Lung Stereotactic Radiation Therapy: Intercomparison of Several Irradiation Devices in Terms of Outcome and Predictive Factors

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Abstract

Background: Stereotactic body radiotherapy (SBRT) is recommended for the treatment of inoperable early stage non-small-cell lung cancer and lung oligometastases. The radiation oncology department of the Lausanne University Hospital (CHUV) gathers three different radiotherapy devices able to treat pulmonary lesions in SBRT conditions: CyberKnife® (CK), Helical Tomotherapy® (HT), and volumetric modulated arc therapy (VMAT). The aim of this study is to define the patients' outcome in terms of irradiation efficacy and toxicities after lung SBRT depending of the choice of the SBRT technique.

Methods: We retrospectively analyzed the clinical, radiological, and dosimetric data of patients with primary lung tumor or pulmonary oligometastases treated with SBRT between January 2016 and February 2020. We analyzed descriptive data using the Chi-2 test for proportions and the T-test for means comparisons, survival data by the Kaplan-Meier method and comparisons between groups by the Log-rank test and Cox-regression.

Results: We identified 111 patients mostly in good condition (82.9% PS 0-1) with a median age of 71.4 years. One hundred forty-two lesions were treated with a typical fractionation of 55 Gy in 5 fractions, delivered by CK (59.9%), VMAT (38.0%), or HT (2.1%). Compared to other techniques, CK technique allowed to treat comparable gross tumor volume (GTV; 2.1 vs 1.4cc, $p = 0.84$) with smaller planning treatment volume (PTV; 12.3 vs 21.9 cc, $p = 0.013$), and was associated with a lower mean lung dose (MLD; 2.6 vs 4.1 Gy, $p < 0.001$), a lower V5 (13.5 vs 19.9 cc, $p = 0.002$) and a lower V20 (2.3 vs 5.4 cc, $p < 0.001$). Local control rates at 2 years were not different depending on the irradiation device, respectively of 96.2% (range, 90.8-100) and 98.1% (range, 94.4-100), $p = 0.68$. Toxicity incidence was significantly increased with V5 value $> 17.2\%$ (56.0 vs 77.4%, $p = 0.021$).

Conclusions: Compared to other SBRT techniques, CK treatments permitted to treat comparable GTV with reduced PTV, MLD, V20, and V5. The dosimetric benefit of CK SBRT was not associated with a clear clinical benefit, with comparable outcome in terms of control rates and toxicity. Toxicity incidence was less frequent when reducing the V5. The use of CK is particularly attractive in case of multiple courses of lung SBRT or in case of local relapse requiring lung re-irradiation.

Trial registration: Registered on February 24th 2021, ID 2021-00267, with the authorization of the CER-VD ethics committee (Switzerland).

Background

Lung cancer is the most common cause of cancer-related death(1). The introduction of pulmonary stereotactic body radiotherapy (SBRT) for early malignancies has been correlated to a reduction in the number of patients who remain untreated(2, 3). SBRT is recommended for early stage non-small-cell lung cancer (NSCLC), either in medically or surgically inoperable patients, or in well-selected operable patients, according to clinical guidelines(4–7). In addition, various SBRT indications for lung oligometastases are well known(8).

The radiation oncology department of the Lausanne University Hospital (CHUV) gathers three different radiotherapy devices able to treat pulmonary lesions in SBRT conditions: Synergy® (Elekta, Sweden), Helical Tomotherapy® (Accuray, USA), and CyberKnife® (Accuray, USA).

Synergy® is a linear accelerator (linac) that uses volumetric modulated arc treatment (VMAT). The second device, termed helical Tomotherapy® (HT), combines a megavoltage computed tomography (MV-CT) and a miniaturized

linac to provide image-guided radiation therapy. During helical irradiation, the machine slowly spins around the patient while the table travels longitudinally. When using Synergy® and HT, an internal target volume is either determined, on a 4D CT or in obstructed inspiration owing to a respiratory servo system called Active Breath Control® (ABC). When using a 4D-CT for planning, the gross tumor volume (GTV) of each phase is combined into an internal target volume (ITV). This method is the most commonly used when irradiation is done using VMAT or HT. The planning target volume (PTV) corresponds to an ITV with a 3-mm margin in this configuration. The CyberKnife® (CK) is a linear accelerator with a head and a robotic arm, totally dedicated to SBRT. Several tracking systems allow for alternative irradiation treatments with this device: i) Synchrony®: respiratory monitoring with placement through fiducial markers; ii) X-sight Spine®: monitoring of the spine associated with a ITV delineated based on a 4D CT-scanner; and iii) X-sight Lung® with monitoring of the tumor itself(9, 10).

