11]	2024	CK	172	30–60 Gy in 1–5 fx, median BED 151.2 Gy	1-year: 97 2-year: 95 3-year: 90	84.9 NA 49	R	S
Stanic et al. [12]	2023	LINAC	206	34–60 Gy in 1–8 fx, median BED 115.5 Gy	1-year: 98 2-year: 96 3-year: 96 5-year: 95	87 74 62 31	R	S
Stephans et al. [29]	2017	LINAC	603	30–60 Gy in 1–10 fx	2-year LF*: 13.1%	NA	R	S
Taremi et al. [25]	2012	LINAC	108	48–60 Gy in 3–10 fx	1-year: 92 4-year: 89	84 30	P	S
Temming et al. [10]	2018	CK	106	25–60 in 1–5 fx	2-year: 88 3-year: 77	77 56	R	S
Wegner et al. [13]	2018	LINAC	196	48–50 Gy in 4–5 fx, BED 100–105.6 Gy	3-year: 94	58	R	S
Giuliani et al. [40]	2016	LINAC	734	18–64 Gy in 1–10 fx	1-year: 98 2-year: 94.4 5-year: 91.7	82.1 63.7 31.8	R	M
Current study	2025	LINAC/CK	401	45–60 Gy in 3–8 fx, median BED 132 Gy	2-year: 94 3-year: 90 4-year: 87	2-year: 79 3-year: 68 4-year: 56	R	S

*Abbreviations: LC=local control, OS=overall survival, BED=biologically effective dose with α/β= 10 Gy Gy, NA=not available, LINAC=gantry-based linear accelerator, CK=CyberKnife , fx=fractions, *LF=local failure*

5.3. Evaluation of toxicities of Study I. and II.

It can be stated, that both studies confirmed low rates of severe adverse events after lung SBRT with 0-2 % of acute-, and 4-5% of late toxicities ≥ Grade 3. Among mild-moderate toxicities, pulmonary fibrosis was the most common late side effect (10.8 and 32%), which is a well-known phenomenon raising differential diagnostic challenges in excluding local relapse during long term follow up. In doubtful cases, follow-up PET/CT is often used to distinguish between fibrosis and true progression. Illustrative cases of simple and complex/challenging follow-up imaging are shown on **Figures 15. and 16.**

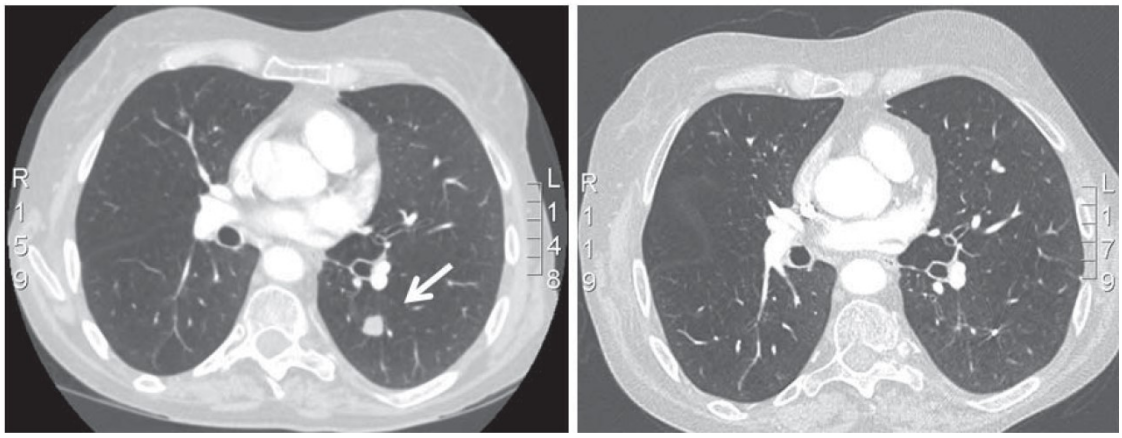


Figure 15. Illustrative case of simple follow-up imaging evaluation: a T1a N0 M0 non-small cell lung cancer. *Left:* before SBRT, *Right:* 12 months follow-up showing complete regression. (figure from: Jánváry 2018 [50])

