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Lung optimized treatment with CyberKnife® in inoperable lung cancer patients: feasibility analysis of a mono-institutional 115 patient series

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CyberKnife® Lung Optimized Treatment (LOT) allows the treatment of lung cancer without invasive fiducial implantation. The aim of this retrospective analysis was to evaluate the feasibility, toxicity and clinical outcome. One hundred fifteen patients (124 lesions) were treated with CyberKnife® using LOT. The median age was 72.6 years (range 31.8–90.3). From 124 treated lesions, 52 were with histopathological confirmation (41 primitive pulmonary cancers, 8 pulmonary metastases) and 72 as untyped tumors. For 5 patients (6 lesions) treatment was an in-field re-irradiation. Concomitant therapy was administered in 7 patients. Zero-View tracking was applied in 69 patients, 1-View in 33 patients, 2-View in 22 patients. The median total dose was 45 Gy (range 18–54), median dose/fraction was 15 Gy (range 4–18) with a median prescription isodose of 80% (range 68–85). The median planning target volume (PTV) was 25 cm^3 (range 3–195). The median follow-up was 20 months (range 7–47). Thirty-seven patients (32%) were alive with no evidence of disease, 39 patients (34%) were alive with clinically evident disease, and 38 patients (33%) died of the disease. The 1- and 2-year overall survival (OS) rate was 83% and 61%. The median time to progression was 19 months (95% confidence interval: 11–19 months), 1- and 2-year progression-free survival (PFS) rates were 62% and 41%, respectively. Smaller PTV was significantly associated with better OS, PFS and in-field PFS in univariate and multivariate analyses. Acute toxicity was observed in 36 patients (41%). Late toxicity was registered in 25 patients (29%). G3 late toxicity was observed in one patient (1.1%). Our data suggest that fiducial less-stereotactic body radiation therapy (SBRT) is a feasible, well-tolerated and potentially effective treatment with high compliance in the setting of inoperable patients due to concomitant disease or previous treatments.

Key words: lung cancer, stereotactic radiotherapy, CyberKnife Lung Optimized Treatment, fiducial-less SBRT

Stereotactic body radiation therapy (SBRT) represents the gold standard in the treatment of inoperable small lung nodules, both primary tumors, and metastases. Recently, it has been accepted as a valid treatment option for operable lung patients as well [1], since it provides a less invasive, less morbid and more convenient treatment [2–5] compared to thoracic surgery.

However, one of the main concerns of this technique is tumor motion, mainly caused by respiratory motion. This can occur in all anatomic directions and affects both intrafractional and interfractional accurate radiation delivery [6–7].

Recent developments in this field focused on the understanding of organ motion and reducing setup error, designing the tightest possible safety margin without compromising the tumor coverage and minimizing lung damage, especially in patients with impaired lung function [8–10].

The Synchrony Respiratory Tracking System (SRTS) implemented in CyberKnife® (Accuray, Incorporated, Sunnyvale, CA) correlates the internal motion of the target, assessed by the X-ray image-guidance system, with the motion of the chest wall, measured using infrared light-emitting diodes as external surface markers [11].

In addition, the Lung Optimized Treatment (LOT) feature for the CyberKnife® provides a range of tracking modalities to offer a fiducial-free treatment option according to tumor visibility in the X-ray images acquired during treatment, thus tracking the lung nodules during breathing without invasive fiducials implantation [12–13]. In the 2-view modality, the tumor is detectable in both orthogonal X-ray images and three-dimensional (3D) motion tracking is performed as Xsight Lung Tracking™. In the 1-view modality, the tumor is visible in only one of the X-ray projections (A or B) and the dynamic tumor tracking compensates the target motion only in the detectable plane. Non-trackable motion is compensated with the definition of the internal target volume (ITV). In the 0-view modality, the tumor cannot be detected in any X-ray images and consequently, the treatment relies entirely on an ITV-based approach, using the Xsight Spine Tracking™ module.

The aim of this study is the evaluation of the feasibility of the treatment, toxicity profile and oncological outcome in patients who underwent SBRT using the LOT system.

Patients and methods

Patient series. This retrospective study was part of the research on SBRT notified to the Ethics Committee of IRCCS European Institute of Oncology and Centro Cardiologico Monzino – via Ripamonti, 435, 20141 Milan, Italy (notification Nr. 93/11). All patients signed written informed consent for stereotactic body radiation therapy (SBRT) and written informed consent for the use of the anonymized data for research or educational purpose.