When using the CK tracking method, the GTV is immediately expanded by 3 mm to the PTV. As a result, CK may be able to lower GTV to PTV margins while avoiding ITV-related volume expansion.

Within the same radiation oncology department, only a few institutions have different devices able to perform pulmonary SBRT. The aim of this study is to determine the patients' outcomes in terms of irradiation efficacy and toxicities after lung SBRT according to the different SBRT techniques.

Methods

Between January 2016 and February 2020, we reviewed the clinical, radiological, and dosimetric data of consenting patients with primary lung tumors or pulmonary oligometastases treated by SBRT at CHUV. All patients were selected for SBRT after a multidisciplinary thoracic oncological tumor board discussion, and signed an informed consent form for irradiation. Patients having a lung tumor treated with a method other than SBRT, such as surgery or conventional radiotherapy, were not included.

Clinical data such as the patient's age, sex, WHO performance index, smoking status, comorbidities, previous medical history including previous irradiation or thoracic surgery, cancer histology, pulmonary location of the tumor (affected lobe, central or peripheral), and the reason for radio-oncological treatment rather than the surgical one, were recorded. The reason for choosing SBRT modality was at the discretion of the physician.

The fractionation schedule, GTV, PTV, PTV dose, dose received by the lungs, i.e. the mean lung dose (MLD), the percent of the volume of the lung receiving 5 Gy (V5) and 20 Gy (V20), and composite dosimetry in the event of multiple courses of irradiation were all part of the dosimetric data record.

Radiological data included tumor response after SBRT (stable disease, complete or partial response to treatment), and any recurrence (local, locoregional or distant metastatic) were described.

Clinical and radiological data were extracted from the institutional clinical software Soarian® (Cerner, United States) and Archimède® (CHUV) software; dosimetric data were recorded from RayStation® (RaySearch Laboratories, Sweden) and VelocityTM (Varian Medical Systems, USA) radiotherapy software. Data were then anonymized by assigning to each patient a neutral identifier of 4 digits, and the study was registered on February 24th 2021, ID 2021-00267, with the authorization of the CER-VD ethics committee (Switzerland). Statistical analyses were performed using the JMP® 15 software. We analyzed descriptive data using the Chi-2 test for proportions and the T-test for mean comparisons. Survival data were analyzed by the Kaplan-Meier method, and

comparisons between groups by the Log-rank test. Confidence intervals (CI) were computed from standard errors. If p-value was ≤ 0.15 in univariate analysis, the variable was tested in multivariate analysis through Cox-regression test.

Results

Patients' and treatment characteristics

We identified 111 patients, mostly smoker (64.9%) men (65.8%) in good condition (82.9% PS 0-1) with a median age of 71.4 years. Patients presenting primary pulmonary tumors (n = 57) and lung metastases (n = 54) were found in equal numbers. Patients, who were medically inoperable due to comorbidities, were the most common cause for not selecting for surgery, and instead choosing SBRT (44.2%). We treated 142 pulmonary lesions, the majority being peripheral tumors (73.9%). More than half of the patients had a history of thoracic surgery (52.3%), and about a quarter had a history of thoracic irradiation (23.4%). The prescribed dose ranged from 34-60 Gy over 1-8 fractions with a typical fractionation of 55 Gy in 5 fractions (66.7%), delivered by CK (59.9%), VMAT (38.0%), or HT (2.1%). A large majority of patients benefited from a tumor tracking through fiducials (51.4%), and many of others from an ITV Planification with 4D-CT (33.8%). The median MLD was 3.7 Gy, with a median V5 at 17.2%. In case of iterative irradiation, the median composite MLD and composite V5 reached 7.9 Gy and 37.9% respectively. Other patients and treatment characteristics are presented in Table 1.

Table 1
Descriptive statistics for patient's demographics, treatment and outcome

Patients	n = 111		
Age: median - minimum - maximum [years]	71.4	32.5	91.6
Gender	n = 111		
Male	73 (65.8%)		
Female	38 (34.2%)		
WHO performance status	n = 111		
0	34 (30.6%)		
1	58 (52.3%)		
2	17 (15.3%)		
3	1 (< 1%)		
4	1 (< 1%)		
Smoker	n = 111		
Yes	72 (64.9%)		
No	39 (35.1%)		
History of cancer	n = 111		
Yes	43 (38.7%)		
No	68 (61.3%)		
History of thoracic irradiation	n = 111		
Yes	26 (23.4%)		
- one previous irradiation	23 (88.5%)		
- two previous irradiations	3 (11.5%)		
No	85 (76.6%)		
1 st history:	n = 26		
- Total dose: median - minimum - maximum [Gy]	60	8	70
- Dose/fraction: median - minimum - maximum [Gy]	2	1.8	30
2 nd history:	n = 3		
- Total dose: median - minimum - maximum [Gy]	36	25	60
- Dose/fraction: median - minimum - maximum [Gy]	6	5	12
History of thoracic surgery	n = 111		