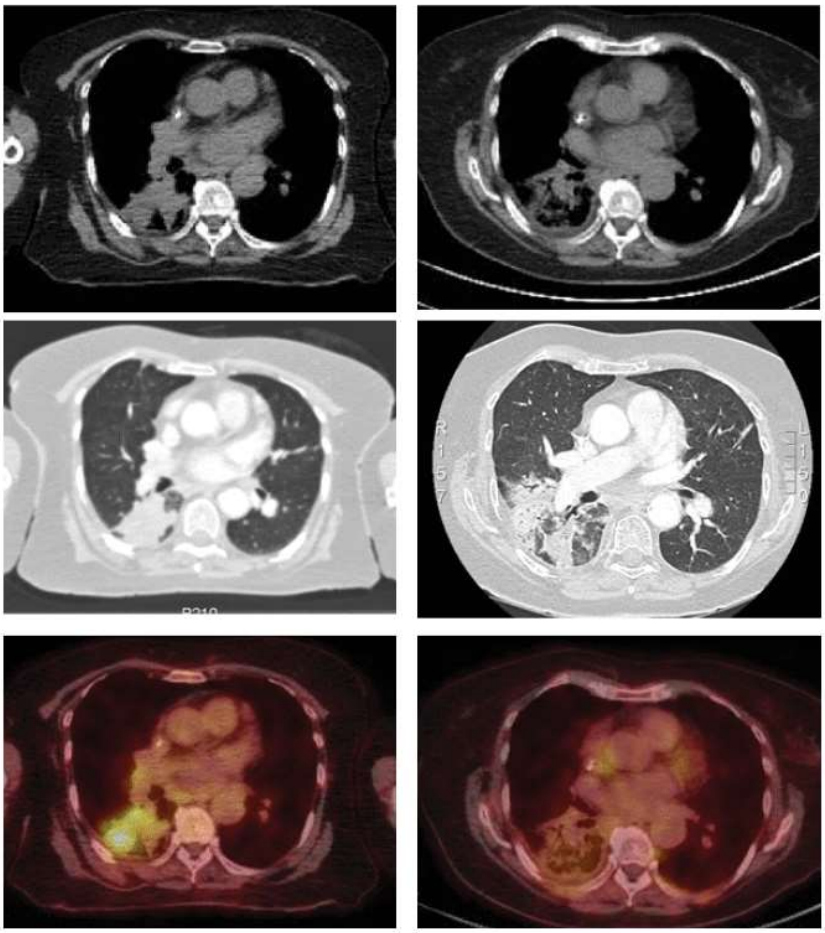


Figure 16. Illustrative case of challenging follow-up imaging : a T2b N0 M0 primary tumor. *Left column:* before SBRT, *Right column*: 6 months after SBRT. The first and second rows show CT images on soft tissue and lung-windowing, and the lowermost row show 18F-FDG PET/CT images. Pronounced fibrosis can be observed on the right side images, with air bronchogram distubring interpretation of follow-up CT images. PET/CT prooves high degree of metabolic response. . (figure from: Jánváry 2018 [50])

5.4. Conjoint assessment of Study I. and II.

Though both studies were addressed on clinical evaluation of patient treated with SBRT, there are many reasons beyond the spatial and temporal differences, why direct comparative analysis cannot be performed between the two cohort. Cohort of Study I. consisted of mixed patient population, including primary and recurrent lung cancer, metastases, larger tumors and some lymph node positive cases as well (Stages I, II. and

IV), therefore the main focus was on local control effectiveness. In contrast, Study II. was designed to be able to investigate more thoroughly the potential predictive factors on LC, LPFS, PFS and OS, and therefore included an even larger, more homogenous patient population with Stage I. and IIA primary lung cancer. In addition, dose schemes of Study I. was more hypofractionated (3 or 5 fractions), 3x20 Gy being the median dose, instead, in Study II. dose schemes were more diversified between 3-5-8 fraction, with 5x12 Gy median SBRT dose regimen, and highest BED_{10} fractionation (3x18 Gy) was applied for peripheral lesions not adjacent to chest wall, on the other hand, for central lesions 8 fraction regimens were applied.

The main limitations of both studies are their retrospective and single-institutional nature, unbalanced subgroups, heterogenous patient population, especially in Study I. These factors could potentially lead to biases and false conclusions. In both cohorts, the rate of unknown histology was high (39 and 62.5%), limiting the validity of the global conclusions on NSCLC.

On the other hand, large sample size, consecutive, real-life patient cohorts, well documented treatments, detailed descriptions are the strengths of our studies. Especially, To our best knowledge, Study II. represents the largest cohort analysis on SBRT of early-stage primary lung cancer in Hungary, and also amongst the largest series reported so far in Europe. The applied dose-fractionation schemes, dose prescription and clinical results-reporting are performed in accordance with international guidelines, allowing established comparison with concerning literature.

LC and OS rates of the two studies are promising, as well as LPFS and PFS rates in Study II., with low incidence of severe toxicities, after the application of diversified dose regimens in function of tumor size, and location, contributing to validation of risk-adapted approach. On the basis of our findings, it could be recommended to apply the highest possible BED_{10} doses within the limitation of OAR constraints.

6. Conclusions

Based on two large-scale retrospective studies, with a total of 531 patients and 561 tumors, our results confirm the clinical effectiveness and safety of stereotactic radiotherapy in primary and secondary lung malignancies.

1. In Study I. we analysed the clinical effectiveness CyberKnife-based robotic SBRT on 130 patients with 160 lung lesions, representing a mixed population of primary, recurrent or metastatic origin, with focus on the investigation of local effectiveness. Promising LC and OS rates were in line with corresponding literature.

2. In Study II. we investigated clinical results of 401 patients of T1-2 N0 M0, early-stage primary lung tumors treated with either LINAC or CyberKnife. During our analysis we observed outstanding local control rates, and good LPFS, PFS and OS rates. Our results were coherent with findings of other workgroups in international comparison.

3. Analysis of data of Study I. showed negative predictive value of metastatic origin, proven histology and larger planning target volume on local control.

Analysis of data of Study 2. revealed positive predictive value of smaller tumor size (T1a, b vs T1c, T2a,b) and better ECOG performance status score on overall survival and applied dose of ≥132 Gy BED_{10} on local progression-free survival. Application of doses of BED≥ 132Gy was associated with an advantage of more than 12 months median, and 6% of 3-year local progression free survival, compared to lower doses-group.

4. Our results were controversial between Study I. and II. concerning the potential effect of proven vs unknown histology on LC. Nevertheless, the significantly larger and more homogenous cohort-based analysis of Study II. did not show difference between the two groups neither in terms of LC, nor of LPFS, PFS and OS, supporting the continuation of SBRT in patients without pathological confirmation, in case of strong PET/CT positivity.

5. Both Study I. and II. confirmed lung SBRT to be a well tolerable treatment method, with low rates of severe acute and late toxicities.

6. In both studies, but especially in Study II., diversified dose levels were applied, with 3 major regimens of 3x18 Gy, 5x12 Gy and 8x7.5 Gy, with further possibility of slight dose-reduction, individually, in case of conflict with nearby organs at risk. Our globally high rates of clinical effectiveness alongside with low rates of severe adverse event in a real-life cohort of a large, consecutive patient cohort of more than 400 patients, validating the safe and effective application of risk-adapted SBRT approach.

7. Summary

The gold standard treatment for lymph node negative, early-stage lung cancer is surgical removal. However, a significant proportion of patients presenting this medical condition, are elderly, suffer from severe chronic lung illnesses, or other comorbidities contraindicating operation. Less frequently, some medically operable patients refuse surgery. Solitary, or oligometastases in the lung, originated from various primary tumors are also conditions could be treated with metastasectomy, but in these cases surgery is a part of a more complex oncological strategy. For these abovementioned situations, stereotactic radiotherapy is a precise, successful non-surgical alternative, however individualized treatment strategy is needed, in function of the size and the location of the target lesions.