The patient inclusion criteria for this study were: age >18 years; Karnofsky performance score (KPS) ≥70; primary lung tumors (with or without histopathological confirmation) or pulmonary metastases; one or two target lesions treated at the same time; first in-field radiotherapy (RT) or re-irradiation; large visible tumors; severe cardiovascular or pulmonary comorbidities; previous major lung surgery or thoracic RT; written informed consensus for the CyberKnife® treatment and for the use of the anonymized data for research and educational purpose.

Any concomitant systemic therapy (chemotherapy, biological therapy, and hormone therapy) was allowed. The indication to perform SBRT was discussed in a multidisciplinary tumor board for thoracic malignancies. The diagnosis was based on imaging and functional studies: computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET/CT). When possible, spirometry was performed for pulmonary baseline functional evaluation.

Lung lesions without histopathological confirmation in patients with previous primary tumors with disease-free interval longer than 24 months from the first event were classified as primitive.

Radiation therapy. A planning four-dimensional (4D) CT was acquired by GE Optima CT580 W scanner (GE Healthcare, Chicago, IL, USA) in a free-breathing modality, with the patient lying supine in a customized external vacuum-type cast with arms along their sides. The same set-up was used during the treatment sessions. The respiratory signal acquired by the Real-time Position Management system (RPM, Varian, Palo Alto, USA) was used for the phase binning of the images.

The gross tumor volume (GTV) was delineated both on the full-inhale and full-exhale phases. The planning target volume (PTV) definition depended on the tracking modality [11]. For 2-view modality, a 3-mm isotropic margin was added to the full-exhale GTV, chosen as the most representative phase of free-breathing. In 1-view modality, the ITV was obtained as the envelope of full-inhale and full-exhale GTVs, and an anisotropic margin was applied with 3-mm expansion in the trackable direction and 5-mm expansion in the non-trackable direction. In the 0-view modality, a 5-mm isotropic margin was added to the ITV.

Follow-up procedure and response evaluation. Toxicity was evaluated with the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) criteria and the Common Terminology Criteria for Adverse Events (CTCAE) version 4.1 [14]. Any toxicity event occurring within 6 months from the end of RT was defined as acute toxicity, whereas events occurring after 6 months from the end of RT were classified as late toxicity.

Radiologic tumor response after SBRT was evaluated by the same imaging modality used for treatment planning (CT or PET-CT) and classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or PET/CT Response Criteria in Solid Tumors (PERCIST) guideline [15–16]. Progression-free survival (PFS) was defined as the time interval between the last day of SBRT and the first disease progression. The in-field PFS was defined as the time interval between the last day of SBRT and the detection of in-field progression. The out-field PFS was defined as the time interval between the last day of SBRT and the detection of out-field progression. Overall survival (OS) was defined as the time interval between the last day of SBRT and the death for tumor or other causes.

Statistical analysis. Patient characteristics were reported as frequency and percentage for categorical variables and median and range for continuous variables. The length of follow-up was calculated from the last day of SBRT to the last follow-up visit.

Univariate and multivariate analyses were performed to quantify the impact of patient, tumor, and treatment-related factors on clinical outcomes (PFS, in-field PFS, out-field PFS, acute/late toxicity, OS). The associations between treatment-related variables, patient, and tumor characteristics, concomitant diseases, and toxicity were investigated by the Chi-squared test or Fisher's exact test for categorical variables. Log-rank tests and multivariate Cox regression models were used to assess the associations of patient and tumor charac-

teristics, recognized prognostic factors, previous treatment modalities, and RT parameters with tumor outcome and toxicity. Survival curves were estimated using the Kaplan-Meier method. The significance threshold for p-values was set at 0.05. Statistical analyses were performed with SAS statistical software (version 9.2; SAS Institute, Cary, NC).

Results

Study population and tumor characteristics. One hundred fifteen patients (124 lesions) treated at the European Institute of Oncology (Milan, Italy) between January 2014 and October 2016 were included in this study. Patient and tumor characteristics are described in Table 1.

Dose prescribed to the target lesion. Total dose and number of fractions were determined on the basis of the tumor (location and size) or patient characteristics (previous surgery or RT and comorbidities).