Yes:	58 (52.3%)
- wedge resection only	13 (22.4%)
- segmentectomy	5 (8.6%)
- lobectomy	28 (48.3%)
- bilobectomy	6 (10.3%)
- pneumonectomy	4 (6.9%)
- others	2 (3.5%)
No	53 (47.7%)
Reason for non-operability:	n = 111
- surgery refused by patient	5 (4.5%)
- surgically non operable	24 (21.6%)
- medically non operable	49 (44.2%)
- systemicdisease	33 (29.7%)
Primary or metastasis	n = 111
Primary tumor	57 (51.4%)
Metastasis:	54 (48.6%)
- lung	22 (40.7%)
- digestive	14 (25.9%)
- ENT	7 (13.0%)
- melanoma	5 (9.3%)
- pleura	1 (1.8%)
- others	5 (9.3%)
Tumor localization:	n = 142
Left lung:	64 (45.1%)
- upper left lobe	32 (50.0%)
- lower left lobe	32 (50.0%)
Right lung:	74 (52.1%)
- upper lobe	35 (47.3%)
- middle lobe	6 (8.1%)
- lower lobe	29 (39.2%)
- two lobes	4 (5.4%)

Bilateral	4 (2.8%)
Central	32 (22.6%)
Peripheral	105 (73.9%)
Central + peripheral	5 (3.5%)
Histology:	
Histological proof:	n = 111
- Yes	77 (69.4%)
- No	34 (30.6%)
Histological type:	n = 111
- NSCLC	3 (2.7%)
- adenocarcinoma	43 (38.7%)
- squamouscell	30 (27.1%)
- adenoidcystic carcinoma	3 (2.7%)
- sarcoma	2 (1.8%)
- melanoma	5 (4.5%)
- hepatocellularcarcinoma	1 (0.9%)
- others	24 (21.6%)
TNM at diagnosis	n = 111
T:	
- TX	9 (8.1%)
- Tis	1 (<1%)
- T1	51 (45.9%)
- T2	28 (25.2%)
- T3	11 (9.9%)
- T4	11 (9.9%)
N:	n = 111
- NX	8 (7.2%)
- N0	75 (67.6%)
- N1	13 (11.7%)
- N2	11 (9.9%)

- N3	4 (3.6%)		
M:	n = 111		
- MX	8 (7.2%)		
- M0	75 (67.6%)		
- M1	28 (25.2%)		
Number of metastatic sites:	n = 111		
- 1	31 (27.9%)		
- 2	21 (18.9%)		
- ≥ 3	2 (1.8%)		
Treatments	n = 142		
PTV volume:	n = 133		
median - minimum - maximum [cc]	8.1	1.3	190.4
Radiotherapy technique:	n = 142		
- CyberKnife®	85 (59.9%)		
- VMAT	54 (38.0%)		
- Tomotherapy®	3 (2.1%)		
SBRT modality:	n = 142		
- ABC	5 (3.5%)		
- fiducials	73 (51.4%)		
- ITV	48 (33.8%)		
- Mid-ventilation	2 (1.4%)		
- X-sight lung®	3 (2.1%)		
- X-sightspine®	11 (7.8%)		
Dosimetry:	n = 142		
Total dose: median - minimum - maximum [Gy]	55	34	60
Duration: median - minimum - maximum [days]	11	1	25
Number of fractions: median – minimum – maximum	5	1	8
Current treatment:	n = 130		
- Mean lung dose (MLD): median - minimum - maximum [Gy]	3.7	0.2	22.3
- Volume of lung receiving 5Gy (V5%): median - minimum - maximum [%]	17.2	2.1	93.6

Cumulative dosimetry:	n = 38
- MLD composite: median - minimum - maximum [Gy]	7.9 0.9 22.3
- V5% composite: median - minimum - maximum [%]	37.9 4.29 93.6
Outcome	
Toxicity:	n = 111
Yes	76 (68.5%)
No	35 (31.5%)
Acute toxicity:	n = 111
Yes	63 (56.8%)
- grade 1	50 (79.3%)
- grade 2	11 (17.5%)
- grade 3	2 (3.2%)
No	48 (43.2%)
Late toxicity:	n = 111
Yes	29 (26.1%)
- grade 1	13 (44.8%)
- grade 2	13 (44.8%)
- grade 3	3 (10.4%)
No	82 (73.9%)
Best local response:	n = 142
- not known	4 (2.8%)
- tumor progression	1 (0.7%)
- complete response	13 (9.2%)
- partial response	48 (33.8%)
- stable disease	76 (53.5%)
Recurrence:	n = 111
Yes	42 (37.8%)
- local recurrence	3 (7.1%)
- regional recurrence	5 (11.9%)

