research article

Clinical outcomes of 130 patients with primary and secondary lung tumors treated with Cyberknife robotic stereotactic body radiotherapy

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Radiol Oncol 2017;

Received 15 December 2016
Accepted 27 February 2017

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Disclosure: No potential conflicts of interest were disclosed.

Background. Authors report clinical outcomes of patients treated with robotic stereotactic body radiotherapy (SBRT) for primary, recurrent and metastatic lung lesions.

Patients and methods. 130 patients with 160 lesions were treated with Cyberknife SBRT, including T1-3 primary lung cancers (54%), recurrent tumors (22%) and pulmonary metastases (24%). The mean biologically equivalent dose (BED_{10Gy}) was 151 Gy (72–180 Gy). Median prescribed dose for peripheral and central lesions was 3x20 Gy and 3x15 Gy, respectively. Local control (LC), overall survival (OS), and cause-specific survival (CSS) rates, early and late toxicities are reported. Statistical analysis was performed to identify factors influencing local tumor control.

Results. Median follow-up time was 21 months. In univariate analysis, higher dose was associated with better LC and a cut-off value was detected at $BED_{10Gy} \leq 112.5$ Gy, resulting in 1-, 2-, and 3-year actuarial LC rates of 93%, *vs* 73%, 80% *vs* 61%, and 63% *vs* 54%, for the high and low dose groups, respectively ($p = 0.0061$, HR = 0.384). In multivariate analysis, metastatic origin, histological confirmation and larger Planning Target Volume (PTV) were associated with higher risk of local failure. Actuarial OS and CSS rates at 1, 2, and 3 years were 85%, 74% and 62%, and 93%, 89% and 80%, respectively. Acute and late toxicities ≥ Gr 3 were observed in 3 (2%) and 6 patients (5%), respectively.

Conclusions. Our favorable LC and survival rates after robotic SBRT, with low rates of severe toxicities, are coherent with the literature data in this mixed, non-selected study population.

Key words: Cyberknife; stereotactic body radiotherapy; non-small cell lung cancer; lung metastasis

Introduction

Although surgical resection is considered as the standard of care in patients with early-stage non-small cell lung cancer (NSCLC), a significant percentage of mostly elderly patients are not eligible for this treatment. Stereotactic body radiotherapy (SBRT) is considered to be an effective and well tolerated, non-invasive treatment option for this population.[1,2] Efforts have already been made to directly compare the effectiveness and toxicity of SBRT to surgery for operable patients in rand-

doi:10.1515/raon-2017-0015

omized trials, but unfortunately, these trials did not reach their accrual target and were prematurily closed because of low recruitment.[2]

However data from prospective trials show consistenly high levels of local control rates with stereotactic irradiation of early stage NSCLC.[3-6] Although SBRT literature is more extensive for early stage primary lung cancer, publications concerning recurrent lung tumors and lung metastases also show high local control rates.[7-9] On the basis of the published clinical experience stereotactic radiotherapy of the lung became one of the most established indications of SBRT.[10-11] A clear dose-effect relationship has been shown by several SBRT studies, and a $BED_{10Gy} \geq 100$ Gy (Biologically Effective Dose with an α/β of 10 Gy) was found to be associated with better results.[12] Nevertheless, the delivered dose and fraction number should be tailored to the anatomical situation and size of the lesion, as the proximity of critical organs can lead to higher probability of toxicity.

Although there have been attemps for single fraction treatments[13-14], generally lung SBRT is delivered in 3 to 8 fractions. Treatment-related severe toxicities are uncommon using "risk-adapted" fractionation schemes with lower dose per fraction for central tumors.[15]

The purpose of this study is to evaluate and report the clinical outcomes of the first 130 consecutively treated patients presented with primary, recurrent primary or secondary lung tumors. The primary objective was to analyse local therapeutic efficacy of robotic SBRT and factors influencing local control. The secondary objectives were to evaluate early and late toxicities and survival results.

TABLE 1. Patient, tumor and treatment characteristcs

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

BED = mean biologically equivalent dose; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; fx = fractions; GTV = gross tumour volume; PTV = planning target volume

Patients and methods

Patients

Cyberknife® (Accuray Inc. Sunnyvale, USA) robotic SBRT treatments were started at the Liege University Hospital in April 2010. Ordinary indications for SBRT treatment include T1-T2 primary NSCLC, recurrent primary lung tumors, and solitary-, or oligometastases. However, more rarely this treatment is appied on T3 tumors or soliter lymph node metastases.[16-19] The majority of primary and recurrent lung tumors in our cohort were considered ineligible for surgical resection because of poor lung functions or severe comorbidities. For metastatic lesions medical inoperability; > 1 lesions in different lobes or lungs; prior lobectomy and patient preference were the major causes leading to the choice of SBRT. Based on individual medical consideration and absence of realistic therapeutic alternatives a small number of unusual indications were also included, like patients harboring T3N0 or T1N1 disease. In the present study 130 consecutive patients treated with $BED_{10Gy} \geq 72$ Gy were evaluated. Central or large tumors were not excluded, but the dose and number of fractions were adapted. Central lesions were defined as lesions located whithin 2 cm from the pulmonary hilum, heart, great vessels, or trachea. Indications for each individual patient were discussed and approved in multi-disciplinary tumor boards. Especially for primary tumors, pathological confirmation was requested either by bronchofiberoscopy or transthoracic biopsy. For patients considered not eligible for histological confirmation (due to technical or medical reasons), the indication was based on strong clinical suspicion supported by positron emission tomography (PET).