Treatments were planned with the MultiPlan v.5.2.1 (Accuray Inc., Sunnyvale, CA, USA) treatment planning system (TPS) using the Ray Tracing algorithm and delivered with CyberKnife® System v.11.1.x. It is well known [17] that the use of the Ray Tracing algorithm implies lesion underdosing – real doses are 10–15% less than those planned. For this reason, this effect has been taken into account in the remainder of the study. The dosimetric and tracking characteristics are reported in Table 2, while the treatment schemes and their frequencies are presented in Table 3.

Oncological outcome. The median follow-up period was 20 months (range, 7–47 months). At the time of analysis, 37 patients (32%) were alive with no evidence of disease, 39 patients (34%) were alive with clinically evident disease, and 38 patients (33%) died of a disease. One patient was lost to follow-up.

The 1- and 2-year OS rate was 83% and 61% (Figure 1A). The first radiological evaluation was available for 112 out of 124 lesions (90.3%). PET-CT or CT scan with or without spirometry was performed in all patients. The treatment response was not assessed for 12 lesions because the patients died before the time of restaging. At the first follow-up, a complete radiologic response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were observed in 31 (27.7%), 37 (33.0%), 39 (34.8%) and 5 (4.5%) of the evaluable lesions, respectively. At last follow-up CR, PR, SD, and PD were observed in 68 (60.7%), 13 (11.6%), 13 (11.6%), and 18 (16.1%), respectively and in-field control was observed in 94 (83.9%) of 112 evaluable lesions. The median time to any progression was 19 months (95% confidence interval: 11–19 months) and the actuarial 1- and 2-year PFS rates were 62% and 41%, respectively (Figure 1B).

The actuarial 1- and 2-year in-field PFS rates were 91% and 76%, respectively (Figure 1C). The median time to out-field progression was 20 months and 1- and 2-year out-field PFS was 67% and 45%, respectively (Figure 1D). The pattern of failure was mainly out-field, and patients whose primary progression was out-field had achieved the disease local control.

Smaller PTV was found significantly associated with OS, PFS and in-field PFS in univariate and multivariate analyses, while lesion size was found to be significantly correlated with in-field PFS only in the univariate test (Log Rank, p=0.05).

Toxicity. Acute toxicity was observed in 36 patients (41%) and included G1 and G2 respiratory symptoms (dyspnea, cough, laryngeal inflammation, pneumonia) with G3 toxicity

Table 1. Patient and tumor characteristics (115 patients, 124 lesions).

Characteristics	
Age (years); median (range)	72.6; (31.8–90.3)
Gender; n (%)	
Male	79; (68.7%)
Female	36; (31.3%)
Karnofsky Performance Status; n (%)	
70	4; (3.5)
80	12; (10.4)
90	51; (44.4)
100	48; (41.7)
Severe comorbidities; n (%)	
Cardiovascular	51; (44.3)
Respiratory	21; (18.3)
Cardiovascular and Respiratory	15; (13.0)
O2 therapy	9; (7.8)
FEV1 [%]; median (range)	64; (24–122)
Previous treatment; n (%)	
Major thoracic surgery (pneumonectomy, lobectomy)	50; (43.5)
Mediastinal/thoracic RT	22; (19.1)
Previous RT in site of treated lesion; n (%)	
Yes	5; (4.3)
No	110; (95.7)
Concomitant systemic therapy; n (%)	7; (6.1)
Tumor size (mm); median (range)	22; (6–58)
No. of treated lesion; n (%)	
1	106; (92.2)
2	9; (7.8)
Histopathological confirmation; n (%)	
Yes	52; (41.9)
Primary lung tumors	41; (33.1)
Second primary lung tumors	3; (2.4)
Metastases	8; (6.4)
No	72; (58.1)
Primary lung tumors	17; (13.7)
Second primary lung tumors	15; (12.1)
Metastases	40; (32.3)
Tumor type	
Primary lung tumor	58; (46.8)
Second primary lung tumor	18; (14.5)
Metastases	48; (38.7)

FEV1 - Forced expiratory volume in the 1st second; RT - Radiotherapy.