- distant metastasis	34 (81.0%)
No	69 (62.2%)
Second primary	10 (9.0%)
Survival:	n = 111
Alive	78 (70.3%)
- without disease	46 (59.0%)
- with disease	32 (41.0%)
Dead	33 (29.7%)
- without disease	12 (36.4%)
- with disease	21 (63.6%)

MLD : Mean Lung Dose ; V5% : percentage of lung receiving 5Gy

Local control

Local response could be achieved in 138 out of 142 lesions, while local control (LC) was 96.8% (92.3-100%, CI 95%) at 2 years and 94.8% (90.3-100%, CI 95%) at 3 years. LC at 2 and 3 years significantly decreased with age, from 100–93.4% and 88.9%, respectively when patients were older than 71 years. ($p = 0.035$), as shown in Table 2. LC was not influenced by the other treatment characteristics: the choice of radiotherapy device, neither by the SBRT modality, nor by the dose/fractionation scheme. We observed 2 mediastinal relapse, corresponding to a loco-regional control rate of 96.2% at 1 year and 94.4% at 2 years, respectively.

Table 2
Predictive factors for local control

Variable	2-y local control (%)	95% CI	3-y local control (%)	95% CI	p-value
All (n = 138)	96.8	92.3-100	94.8	90.3-100	
Age [years]:	100	85.2-100	100	77.6-100	0.035*
≤ 71 (n = 66)	93.4		88.9		
> 71 (n = 72)					
Gender:	97.8	93.3-100	90.8	70.1-100	0.466
Women (n = 45)	96.1		96.1		
Men (n = 93)		90.5-100		90.5-100	
Radiotherapy technique:	96.2	90.8-100	93.3	85.6-100	0.893
		94.4-100		94.4-100	
CyberKnife (n = 82)	98.1	44.9-100	98.1	44.9-100	0.216
VMAT (n = 53)	100	88.6-100	100	82.5-100	
Tomotherapy (n = 3)	80		80		
SBRT modality:	95.3		91.8		
ABC (n = 4)	100		100		
Fiducials (n = 70)	100		100		
ITV (n = 48)	100		100		
Mid-ventilation (n = 2)	100		100		
X-sight lung (n = 3)					
X-sight spine (n = 11)					
Dose [Gy]:	100	90.8-100	100	44.9-100	0.990
≤ 50 (n = 10)	100		80		
54 (n = 15)	96.2	86.8-100	96.2	90.8-100	
55 (n = 92)	95.5		95.5	86.8-100	
60 (n = 21)					

Missing values (n = 4)

Variable	2-y local control (%)	95% CI	3-y local control (%)	95% CI	p-value
Treatment duration [days]:	100	88.8-100	95.7	87.4-100	0.553
≤ 11 (n = 48)	94.9		94.9		
> 11 (n = 90)				88.8-100	
History of cancer:	97.4	93.9-100	93.8	85.7-100	0.519
No (n = 80)	96.2		96.2		
Yes (n = 58)		88.8-100		88.8-100	
History of thoracic irradiation:	96.4	91.3-100	93.4	85.9-100	0.758
No (n = 90)	97.9		97.9		
Yes (n = 48)		93.9-100		93.9-100	
History of thoracic surgery:	96.8	92.4-100	96.8	92.4-100	0.944
No (n = 69)	96.9		93.2		
Yes (n = 69)		90.9-100		84.0-100	
Reason of non-operability:	100	81.4-100	100	48.8-100	0.333
Surgery refused by patient (n = 5)	100		77.1		
	98.6	95.9-100	98.6	95.9-100	
Surgically non operable (n = 27)					
Medically non operable (n = 70)	96.8	90.6-100	96.8	90.6-100	
Systemic disease (n = 36)					
Primary tumor (n = 74)	95.9	89.9-100	92.3	83.4-100	0.416
Metastasis (n = 64)	98.2	94.7-100	98.2	94.7-100	

Missing values (n = 4)