The purpose of this thesis was investigation of local and overall effectiveness and safety of lung SBRT in large-scale cohorts after application of risk adapted dose regimens, as well as evaluation of potential predictive factors on survival metrics. Also, we aimed to confirm the legitimacy of SBRT in patients without histological verification.

In Study I. we analysed 130 patients with 160 pulmonary lesions treated with CyberKnife SBRT. In this mixed cohort of primary, recurrent and secondary tumors in the lung, we essentially investigated local control rates, early and late toxicities and factors influencing local effectiveness.

In Study 2. we focused on a more homogenous, and even larger cohort of a total of 401 early-stage lung cancer patients. Beyond the analysis of local control, local progression-free survival, progression free survival and overall survival, we investigated the potential predictive factors, and adverse events.

In summary, we observed high LC, LPFS, PFS and OS rates, consistently to those reported in the literature, as well as low rates of severe toxicities. In multivariate analysis we found that smaller tumor size and better ECOG performance status predict better OS, and prescribed BED_{10} doses of $\geq$132 Gy predict better LPFS.

Our positive clinical experiences with the application of risk adapted dose fractionation, especially 3x18 Gy, 5x12 Gy and 8x7.5 Gy regimens (occasionally with further dose-

reduction in case of conflicts with OAR constraints) confirm the successful application of this dose-diversification strategy.

8. References

[1] Buwaider A, Backlund EO, Almqvist P, Lippitz B, Fletcher-Sandersjöö A, Bartek J. 55-Year Follow-Up of the First Adult Patient With Craniopharyngioma Treated With Gamma Knife Radiosurgery. Neurosurgery. 2024 Sep 1;95(3):e71-e78.

[2] Lax I, Blomgren H, Näslund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. Acta Oncol. 1994;33(6):677-83.

[3] Macià I Garau M. Radiobiology of stereotactic body radiation therapy (SBRT). Rep Pract Oncol Radiother. 2017 Mar-Apr;22(2):86-95.

[4] Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010 Mar 17;303(11):1070-6.

[5] Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008 Mar 1;70(3):685-92.

[6] Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, Tanadini-Lang S, Lartigau E, Méndez Romero A, Senan S, Verellen D. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol. 2017 Jul;124(1):11-17.

[7] Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR, Lally BE, Latzka K, Lo SS, Moghanaki D, Movsas B, Rimner A, Roach M, Rodrigues G, Shirvani SM, Simone CB 2nd, Timmerman R, Daly ME. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol. 2017 Sep-Oct;7(5):295-301.

[8] De Ruysscher D, Faivre-Finn C, Moeller D, Nestle U, Hurkmans CW, Le Péchoux C, Belderbos J, Guckenberger M, Senan S; Lung Group and the Radiation Oncology Group of the European Organization for Research and Treatment of Cancer (EORTC). European Organization for Research and Treatment of Cancer (EORTC) recommendations for

planning and delivery of high-dose, high precision radiotherapy for lung cancer. Radiother Oncol. 2017 Jul;124(1):1-10.

[9] Janvary ZL, Jansen N, Baart V, Devillers M, Dechambre D, Lenaerts E, Seidel L, Barthelemy N, Berkovic P, Gulyban A, Lakosi F, Horvath Z, Coucke PA. Clinical Outcomes of 130 Patients with Primary and Secondary Lung Tumors treated with Cyberknife Robotic Stereotactic Body Radiotherapy. Radiol Oncol. 2017 Apr 3;51(2):178-186.

[10] Jánváry ZL, Bajcsay A, Stelczer G, Kontra G, Pócza T, Gerdán M, Lövey J, Kocsis ZS, Ladányi K, Pap É, Major T, Polgár C. Long-term clinical results of early-stage lung cancer patients treated with risk-adapted stereotactic body radiotherapy using LINAC or CyberKnife: A single-institution analysis of more than 400 cases. Strahlenther Onkol. 2025 Nov;201(11):1208-1218.

[11] Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. Semin Radiat Oncol. 2008 Oct;18(4):215-22.

[12] Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, Keall P, Lovelock M, Meeks S, Papiez L, Purdie T, Sadagopan R, Schell MC, Salter B, Schlesinger DJ, Shiu AS, Solberg T, Song DY, Stieber V, Timmerman R, Tomé WA, Verellen D, Wang L, Yin FF. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010 Aug;37(8):4078-101.

[13] Luo G, Zhang Y, Rumgay H, Morgan E, Langselius O, Vignat J, Colombet M, Bray F. Estimated worldwide variation and trends in incidence of lung cancer by histological subtype in 2022 and over time: a population-based study. Lancet Respir Med. 2025 Apr;13(4):348-363.

[14] Lu T, Yang X, Huang Y, Zhao M, Li M, Ma K, Yin J, Zhan C, Wang Q. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. Cancer Manag Res. 2019 Jan 21;11:943-953.

[15] Kenessey I, Parrag P, Dobozi M, Szatmári I, Wéber A, Nagy P, Polgár C. The epidemiology of lung cancer in Hungary based on the characteristics of patients diagnosed in 2018. Sci Rep. 2024 Aug 29;14(1):20064.

[16] Wisnivesky JP, Bonomi M, Henschke C, Iannuzzi M, McGinn T. Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. Chest. 2005 Sep;128(3):1461-7.

[17] Wulf J, Hädinger U, Oppitz U, Olshausen B, Flentje M. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. Radiother Oncol. 2000 Nov;57(2):225-36.

[18] Timmerman R, Papiez L, McGarry R, Likes L, DesRosiers C, Frost S, Williams M. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest. 2003 Nov;124(5):1946-55.

[19] Abel S, Hasan S, Horne ZD, Colonias A, Wegner RE. Stereotactic body radiation therapy in early-stage NSCLC: historical review, contemporary evidence and future implications. Lung Cancer Manag. 2019 Feb 27;8(1):LMT09.

[20] Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruysscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol. 2010 Apr;95(1):32-40.