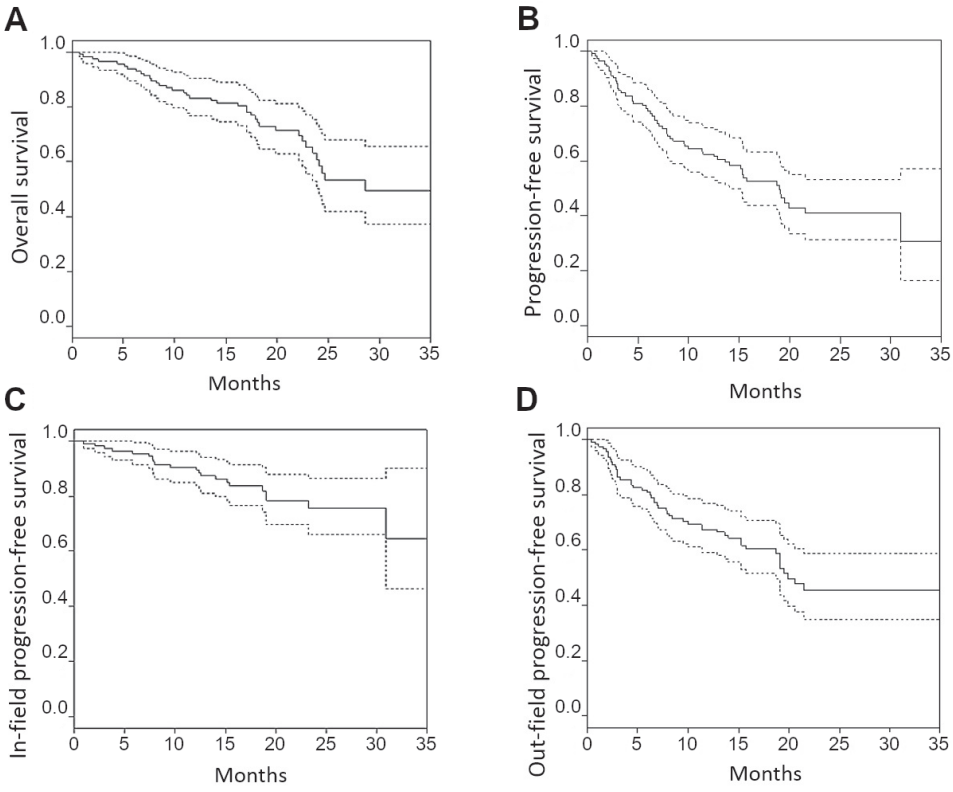

Figure 1. Kaplan-Meier survival analysis. Filled lines represent overall analysis (A), progression-free survival (B), in-field (C) and out-field (D) progression-free survival. Dotted lines represent the lower and upper limit of the confidence intervals.

Table 2. Treatment characteristics (115 patients, 124 lesions).

Characteristics	
Total dose (Gy); median (range)	45; (18–54)
Dose for fraction (Gy); median (range)	15; (4–18)
Number of fractions; median (range)	3; (2–8)
Isodose of prescription (%); median (range)	80; (68–85)
PTV (cm^3); median (range)	25; (3–195)
Lung mean dose (Gy); median (range)	4; (1–70)
Lung V_{20Gy} (cm^3); median (range)	127; (0–617)
V_{5Gy} (cm^3); median (range)	538; (7–2757)
0-view modality; n (%)	69; (55.6)
1-view modality; n (%)	33; (26.6)
2-view modality; n (%)	22; (17.7)

PTV - Planning target volume; V_{20Gy} - Volume receiving the 20 Gy; V_{5Gy} - Volume receiving the 5 Gy.

Table 3. Treatment schemes.

Dose per fraction (Gy)	Number of fractions	Number of patients (%)
18	3	40; (34.8)
15	3	34; (29.6)
12	3	11; (9.6)
8	5	9; (7.8)
7	5	4; (3.5)
other schemes		17; (14.8)

(dyspnea, cough, and pneumonia) in only 3 patients (3%). Late toxicity data were available for 85 patients and included cough, bronchospasm, laryngeal inflammation, pneumonia, and pulmonary fibrosis. Late toxicity was registered in 25 patients (29%). G3 late toxicity (dyspnea) was observed in only one patient (1.1%) (Table 4). No grade 4 acute or late events were observed.

No statistically significant correlations were found between clinical-related characteristics and acute toxicity, with the exception of the respiratory comorbidities (χ^2 test, $p<0.001$).

On univariate analyses, a statistically significant correlation between late toxicity and previous thoracic/mediastinal surgery (Figure 2A) or RT (Figure 2B) was found (Log Rank $p=0.02$ and $p=0.03$, respectively). Results of oncological outcome and toxicity are reported in Table 5.