Variable	2-y local control (%)	95% CI	3-y local control (%)	95% CI	<i>p</i> -value
Tumor localization:	100	87.3-100	95.5	86.8-100	0.670
Laterality:	94.2	90.1-100	94.2	87.3-100	0.443
- Left lung (n = 61)	100	100	100	100	
- Right lung (n = 73)	100		100	85.0-100	
- Bilateral (n = 4)	95.5		92.6		
Central or peripheral:	100		100		
- Central (n = 32)					
- Peripheral (n = 101)					
- Central + peripheral (n = 5)					

Missing values (n = 4)

Variable	2-y local control (%)	95% CI	3-y local control (%)	95% CI	p-value
Histology:	96.2	88.8-100	96.2	88.8-100	0.519
Histological proof:	97.5		93.7		0.837
- no (n = 55)	83.3	94.0-100	83.3	85.8-100	
- yes (n = 83)	100	53.5-100	95.0	53.5-100	
Histological type:	96.6		96.6		
- NSCLC (n = 5)	100	90.0-100	100	85.5-100	
- adenocarcinoma (n = 46)	100	79.4-100	100	90.0-100	
				79.4-100	
- squamous cell (n = 35)	100		100		
- adenoid cystic carcinoma (n = 4)	100		100		
	100		100		
- melanoma (n = 5)	100		100		
- sarcoma (n = 2)	100		100		
	92.9		92.9		
- hepatocellular carcinoma (n = 1)					
- mesothelioma (n = 1)					
- nerves (n = 1)					
- not known (n = 38)					
Number of metastatic sites:	100	91.2-100	100	91.2-100	0.948
0 (n = 1)	97.0		97.0		
1 (n = 38)	100		100		
≥ 2 (n = 26)					
PTV volume [cc]:	98.0	94.0-100	93.7	84.7-100	0.904
≤ 8.1 (n = 65)	95.6		95.6		
> 8.1 (n = 64)		89.3-100		89.3-100	
Missing values (n = 4)					

Survival

Median follow up was 28.7 months (22.7-35.6 months, CI 95%). Overall survival (OS) rates at 2 and 3 years were respectively 58.5% (CI 95%, 48.4-68.6%) and 35.7% (CI 95%, 25.2-45.9%), with no difference regarding both SBRT modalities. Metastasis-free survival (MFS) and progression-free survival (PFS) significantly decreased in case of

first recurrence at brain (13.5 vs 5.5 months, $p = 0.007$ and 0.010 , respectively). MFS and PFS were significantly longer when treated lesions were primary lung tumors compared to metastases, while median MFS was not reached and PFS nearly doubled in case of primary lung cancer. However this last factor was not confirmed after multivariate analysis. Median survival, significantly decreased in case of first metastatic relapse occurred before 13.1 months. Median OS was 37.8 months when first metastatic relapse occurred before 13.1 months compared to a median OS of 64.5 months when first metastatic relapse occurred after 13.1 months ($p = 0.035$), and remained predictive after Cox-regression ($p < 0.0001$). Other predictive factors for survival (OS, MFS, and PFS) are depicted in Table 3.

Table 3
Predictive factors for survival (OS, MFS, and PFS)

Variable	Median overall survival (OS) [months]	p-value (log-rank/Cox regression)	Median metastasis-free survival (MFS) [months]	p-value(log-rank/Cox regression)	Median progression-free survival (PFS) [months]	p-value(log-rank/Cox regression)
Age [years]:	64.5	0.945	25.9	0.037*/NS	24.8	0.075/ 0.02
≤ 71 (n = 54)	40.1		NR		NR	
> 71 (n = 57)						
Radiotherapy technique:	NR	0.338	27.9	0.334	25.9	0.179
CyberKnife (n = 71)	64.5		48.0		48.0	
Other (n = 40)						
Smoker:	41.1	0.459	25.9	0.976	25.9	0.941
No (n = 39)	64.5		48.0		28.8	
Yes (n = 72)						
History of thoracic irradiation:	64.5	0.192/ NS	45.0	0.826	68.9	0.76
	29.6		28.4		48.7	
No (n = 84)						
Yes (n = 27)						
Reason of non-operability:	NR	0.820	NR	0.114/ NS	NR	0.15/ NS
	40.1		45.0		28.8	
Surgery refused (n = 5)	NR		48.0		48	
Surgically inop (n = 24)	41.1		19.3		17.7	
Medically inop (n = 49)						
Systemicdisease (n = 33)						