[21] Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, Sakamoto M, Mitsumori M, Shibuya K, Araki N, Yano S, Hiraoka M. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys. 2005 Dec 1;63(5):1427-31.

[22] Ernst-Stecken A, Lambrecht U, Mueller R, Sauer R, Grabenbauer G. Hypofractionated stereotactic radiotherapy for primary and secondary intrapulmonary tumors: first results of a phase I/II study. Strahlenther Onkol. 2006 Dec;182(12):696-702.

[23] Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, Yamashita T, Niibe Y, Karasawa K, Hayakawa K, Takai Y, Kimura T, Hirokawa Y, Takeda A, Ouchi A, Hareyama M, Kokubo M, Hara R, Itami J, Yamada K. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer. 2004 Oct 1;101(7):1623-31.

[24] Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, Groen HJ, McRae SE, Widder J, Feng L, van den Borne BE, Munsell MF, Hurkmans C, Berry DA, van Werkhoven E, Kresl JJ, Dingemans AM, Dawood O, Haasbeek CJ, Carpenter LS, De Jaeger K, Komaki R, Slotman BJ, Smit EF, Roth JA. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015 Jun;16(6):630-7.

[25] Lagerwaard FJ, Verstegen NE, Haasbeek CJ, Slotman BJ, Paul MA, Smit EF, Senan S. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):348-53.

[26] Bral S, Gevaert T, Linthout N, Versmessen H, Collen C, Engels B, Verdries D, Everaert H, Christian N, De Ridder M, Storme G. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a Phase II trial. Int J Radiat Oncol Biol Phys. 2011 Aug 1;80(5):1343-9

[27] Verstegen NE, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol. 2011 Nov;101(2):250-4.

[28] Taremi M, Hope A, Dahele M, Pearson S, Fung S, Purdie T, Brade A, Cho J, Sun A, Bissonnette JP, Bezjak A. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):967-73.

[29] Videtic GM, Paulus R, Singh AK, Chang JY, Parker W, Olivier KR, Timmerman RD, Komaki RR, Urbanic JJ, Stephans KL, Yom SS, Robinson CG, Belani CP, Iyengar P, Ajlouni MI, Gopaul DD, Gomez Suescun JB, McGarry RC, Choy H, Bradley JD. Long-term Follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2019 Apr 1;103(5):1077-1084.

[30] Singh AK, Gomez-Suescun JA, Stephans KL, Bogart JA, Hermann GM, Tian L, Groman A, Videtic GM. One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial. Int J Radiat Oncol Biol Phys. 2019 Nov 15;105(4):752-759.

[31] Videtic GMM, Reddy CA, Woody NM, Stephans KL. Ten-Year Experience in Implementing Single-Fraction Lung SBRT for Medically Inoperable Early-Stage Lung Cancer. Int J Radiat Oncol Biol Phys. 2021 Oct 1;111(2):436-442.

[32] Duncker-Rohr V, Nestle U, Momm F, Prokic V, Heinemann F, Mix M, Reusch J, Messmer MB, Marschner N, Waller CF, Weber WA, Grosu AL. Stereotactic ablative radiotherapy for small lung tumors with a moderate dose. Favorable results and low toxicity. Strahlenther Onkol. 2013 Jan;189(1):33-40.

[33] Guckenberger M, Wulf J, Mueller G, Krieger T, Baier K, Gabor M, Richter A, Wilbert J, Flentje M. Dose-response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4D dose calculation. Int J Radiat Oncol Biol Phys. 2009 May 1;74(1):47-54.

[34] Yamamoto T, Jingu K, Shirata Y, Koto M, Matsushita H, Sugawara T, Kubozono M, Umezawa R, Abe K, Kadoya N, Ishikawa Y, Kozumi M, Takahashi N, Takeda K, Takai Y. Outcomes after stereotactic body radiotherapy for lung tumors, with emphasis on comparison of primary lung cancer and metastatic lung tumors. BMC Cancer. 2014 Jun 23;14:464.

[35] Wegner RE, Ahmed N, Hasan S, Schumacher LY, Van Deusen M, Colonias A. SBRT for early-stage lung cancer: outcomes from biopsy-proven and empirically treated lesions. Lung Cancer Manag. 2018 Apr 17;7(1):LMT01.

[36] Takeda A, Kunieda E, Sanuki N, Aoki Y, Oku Y, Handa H. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. Lung Cancer. 2012 Jul;77(1):77-82.

[37] Parker SM, Siochi RA, Wen S, Mattes MD. Impact of Tumor Size on Local Control and Pneumonitis After Stereotactic Body Radiation Therapy for Lung Tumors. Pract Radiat Oncol. 2019 Jan;9(1):e90-e97

[38] Fischer-Valuck BW, Durci M, Katz SR, Wu HT, Syh J, Syh J, Patel B, Rosen LR. Influence of patient characteristics on survival following treatment with helical stereotactic body radiotherapy (SBRT) in stage I non-small-cell lung cancer. Thorac Cancer. 2013 Feb;4(1):27-34.

[39] Davis JN, Medbery C 3rd, Sharma S, Perry D, Pablo J, D'Ambrosio DJ, McKellar H, Kimsey FC, Chomiak PN, Mahadevan A. Stereotactic body radiotherapy for early-stage non-small cell lung cancer: clinical outcomes from a National Patient Registry. J Radiat Oncol. 2015;4(1):55-63.

[40] Klement RJ, Belderbos J, Grills I, Werner-Wasik M, Hope A, Giuliani M, Ye H, Sonke JJ, Peulen H, Guckenberger M. Prediction of Early Death in Patients with Early-Stage NSCLC-Can We Select Patients without a Potential Benefit of SBRT as a Curative Treatment Approach? J Thorac Oncol. 2016 Jul;11(7):1132-9.

[41] Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, Niibe Y, Karasawa K, Hayakawa K, Takai Y, Kimura T, Takeda A, Ouchi A, Hareyama M, Kokubo M, Hara R, Itami J, Yamada K, Araki T. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol. 2007 Jul;2(7 Suppl 3):S94-100.