Discussion

This study showed that fiducial-less CyberKnife-LOT-SBRT provides good local control with a PFS at 2 years of almost 50%, achieving low toxicity rates. These data represent relevant results especially considering that the treated population was comprehensive of patients with severe respiratory comorbidities or with a previous history of thoracic

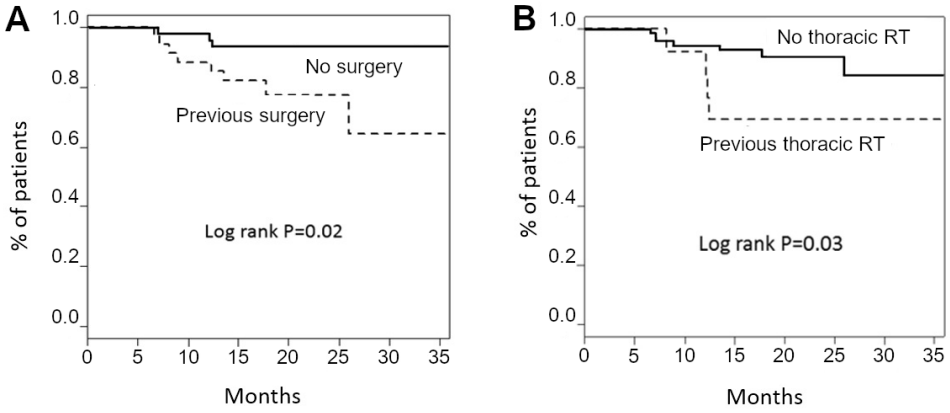

Figure 2. Univariate analysis of freedom for G >1 late toxicity by thoracic surgery (A) and thoracic radiotherapy (B) pre-CyberKnife treatment.

Table 4. Percentage of observed acute and late toxicity

		Grade of toxicity		
		G1-G2 (% pts)	**G3 (% pts)**	**G4 (% pts)**
Kind of toxicity	**Acute**	**38%** (dyspnea, cough, laryngeal inflammation, pneumonia)	**3%** (dyspnea, cough, pneumonia)	No cases
	Late	**27.9%** (cough, bronchospasm, laryngeal inflammation, pneumonia, pulmonary fibrosis)	**1.1%** (dyspnea)	No cases

Table 5. Multivariate proportional hazard models.

		HR	Low	Up	p-value
Progression-free survival	Age	0.96	0.93	0.98	0.0003
	PTV (cm^3)	1.01	1.00	1.02	0.01
In-field progression-free survival	Age	1.01	0.96	1.05	0.78
	PTV (cm^3)	1.01	1.00	1.02	0.02
Out-field progression-free survival	Age	0.95	0.93	0.97	<0.0001
	PTV (cm^3)	1.01	1.00	1.02	0.01
Overall survival	Age	1.02	0.98	1.05	0.29
	PTV (cm^3)	1.01	1.00	1.02	0.01
Late toxicity	Age	1.02	0.96	1.09	0.52
	PTV (cm^3)	1.01	1.00	1.03	0.16

PTV – Planning target volume; HR – Hazard ratio; Low and Up refer to 95% confidence interval

treatments (surgery and/or RT). In many "real world" cancer practices, these patients, unfortunately, are not candidates to active cancer treatment and receive only the best supportive care. Therefore non-invasive outpatient based, short and comfortable CyberKnife-LOT-SBRT may represent a great opportunity for this particular patient population.

The main advantage of CyberKnife-LOT-SBRT is the ability to perform fiducial-less real-time tumor tracking [11], potentially improving the outcome in patients with poor pulmonary function. Before the introduction of tracking systems, fiducial marker insertion was necessary for tumor tracking. However, the insertion of such markers has been associated with complications, such as pneumothorax, migration of the marker, and arrhythmia [18–19]. Fiducial-less CyberKnife-LOT-SBRT allows non-invasive and more comfortable tracking.

As previously mentioned, this treatment was reserved for a population of patients that were "negatively selected" for both performance status (KPS <100, severe cardiovascular or pulmonary comorbidities) and prognostic factors. Despite this, we obtained a 1- and 2-year actuarial OS of 83% and 61%, respectively and 1- and 2-year actuarial local control rate of 90% and 76%, respectively.

Our results are comparable with published data on lung SBRT series, with local control and OS slightly inferior to results from primary tumor treatment [4, 20–23]. It is worth noting that our population comprised both primary and secondary tumors. This heterogeneity hinders direct comparison with most of the data present in literature, which refers to early stage primary tumors, whereas lung metastases show a worse outcome [7, 24–25].