NR = not reached

NS : not significant

inop :inoperable

Variable	Median overall survival (OS) [months]	p-value (log-rank/Cox regression)	Median metastasis-free survival (MFS) [months]	p-value(log-rank/Cox regression)	Median progression-free survival (PFS) [months]	p-value(log-rank/Cox regression)
Mean lung dose (MLD)(Gy)	NR	0.15/ NS	28.4	0.78	45.0	0.85
≤3.7 (n=52)	41.1		48		20.0	
>3.7 (n=52)						
Number of metastatic sites:	31.3	0.753	24.8	0.097/ NS	26.2	0.12/ NS
< 2 (n = 32)	41.1		13.5		15.4	
≥ 2 (n = 23)						
Time before new metastasis [months]:	37.8	0.035*/<0.0001	5.0	<0.001*/<0.0001	4.9	<0.001*/<0.0001
≤ 13.1 (n = 19)	64.5		19.7		19.1	
> 13.1 (n = 20)						
Metastatic recurrence:	16.4	0.143/ NS	5.5	0.007*/ NS	5.5	0.010*/ 0.04
Brain (n = 6)	64.5		13.5		13.5	
Other (n = 33)						
Primary tumor (n = 57)	64.5	0.131/ NS	NR	0.0034*/NS	48.0	0.006*/ NS
Metastasis (n = 54)	41.1		24.8		20.4	

NR = not reached

NS : not significant

inop :inoperable

Variable	Median overall survival (OS) [months]	p-value (log-rank/Cox regression)	Median metastasis-free survival (MFS) [months]	p-value(log-rank/Cox regression)	Median progression-free survival (PFS) [months]	p-value(log-rank/Cox regression)
V5% [cc]:	64.5	0.779	45.0	0.91	27.0	0.589
≤ 17.2 (n = 52)	41.1	27.8	27.9	0.291	27.9	0.64
> 17.2 (n=52)	NR	0.28	24.8		25.7	
Composite V5% [cc]:	29.57		28.4		NR	
≤ 37 (n = 9)						
> 37 (n = 10)						
PTV volume [cc]:	NR	0.722	27.9	0.222	27.0	0.300
≤ 8.1 (n = 52)	41.1		48.0		48.0	
> 8.1 (n = 52)						
NR = not reached						
NS : not significant						
inop :inoperable						

Variable	Relative Risk	SD	p-value
OS			
Time to first metastasis < 13.1 months	9.0	0.02	<0.0001
PFS			
Age >71 years	1.2	0.37	0.02
Time to first metastasis < 13.1 months	2.6	0.06	<0.0001
Metastatic recurrence at brain	1.2	0.6	0.04

Toxicity

Patients presented at least one toxicity in 68.5% of the cases, mainly grade 1 acute toxicity (n = 50). About three quarter of patients did not develop any late toxicity (73.9%), 3 patients presented a late grade 3 toxicity (Table 1). Toxicity incidence significantly increased beyond the median V5 value of 17.2% (56.0 vs 77.4%, p = 0.021). Toxicity is described in Table 4.

Table 4
Predictive factors for toxicity

Variable	Toxicity (%)		p-value	Acute toxicity (%)		p-value	Late toxicity (%)		p-value
	Yes	No		Yes	No		Yes	No	
CK (n = 71)	70.4	29.6	0.557	54.9	45.1	0.793	28.2	71.8	0.511
Others (n = 40)	65.0	35.0		57.5	42.5		22.5	77.5	
PTV volume [cc]:	65.4	34.6	0.486	50.0	50.0	0.205	21.2	78.8	0.288
≤ 8.1 (n = 52)	71.7	28.3		62.3	37.7		30.2	69.8	
> 8.1 (n = 52)									
V5% [cc]:	56.0	44.0	0.021*	46.0	54.0	0.063	22.0	78.0	0.601
≤ 17.2 (n = 52)	77.4	22.6		64.2	35.8		26.4	73.6	
> 17.2 (n = 52)									
V20% [cc]:	60.4	39.6	0.140	50.9	49.1	0.355	18.9	81.1	0.187
< 2.4 (n = 52)	74.0	26.0		60.0	40.0		30.0	70.0	
> 2.4 (n = 52)									
Meanlung dose (MLD) [Gy]:	61.5	38.5	0.209	50.0	50.0	0.236	25.0	75.0	1.000
< 3.7 (n = 52)	73.1	26.9		61.5	38.5		25.0	75.0	
> 3.7 (n = 52)									
Cumulative MLD [Gy]:	61.1	38.9	0.141	53.7	46.3	0.597	22.2	77.8	0.535
< 7.9 (n = 12)	74.5	25.5		58.8	41.2		27.5	72.5	
> 7.9 (n = 8)									

Table 5. CyberKnife (CK) versus other techniques: outcome, dosimetry, and toxicity