[42] Olsen JR, Robinson CG, El Naqa I, Creach KM, Drzymala RE, Bloch C, Parikh PJ, Bradley JD. Dose-response for stereotactic body radiotherapy in early-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):e299-303.

[43] Grills IS, Hope AJ, Guckenberger M, Kestin LL, Werner-Wasik M, Yan D, Sonke JJ, Bissonnette JP, Wilbert J, Xiao Y, Belderbos J. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. J Thorac Oncol. 2012 Sep;7(9):1382-93.

[44] Stephans KL, Woody NM, Reddy CA, Varley M, Magnelli A, Zhuang T, Qi P, Videtic GMM. Tumor Control and Toxicity for Common Stereotactic Body Radiation Therapy Dose-Fractionation Regimens in Stage I Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2018 Feb 1;100(2):462-469.

[45] Zhang J, Yang F, Li B, Li H, Liu J, Huang W, Wang D, Yi Y, Wang J. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):e305-16.

[46] Ruggieri R, Stavrev P, Naccarato S, Stavreva N, Alongi F, Nahum AE. Optimal dose and fraction number in SBRT of lung tumours: A radiobiological analysis. Phys Med. 2017 Dec;44:188-195.

[47] Fan S, Zhang Q, Chen J, Chen G, Zhu J, Li T, Xiao H, Du S, Zeng Z, He J. Comparison of long-term outcomes of stereotactic body radiotherapy (SBRT) via Helical tomotherapy for early-stage lung cancer with or without pathological proof. Radiat Oncol. 2023 Mar 8;18(1):49.

[48] Haidar YM, Rahn DA 3rd, Nath S, Song W, Bazhenova L, Makani S, Fuster MM, Sandhu AP. Comparison of outcomes following stereotactic body radiotherapy for non-small cell lung cancer in patients with and without pathological confirmation. Ther Adv Respir Dis. 2014 Feb;8(1):3-12.

[49] Chaurasia AR, White J, Beckmann RC, Chamberlin M, Horn A, Torgeson AM, Skinner W, Erickson D, Reed A. Early-Stage Non-Small Cell Lung Cancer Stereotactic Body Radiation Therapy (SBRT) Outcomes in an Equal Access Military Setting. Cureus. 2021 Feb 22;13(2):e13485.

[50] Jánváry L, Bajcsay A, Polgár C: Sztereotaxiás sugárterápia – új lehetőség az I. stádiumú tüdőrák és a tüdőáttétek kezelésében. Medicina Thoracalis 2018, 71 (4) 242-249

9. Bibliography of the candidate's publications

List of publications on the topic of the dissertation:

English-language peer-reviewed publications:

Jánváry ZL, Bajcsay A, Stelczer G, Kontra G, Pócza T, Gerdán M, Lövey J, Kocsis ZS, Ladányi K, Pap É, Major T, Polgár C. (2025) Long-term clinical results of early-stage lung cancer patients treated with risk-adapted stereotactic body radiotherapy using LINAC or CyberKnife : A single-institution analysis of more than 400 cases. Strahlenther Onkol. 2025;201(11):1208-1218.

IF: 2.5

Janvary ZL, Jansen N, Baart V, Devillers M, Dechambre D, Lenaerts E, Seidel L, Barthelemy N, Berkovic P, Gulyban A, Lakosi F, Horvath Z, Coucke PA. (2017) Clinical Outcomes of 130 Patients with Primary and Secondary Lung Tumors treated with Cyberknife Robotic Stereotactic Body Radiotherapy. Radiol Oncol. 2017 Apr 3;51(2):178-186.

IF: 1.722

Hungarian-language peer-reviewed publications:

Jánváry L, Bajcsay A, Polgár C: Sztereotaxiás sugárterápia – új lehetőség az I. stádiumú tüdőrák és a tüdőáttétek kezelésében. Medicina Thoracalis (Budapest) 2018, 71 (4) 242-249

IF: -

The cumulative impact factor of publications on the topic of the dissertation: 4.222

List of publications closely related to the topic of the dissertation:

Colin, Gilles; Ben Mustapha, Selma; Jansen, Nicolas; Coucke, Philippe; Seidel, Laurence; Berkovic, Patrick; Janvary, Levente (2023) Interval From Simulation Imaging

to Treatment Delivery in SABR of Lung Lesions : How Long is Too Long for the Lung? Advances in Radiation Oncology 8:2 Paper: 101132 (2023)

IF: 2.2

Berkovic, Patrick; Gulyban, Akos; Defraene, Gilles; Swenen, Laurie; Dechambre, David; Nguyen, Paul Viet; Jansen, Nicolas; Mievis, Carole; Lovinfosse, Pierre; Janvary, Levente et al.(2020) Stereotactic robotic body radiotherapy for patients with oligorecurrent pulmonary metastases BMC CANCER 20 : 1 Paper: 402 (2020)

IF: 4.43

Bajcsay, András; Jánváry, Levente Zsolt; Ladányi, Katalin; Pócza, Tamás; Major, Tibor; Polgár, Csaba , (2020) A tüdőrák modern sugárterápiája, MAGYAR ONKOLÓGIA 64:3 pp. 255-261., 7 p.

IF:-

Dechambre, D; Janvary, LZ; Jansen, N; Berkovic, P; Mievis, C; Baart, V; Cucchiaro, S; Coucke, AP; Gulyban A. (2018) Prediction of GTV median dose differences eases Monte Carlo re-prescription in lung SBRT, PHYSICA MEDICA-EUROPEAN JOURNAL OF MEDICAL PHYSICS 45 pp. 88-92. 5 p. (2018), DOI: 10.1016/j.ejmp.2017.12.002

IF: 2,532

Lovinfosse, Pierre; Janvary, Zsolt Levente; Coucke, Philippe; Jodogne, Sébastien; Bernard, Claire; Hatt, Mathieu ; Visvikis, Dimitris; Jansen, Nicolas; Duysinx, Bernard; Hustinx, Roland (2016) FDG PET/CT texture analysis for predicting the outcome of lung cancer treated by stereotactic body radiation therapy EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING 43 : 8 pp. 1453-1460. , 8 p. (2016) , D1, DOI: 10.1007/s00259-016-3314-8