Over the last 20 years, several research groups conducted phase I–II trials of SBRT for inoperable early-stage NSCLC. Total doses ranged from 45 to 66 Gy delivered in 3 or 4 fractions, with 2–3 years tumor local control rates and 1–3 years OS projections ranging between 84 and 98%, and between 43 and 72%, respectively [19, 26–30]. Timmermann et al. in the multi-institutional RTOG 0236 Trial for inoperable early-stage NSCLC demonstrated a 3-year survival rate of 56% and a 3-year local control rate of 98% [8]. Baumann

et al. founded a local control rate at 33 months of 88% and a 3-year OS rate of 55% [26]. Nagata et al. reported, in their phase II clinical trial for a medically operable case group, a 3-year OS rate of 76% and a 3-year in-field PFS of 69% [31]. For metastatic patient groups, Janvary et al. showed 1-, 2- and 3-year local control rates of 84%, 59%, and 53%, respectively [32]. An analysis of the RSSearch database, including patients with centrally located lung tumors, both primary and metastases, reported a median OS of 24 months and 2-year local control of 76.4% and 69.8% for primary NSCLC and lung metastases, respectively [33], whereas Lischalk et al. reported a median OS of 16 months and local control at 2 years of 57% [34]. Wulf et al. described an actuarial local control rate of 92% for primary lung cancer and 72% for pulmonary metastases at 12 months [35].

The incidence of G3 toxicities was consistent with data in the literature and even inferior, but this could be due to the retrospective character of our analysis and the higher probability to underestimate chronic toxicity events since data collection is not immediate and standardized as in prospective studies. In the RTOG 0236 trial, a multi-institutional clinical trial undertaken in the USA, 12.7% and 3.6% of 32 patients were reported to experience protocol specified treatment-related grade 3 and 4 adverse events [8]. Fakiris et al. described G3 toxicities (pneumonia and skin erythema) in 2.8% of patients [36], while Onishi et al. described G3 toxicities (namely esophagitis, dermatitis, and pulmonary toxicity) in 9.2% of patients and G3 radiation-induced pulmonary complications in 1.1% of patients [20]. It is worth underlying that the Ray Tracing algorithm has been declared outdated because of its relevant uncertainty in inhomogeneous anatomic sites [37, 38]. Nevertheless, at the time of the present study design (2014–2016), the computational cost of a Monte Carlo calculation was not feasible in the clinical routine. Therefore the Ray Tracing was used to optimize and calculate these retrospectively selected plans. Nowadays the upgrade to the Precision® TPS v.1.1.x (Accuray Inc., Sunnyvale, CA) has increased the computational power allowing to run a Monte Carlo calculation in less than 30 minutes. The new Precision® TPS and the Monte Carlo algorithm have been commissioned in our Department at the beginning of 2019 for routine use in the medical practice and in related future research projects [39]. Another criticism of our study is the inclusion of a heterogeneous group of patients. The main endpoint of this present study was to assess the feasibility of the treatment, which justifies the inclusion of patients with different characteristics including different tumors (primary and metastases), therapeutic intent (curative vs. palliative), disease extent, previous RT or surgical history (some patients previously underwent mediastinal/thoracic RT or pulmonary major surgery), fractionation regimens, eventual concomitant systemic and adjuvant therapies. The results on oncological outcome and toxicity must be intended as literature confirmation for appropriately selected patients.

Therefore, lung fiducial-less CyberKnife-LOT-SBRT may be safely delivered in patients with severe pulmonary comorbidities, with poor pre-treatment pulmonary function and those who previously underwent thoracic surgery or RT. The correlation between toxicity and dose-volume points to the lung was analyzed in order to identify statistically significant dose-volume points that could potentially be predictive for toxicity. In our dataset, no correlation between $V_{20\%}$ and mean dose to lung and toxicity was found. This could be due to the safety of the constraints used for treatment planning or to the insufficient sample size in terms of the total number of high-grade toxicity events.

A remarkable finding might be the observed correlation between late toxicity and previous thoracic surgery and/or thoracic RT. Another interesting finding of our study was the absence of chest wall complications.

Our preliminary data based on a retrospective analysis shows that fiducial less-SBRT is a feasible, well-tolerated and potentially effective treatment with high compliance in the setting of inoperable patients due to concomitant diseases or previous treatments. The identification of patient selection criteria, together with the definition of fractionation, is warranted. Arguably, the incorporation of such parameters in structured prospective studies might contribute to improving the level of evidence for fiducial-less SBRT in lung cancer for appropriately selected patients.

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