Local control						
Variable		2-year local control (%)	95% CI	3-year local control (%)	95% CI	p-value
CyberKnife (n = 82)		96.2	90.8-100	93.3	85.6-100	0.68
Other (n = 56)		98.2	94.4-100	98.2	94.4-100	
Survival						
Variable	Median overall survival [months]	p-value	Median metastasis-free survival (MFS) [months]	p-value	Median progression-free survival (PFS) [months]	p-value
CK (n = 71)	NR	0.338	27.9	0.334	25.9	0.18
Others(n = 40)	64.5		48.0		48.0	
Dosimetry characteristics for CyberKnife (CK) versus VMAT treatments						
Variable			Mean for CK	Mean for VMAT		p-value
GTV volume [cc]:			(n = 81)	(n = 52)		0.84
			2.1	1.4		
PTV volume [cc]:			(n = 81)	(n = 52)		0.013*
			12.3	21.9		
Ratio GTV/reduced PTV in CK			(n = 81)	(n = 52)		0.0013*
			2.9	4.8		
Meanlung dose (MLD) [Gy]:			(n = 79)	(n = 51)		<0.0001*
			2.6	4.1		
Volume of lung receiving 5Gy (V5%) [cc]:			(n = 79)	(n = 51)		0.002*
			13.5	19.9		
Volume of lung receiving 20Gy (V20%) [cc]:			(n = 79)	(n = 51)		<0.0001*
			2.3	5.4		
Composite MLD [Gy]:			(n = 19)	(n = 19)		0.849
			7.8	7.5		
Composite V5% [cc]:			(n = 19)	(n = 19)		0.513
			40.4	35.9		
Toxicity						

Local control			
Variable	Proportion for CK (%) n = 71	Proportion for VMAT (%) n = 40	p-value
Toxicity:	29.6	35.0	0.56
No	70.4	65.0	
Yes			
Acute toxicity:	45.1	42.5	0.79
No			0.98
Yes	54.9	57.5	
Grade 0	43.7	42.5	
Grade 1	45.1	45.0	
Grade 2	9.9	10.0	
Grade 3	1.3	2.5	
Late toxicity:	71.8	77.5	0.51
No	28.2	22.5	0.26
Yes	71.8	77.5	
Grade 0	15.5	5.0	
Grade 1	11.3	12.5	
Grade 2	1.4	5.0	
Grade 3			

CK versus other treatment modalities

Local control rate were comparable between CK and other treatment modalities, with a local control rate of 96.2% vs 98.2%, at 2 years and 93.3% vs 98.2% at 3 years, $p=0.68$ (Figure1). OS, MFS, and PFS were not influenced by the choice of the machine neither.

Dosimetric analysis revealed significant differences depending of the choice of the machine. GTV were comparable between CK and other modalities (2.1 vs 1.4 cc, $p = 0.84$). Nevertheless, treatments with CK resulted in significantly smaller PTV (12.3 vs 21.9 cc, $p = 0.013$), and were associated with significant dosimetric benefit with lower MLD (2.6 vs 4.1 Gy, $p < 0.001$), lower V5 (13.5 vs 19.9%, $p = 0.002$) and lower V20 (means at 2.3 vs 5.4%, $p < 0.001$). This dosimetric benefit was not associated with a clear clinical benefit after SBRT. There was no significant difference in terms of incidence of toxicity ($p = 0.56$), in acute toxicity ($p = 0.79$), in late toxicity ($p = 0.51$), or in terms of maximal grade of toxicity acute and late toxicity ($p = 0.98$ and $p = 0.26$).

Discussion

This retrospective study describes factors associated with outcome, toxicity, and dosimetric parameters after lung SBRT, depending on the chosen delivery device. Our results revealed excellent local control rates of 96.8% and 94.8% at 2 and 3 years after SBRT, and a low rate of moderate-severe toxicity, values that are comparable with the literature(11–13). We have not obtained a significant difference in terms of local control rate after SBRT depending on the technique choice.

Claude *et al*, prospectively analyzed the efficiency and toxicity of SBRT with CK compared to linear accelerator SBRT treatments for peripheral early stage NSCLC. A total of 68 patients were treated using a linac and 38 by means of CK. Authors have not described a significant difference in terms of local control depending on the employed device; 2-year local control rate was 97.0% (95% CI: 90.6-99.4%) with linear accelerator vs 100% with CK, respectively ($p = 0.2839$). Neither, acute and late toxicity differed between the 2 modalities. However, we can notice that this study did not report the dosimetrical parameters specific to the device choice. The study of Claude *et al*, represents the only prospective trial other that confronted the two modalities; however, we can underline that the treatments were not performed in the same institution (multicentric study), and could induce bias for this direct comparison(13). Even retrospective, our study represents the first one directly comparing the outcomes of patients receiving lung SBRT using three different modalities in the same radiotherapy department.