IF: 7.277

List of publications not related to the topic of the dissertation:

Vízkeleti, Júlia; Jánváry, Zsolt Levente; Kispál, Mihály; Polgár, Csaba. A sugárterápia szerepe, In: Liszkay, Gabriella (szerk.) A melanoma komplex onkoterápiája. Budapest, Magyarország : Medicina Könyvkiadó Zrt. (2025) 182 p. pp. 123-129. , 7 p. (book chapter)

IF: -

Bukovszky, Bence; Vízkeleti, Júlia; Jánváry, Levente; Szarvas, Gábor; Felkai, Luca; Bánusz, Rita; Varga, Edit; Sápi, Zoltán; Major, Tibor; Csóka, Monika. CyberKnife radiation therapy for malignant myopericytoma in a pediatric patient: a case report and review of the literature STRAHLENTHERAPIE UND ONKOLOGIE 201 : 9 pp. 963-970. , 8 p. (2025)

IF: 2.5

Fedorcsák, Imre; Bajcsay, András; Jánváry, Levente. Agyi daganatos elváltozások sztereotaxiás besugárzása. MAGYAR ONKOLÓGIA 68: 1 pp. 53-59. , 7 p. (2024)

IF:-

Tóth, Erika; Kürönya, Zsófia; Soós, Edina; Pintér, Tamás; Butz, Henriett; Horváth, Zsolt; Csernák, Erzsébet; Grolmusz, Vince Kornél; Székely, Judit; Straussz, Tamás József Lövey, Levente Jánváry, László Báthory-Fülöp, Péter Nagy, Csaba Polgár, Attila Patócs. Application of comprehensive molecular genetic profiling in precision cancer medicine, Hungarian experiences. ACTA ONCOLOGICA 63 pp. 433-440. , 8 p. (2024)

IF: 2.2

Jánváry, Levente Zsolt; Kispál, Mihály. CyberKnife és lineáris gyorsító alapú sztereotaxiás sugárkezelés alkalmazása melanómában MAGYAR ONKOLÓGIA 66: 2 pp. 127-133., 7 p. (2022)

IF: -

Kispál, Mihály; Jánváry, Levente Zsolt; Balatoni, Tímea; Gábor, Stelczer; Fedorcsák, Imre; Katalin, Bőcs; Kenessey, István; Liszkay, Gabriella. The Role of Stereotactic

Radiotherapy in the Management of Melanoma, A Retrospective Single Institute-Preliminary Study of 30 Patients PATHOLOGY AND ONCOLOGY RESEARCH 28 Paper: 1610550 (2022)

IF: 2.8

Jánváry, Levente Zsolt; Lövey, József. A hasnyálmirigyrák sugárterápiája MAGYAR ONKOLÓGIA 65:3 pp. 265-271., 7 p. (2021)

IF: -

Kispál, Mihály Tamás; Jánváry, Zsolt Levente; Bőcs, Katalin; Liszkay, Gabriella. CyberKnife-kezelés melanomában egy eset kapcsán DERMATOLOGY TIMES (MAGYAR KIADÁS) 4: 1 pp. 18-20. , 3 p. (2020)

IF: -

Mészáros, Norbert; Major, Tibor; Stelczer, Gábor; Jánváry, Levente; Zaka, Zoltán; Pukancsik, Dávid; Takácsi-Nagy, Zoltán; János Fodor; Polgár, Csaba. Accelerated partial breast irradiation with 3-dimensional conformal and image-guided intensity-modulated radiotherapy following breast conserving surgery - 7-Year results of a phase II trial BREAST 54 pp. 222-228. , 7 p. (2020)

IF: 4.38

Mészáros, Norbert; Smanykó, Viktor; Major, Tibor; Stelczer, Gábor; Jánváry, Levente; Kovács, Eszter; Mária, Bahéri; Zaka, Zoltán; Pukancsik, Dávid; Takácsi-Nagy, Zoltán et al. Implementation of Stereotactic Accelerated Partial Breast Irradiation Using Cyber-Knife – Technical Considerations and Early Experiences of a Phase II Clinical Study PATHOLOGY AND ONCOLOGY RESEARCH 26 : 4 pp. 2307-2313. , 7 p. (2020)

IF: 3.201

Jorgo, Kliton; Ágoston, Péter; Jánváry, Levente; Gesztesi, László; Stelczer, Gábor; Kontra, Gábor; Major, Tibor; Polgár, Csaba Kis és közepes kockázatú prosztatarákos betegek sztereotaxiás sugárkezelése CyberKnife gyorsítóval: korai radiogén mellékhatások [Stereotactic body radiation therapy with CyberKnife accelerator for low-

and intermediate risk prostate cancer] MAGYAR ONKOLÓGIA 63: 1 pp. 52-59., 8 p. (2019)

IF: -

Sipos, László; Bajcsay, András; Kontra, Gábor; Czirják, Sándor; Jánváry, Levente; Fedorcsák, Imre; Polgár, Csaba. Korai tapasztalataink Cyberknife-kezeléssel suprasellarisan is terjedő hypernephroma-áttét esetén IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 72: 11-12 pp. 427-431., 5 p. (2019)

IF: 0.337

Jánváry, Levente. Sztereotaxiás sugársebészet

In: Mangel, László; Bellyei, Szabolcs; Boronkai, Árpád (szerk.) Onkológiai jegyzet Pécs, Magyarország : Pécsi Tudományegyetem, Általános Orvostudományi Kar, Onkoterápiás Intézet (2019) pp. 87-90. , 4 p. (book chapter)

IF: -

Ágoston, P; Major, T; Jánváry, L . Képvezérelt és intenzitásmodulált sugárkezelés és sugársebészet

In: Polgár, Cs (szerk.) Onkológia és sugárterápia Budapest, Magyarország : Semmelweis Kiadó és Multimédia Stúdió (2018) 261 p. pp. 61-67., 7 p. (book chapter)

IF: -

Jánváry, Levente Zsolt; Ferenczi, Örs; Takácsi-Nagy, Zoltán; Bajcsay, András; Polgár, Csaba. A CyberKnife sztereotaxiás sugárterápia alkalmazásának lehetősége fej-nyaki daganatok kezelésében MAGYAR ONKOLÓGIA 62: 3 pp. 180-185., 6 p. (2018)

IF: -

Jánváry, Zsolt Levente; Bajcsay, András; Polgár, Csaba. Robotkaros besugárzó (CyberKnife): a precíziós sugárkezelés új lehetősége HÁZIORVOS TOVÁBBKÉPZŐ SZEMLE 23: 8 pp. 508-512., 5 p. (2018)

IF: -

Berkovic, P; Gulyban, A; Nguyen, PV; Dechambre, D; Martinive, P; Jansen, N; Lakosi, F; Janvary, L; Coucke, PA. Stereotactic Robotic Body Radiotherapy for Patients With Unresectable Hepatic Oligorecurrence CLINICAL COLORECTAL CANCER 16: 4 pp. 349-357.e1. (2017)

IF: 3.861

Kocsis, Judit; Gráf, László; Jánváry, Levente; Horváth, Zsolt. A gyomordaganatok multimodális kezelése. MAGYAR BELORVOSI ARCHIVUM 70: 2 pp. 78-83. , 6 p. (2017)

IF: -

Kocsis, Judit; Árokszállási, Anita; András, Csilla; Balogh, Ingrid; Béres, Edit; Déri, Júlia; Peták, István; Jánváry, Levente; Horváth, Zsolt. Combined dabrafenib and trametinib treatment in a case of chemoterapy-refractory extrahepatic BRAF V600E mutant cholangiocarcinoma: dramatic clinical and radiological response with a confusing synchronic new liver lesion JOURNAL OF GASTROINTESTINAL ONCOLOGY 8:2 pp. E32-E38. (2017)

IF: -

Ferenc, Lakosi; Akos, Gulyban; Selma, Ben-Mustapha Simoni; Paul, Viet Nguyen; Séverine, Cucchiaro; Laurence, Seidel; Levente, Janvary; Sophie, Nicolas; Peter, Vavassis; Philippe, Coucke. The Influence of Treatment Position (Prone vs. Supine) on Clip Displacement, Seroma, Tumor Bed and Partial Breast Target Volumes: Comparative Study PATHOLOGY AND ONCOLOGY RESEARCH 22: 3 pp. 493-500., 8 p. (2016)

IF: 1.736

Jánváry, Zsolt Levente; Horváth, Zsolt. Robotikus és lineáris gyorsító alapú, koponyán kívüli sztereotaxiás sugárkezelések ONKOLÓGIA (AZ ONCOLOGY MAGYAR KIADÁSA) 1:6 pp. 41-47., 7 p. (2016)

IF: -

Jánváry, Zsolt Levente; Simon, Mihály; Dér, Ádám; Szántó, Erika; Fodor, Andrea; Kardos, Tamás; Szilasi, Mária; Horváth, Zsolt. Sztereotaxiás sugárterápia> új, kuratív

terápiás lehetőség az inoperábilis I. stádiumú nem-kissejtes tüdőrák kezelésében. MEDICINA THORACALIS (BUDAPEST) 69 : 3 pp. 13-137. , 125 p. (2016)

IF: -

Lakosi, F; Gulyban, A; Janvary, L; Simoni, SB-M; Jansen, N; Seidel, L; Kovacs, A; Vavassis, P; Coucke, P. Respiratory Motion, Anterior Heart Displacement and Heart Dosimetry: Comparison Between Prone (Pr) and Supine (Su) Whole Breast Irradiation PATHOLOGY AND ONCOLOGY RESEARCH 21:4 pp. 1051-1058., 8 p. (2015)

IF: 1.94

Valastyánné, Nagy Julianna; Jánváry, Zsolt Levente; Balogh, István; Horváth, Zsolt. CT-képvezérelt, intenzitásmodulált ívterápiás sugárterápiás program klinikai rutinba való bevezetése és a megfelelő rendszeres fizikusi minőségbiztosítás protokollizálása MAGYAR ONKOLÓGIA 59:2 pp. 125-132., 8 p. (2015)

IF: -

Coucke, P; Janvary, Z; Jansen, N

L'interet de la radiotherapie "ablative" en prenant comme modele la metastase d'un cancer renal a cellules claires. REVUE MÉDICALE DE LIEGE: JOURNAL DU PRATICIEN 69: Suppl 1 pp. 94-100., 7 p. (2014)

IF: -

Cselik, Zsolt; Hadjiev, Janaki; Horváth, Ákos; Jánváry, Levente; Kovács, Árpád; Liposits, Gábor; Vallyon, Márta; Mangel, László; Antal, Gergely; Kovács, Árpád (szerk.) et al.: Sugárterápia. Budapest, Magyarország : Medicina Könyvkiadó (2014) , 464 p. ISBN: 9789632264530 (book chapter)

IF: -

Jansen, N; Coucke, P; Janvary, Z. La radiotherapie moderne pre- ou postoperatoire pour les sarcomes des tissus mous des membres. REVUE MÉDICALE DE LIEGE: JOURNAL DU PRATICIEN 69: Suppl. 1 pp. 53-57., 5 p. (2014)

IF: -

Janvary, Z; Jansen, N; Coucke, P. Le CyberKnife aime les defis! Apercu d'indications pour la radiotherapie extracranienne robotisee. REVUE MÉDICALE DE LIEGE: JOURNAL DU PRATICIEN 69: Suppl 1 pp. 87-93., 7 p. (2014)

IF: -

Jánváry, Zsolt. A korai stádiumú, inoperábilis primer tumorok sztereotaxiás sugárterápiája

In: Bodoky, György; Kopper, László; Hideghéty, Katalin; Strausz, János (szerk.) Tüdő- és mediastinalis onkológia, Budapest, Magyarország : Semmelweis Kiadó (2013) 368 p. pp. 199-203., 5 p. ISBN: 978-963-008-7379-6 (book chapter)