In our study, all patients that presented a local relapse were older than 71 years old. We identified that oldest patients presented a significantly lower local control compared to younger ones. A retrospective study of 219 patients also reported that age significantly influenced the local outcome after SBRT(14). On the other hand, Watanabe, *et al*/depicted a preserved local control in a cohort of 64 patients older than 80 years old, which was 98.4% at 3 years(15).

In our cohort about 40% of patients were treated without histological proof of malignancy and indication for irradiation was based on clinical and radiological criterias and this subset of patients presented similar outcomes compared to those with a histological proof of malignancy. In this context, several publications already showed comparable outcomes in patients after empiric SBRT, supporting the hypothesis that patients did have lung cancers(16–18).

Loco-regional control was good and comparable to other studies of lung SBRT and also in compare to surgical outcomes after video-assisted thoracoscopic surgical lobectomy with mediastinal lymph node dissection(19).

OS was significantly decreased in case of early metastatic recurrence (< 13.1 months), and PFS was significantly shorter when the first identified relapse site was the brain corresponding to the usual clinical factors and influencing the outcome in metastatic patients(20, 21).

More than half of our patients presented at least one toxicity (68.5%), and the most common form was Grade 1 acute toxicity (79.3%). About three quarter (73.9%) of patients have not developed any late toxicity. Incidence of toxicity was comparable with the literature(22–25). In our cohort, several dosimetric parameters were analyzed in order to identify predictive factors for toxicity such as PTV, V5, V20, MLD, and composite MLD. Compared to other techniques, and even though comparable GTV, CK treatments significantly permitted to decrease PTV, MLD, V5, and V20; which are dosimetric parameters usually found to be related with toxicity(26, 27). In our cohort, an increased V5 value correlated with a higher incidence of toxicity. Reducing the V5 value could be particularly interesting in case of multiple courses of SBRT lung irradiations(27). Hence, even if we not found a significant difference regarding toxicity in relation to the delivery device employed, it can be appropriate to favor CK

irradiation in order to improve dosimetric parameters. Indeed, our study showed that cumulative MLD and cumulative V5 values are approximately doubled in case of multiple courses of lung irradiations, and techniques able to spare healthy lung reducing these dosimetric parameters could be preferred from the first lung SBRT. Moreover, CK could be particularly of interest in the event of local relapse re-irradiation, situation known to be at risk of high rates of severe toxicity(28, 29).

Conclusion

Compared to other SBRT techniques, CK treatments are able to treat comparable GTV with reduced PTV, MLD, V5, and V20. The dosimetric benefit of CK irradiation was not associated with a clinical benefit, with comparable outcome in terms of control rates and toxicity. Toxicity incidence was less frequent when reducing V5. Altogether, it seems appropriate to favor the use of CK, particularly in the event of multiple courses of irradiations or in case of re-irradiation.

Abbreviations

SBRT

stereotactic body radiotherapy

NSCLC

non-small-cell lung cancer

CHUV

University Hospital Center of Lausanne (*Centre Hospitalier Universitaire Vaudois*)

VMAT

volumetric modulated arc therapy

Linac

linear accelerator

CT

computed tomography

ABC

Active Breath Control®

CK

CyberKnife®

GTV

Gross tumor volume

ITV

Internal target volume

CTV

Clinical target volume

PTV

Planning target volume

WHO

World Health Organization

MLD

mean lung dose

V5
Percent volume of lung receiving 5Gy
V20
Percent volume of lung receiving 20Gy
OS
overall survival
CI
confidence interval
MFS
metastasis-free survival
PFS
progression-free survival
LC
local control

Declarations

Ethics approval and consent to participate

This project met the regulatory requirements of the Swiss Federal Law on Research on Human Beings (LRH) and the Swiss Ordinance on Research on Human Being (ORH). The study protocol obtained the prior approval of the Swiss cantonal commission for the ethics of research on human beings (CER-VD).

Registered on February 24th 2021, ID 2021-00267, with the authorization of the CER-VD ethics committee (Switzerland).

Consent for publication

Not applicable for that section.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ELR, EMO, and RK collected and analyzed the patient data, and were major contributors in writing the manuscript. AC, AD, HB, ERO, AL, CVG and TK contributed in writing the manuscript. All authors read and approved the final manuscript.

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No.

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Figures

Number at risk (cumulative number of events)	0 months	12 months	24 months	36 months	48 months
Cyberknife	82 (0)	60 (1)	40 (2)	20 (3)	4 (3)
Others	56 (0)	29 (1)	21 (1)	12 (1)	8 (1)

Figure 1

Local control rate depending on the machine choice