IF: -

Jánváry, Zsolt. Áttétes tüdőrák sugárkezelése

In: Bodoky, György; Kopper, László; Hideghéty, Katalin; Strausz, János (szerk.) Tüdő- és mediastinalis onkológia, Budapest, Magyarország : Semmelweis Kiadó (2013) 368 p. pp. 203-207., 5 p. ISBN: 978-963-008-7379-6 (book chapter)

IF: -

Mózsa, Emőke; Polgár, Csaba; Fröhlich, Georgina; Major, Tibor; Jánváry, Levente; Lövey, Katalin; Sulyok, Zoltán; Takácsi, Nagy László; Fodor, János; Kásler, Miklós Akcelerált parciális konformális külső emlőbesugárzás emlőmegtartó műtét után: fázis II prospektív klinikai vizsgálat előzetes eredményei MAGYAR ONKOLÓGIA 56: 4 pp. 235-241., 7 p. (2012)

IF: -

Coucke, P; Janvary, ZL; Baart, V; Devillers, M; Jansen, Lenaerts, E. Ai-je bien entendu? Je peux me faire traiter autrement que par chirurgie pour mon schwannome de l'acoustique. REVUE MÉDICALE DE LIEGE: JOURNAL DU PRATICIEN 66: 10 pp. 521-528., 8 p. (2011)

IF: -

Coucke, P; Lakosi, F; Rorive, A; Janvary, ZL; Collignon, J ; Jansen, N; Andre, C; Jerusalem, G. Radiotherapie et cancer du sein: "standards" de traitement, prediction de

rechute locale et questions ouvertes. REVUE MÉDICALE DE LIEGE: JOURNAL DU PRATICIEN 66: 5-6 pp. 320-325., 6 p. (2011)

IF: -

L., Jánváry; N., Jansen; P., Martinive; P.A., Coucke. New indications for radiotherapy: primary liver cancer and secondary liver oligometastases, Belgian Journal of Medical Oncology 5:1 pp. 8-13., 6 p. (2011)

IF: -

Lallemand, F; Janvary, ZL; Jansen, N; Coucke, P. Cyberknife et pathologies benignes. REVUE MÉDICALE DE LIEGE: JOURNAL DU PRATICIEN 66: 11 pp. 568-574., 7 p. (2011)

IF: -

P.A., Coucke; N., Jansen; L., Jánváry; C., Louis; J., Vanderick; A., Rorive ; J., Collignon; E., Lifrange; S., Maweja ; G., Jerusalem. Accelerated partial breast irradiation: state of the art, Belgian Journal of Medical Oncology 5: 1 pp. 3-7., 5 p. (2011)

IF: -

Philippe, A Coucke; Nicolas, Jansen; Zsolt-Levente, Janvary; Magalie, Devillers; Véronique, Baert; Eric, Lenaerts. Le robot cyberKnife® adapte L'irradiation aux mouvements de La cible avec une précision millimétrique grâce à L'imagerie embarquée, Neurone 16: 8 pp. 287-294., 8 p. (2011)

IF: -

Coucke, PA; Jansen, N; Collignon, J; Janvary, L; Rorive, A; Vanderick, J ; Jerusalem, G. Pourquoi les traitements de radiotherapie adjuvante pour cancer du sein ne comptent-ils plus autant de seances? REVUE MÉDICALE DE LIEGE: JOURNAL DU PRATICIEN 65:1 pp. 10-14., 5 p. (2010)

IF: -

Coucke, PA; Withofs, N; Jansen, N; Janvary, Z; Hustinx, R. Vers une radiotherapie chirurgicale: necessite d'une radiotherapie guidee par l'imagerie. REVUE MÉDICALE DE LIEGE: JOURNAL DU PRATICIEN 65 Spec no. pp. 17-22. , 6 p. (2010)

IF: -

Lovey, K; Fodor, J; Major, T; Szabo, E; Orosz, Z; Sulyok, Z; Janvary, L; Frohlich, G; Kasler, M; Polgar, C. Fat necrosis after partial-breast irradiation with brachytherapy or electron irradiation versus standard whole-breast radiotherapy--4-year results of a randomized trial. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS 69: 3 pp. 724-731., 8 p. (2007)

IF: 4.29

Cumulative impact factor of the author of the dissertation: 42.906

Citations: (independent / total) 365 / 431 (Oct 2025)

10. Acknowledgements

I would like to express my sincere gratitude to the following persons, who have directly or indirectly helped me in my work. Special thanks to:

-**Prof. Dr. Csaba Polgár**, my supervisor, for professional and scientific support from the beginning of my career

-**Prof. Dr. Philippe Coucke**, my former supervisor during my years in Belgium for all the support and encouragements

-**Dr. András Bajcsay**, radiation oncologist colleague and friend, for fundamental contribution in this scientific work and for the implementation and practice of SBRT in NIO

-**Dr. Gábor Stelczer, Dr. Zsuzsa Kocsis and Dr. Tamás Pócza**, for all the scientific discussions, advice and contribution in statistical analysis and evaluation of data

-**Dr. Nicolas Jansen, and the complete Cyberknife team (radiation oncologists, RTTs and physicists) in the Liège University Hospital in Belgium** (CHU de Liège)

-**Radiation oncologists, physicists, RTTs, nurses, in the Center of Radiotherapy in NIO**, Budapest, who participated in the enormous work of hundreds of SBRT treatments

-More specifically **my closer workgroup of Cybernife in NIO**, Budapest for daily support and good vibes

-**Pulmonologist-, thoracic surgeon-, diagnostic and interventional radiologist-, pathologist and oncologist colleagues of**: the NIO, the Törökbálint Reformed Pumonology Center, the National Korányi Pulmonology Institute, the Székesfehérvár Szent György Hospital, the Pulmonology Clinic of Semmelweis University and the CHU de Liège: for their contribution

-**My Mother,** for raising me and being my mother

-**Dr. Zoltán Zaka,** for his friendship

-And I am especially grateful to my little family: **my wife Márta and my children: Zsombor, Rege and Tünde** for their sustained encouragement, love and positive energy.