One hundred and thirty patients, with a total of 160 lung lesions were treated between April 2010 and June 2012. Patient and tumor characteristics are listed in Table 1.

Median age of patients at treatment was 71 years (range 40–93), and 59% (n = 77) were males. Distribution of lesions were: 53% (n = 86) primary, 22% (n = 35) recurrent tumor/intrapulmonary metastasis of a lung tumor and 25% (n = 39) metastases from other cancer. Cancer of origin for metastatic lesions were: colorectal (49%; n = 19), salivary gland (13%; n = 5), breast (10%; n = 4) , melanoma (5%; n = 2), kidney (5%; n = 2), neuroendocrin (3%; n = 1), multiple primary (13%; n = 5) , unkown (2%; n = 1). Distribution of histological types for the patient group with pathologically confirmed primary lung cancer was: 47% adenocarcinoma (n = 29), 33% squamosus cell carcinoma (n = 21), 15% NSCLC (n = 9), 5% undifferentiated (n = 3). The maximal number of lesions treated by SBRT in the same patient was four. Four patients were presented with stage T1N1 disease. For these patients the affected lymph node(s) were also treated with SBRT. Positivity of these lymph nodes were based on high SUVmax value on PET CT, without cytological confirmation, but usually the histology of the belonging primary tumors were known.

One patient was categorized as T3 for tumor size, the other four T3 patients had mediastinal pleura invasion or separate nodule in the same lobe.

Distribution of the 113 peripheral lesions was : n = 66 primary, n = 21 recurrent, n = 26 metastasis. The group of 47 central lesions was composed of 17 primary tumors plus 3 synchronous N1 lymph nodes, 14 recurrent cancers and 13 metastases.

Treatment preparation

Technical characteristics and tracking options of the Cyberknife robotic SBRT system have been exhaustively detailed elsewhere.[16-17] For thoracic tumors there are three different tracking types, which can be appropriately selected according to each clinical case. Synchrony® is a real-time tumor tracking algorithm which requires fiducial markers to be previously inserted inside or near to the target. The fiducials are detected by orthogonal X-rays at the treatment room. The system includes an infrared camera that monitors the movement of the chest. During treatment, spatial information on the location of the fiducials and data of the respiratory cycle are connected to redirect the robot, and realize real-time tracking. Fiducial insertion can be contraindicated for some patients because of the inherent risk of pneumothorax. For selected cases, when tumor silhouette is sharply identified on both ortogonal X-ray detector panels, the algorithm of Xsight Lung® can be used for tracking the target, without the need for implanted markers. When none of these two previously mentioned tracking algorithm is feasible, tracking is performed on the vertebra (XsightSpine®).

Planning CT images were obtained with a slice thickness of 1 mm. Patients were immobilised using an individual vacuum bag ˝in supine position, with arms next to the body. Four-dimensional (4D) CT simulation was not introduced for Cyberknife treatment, thus expiration and moderate inspiration CT scans were acquired to estimate magnitude of respiratory releated tumor movement. In case of fiducial-, or direct tumor tracking, only expiration CTs were used for delineation. For patients with fiducial markers, CT simulation was delayed with a minimum of 10 days after implantation to minimise uncertainity linked to the potential marker migration.

The vast majority of patients (n = 125; 96%) had PET CT scans in treatment position using the same individual vacuum bag used at the CT simulation, to optimize target volume definition.

For patients with real-time tumor tracking generally a margin of 3 mm was applied around the gross tumor volume (GTV) to achieve clinical target volume (CTV). CTV contours were then, corrected manually when overlapping with ribs or mediastinal structures. An additional 2 mm was added to create planning target volume (PTV).

When real time tumor tracking was not feasible, we used an internal target volume of GTV, large enough to cover all possible tumor positions during the respiratory cycle. After that, the method and the margins for creating CTV-internal target volume (ITV) and PTV was similar to real time tracked patients.

SBRT procedure

Treatment plans were implemented with Multiplan treatment planning system (TPS) version 5.1 (Accuray Inc. Sunnyvale, USA), using Ray Tracing calculation algorythm. Prescription doses varied between 40 to 60 Gy in 3 to 5 fractions, depending on proximity to organs at risk (OAR) and on tumor size. Dose was typically prescribed to the 80% isodose line (75–82%) encompassing the PTV. Dose constrains to OARs were applied according to a class solution (Table 2) which was based on published data of Timmerman and AAPM Taskgroup 101 guidelines.[18-19]

SBRT treatments were performed by Cyberknife Robotic Radiosurgery treatment unit (Accuray Inc.

TABLE 2. Dose constraints for organs at risk

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

Sunnyvale, USA). Treatment consisted of typically 100–200 non-coplanar beams using Iris® various aperture collimator in a range between 15 to 60 mm with a dose rate of 600 MU/min.

Follow up and toxicity evaluation

Patients were followed up by the treating radiation oncologist and/or by referring pulmonologist or oncologist. In addition to regular CT-scans, metabolic follow up of treatment effect by PET CT was performed in 118 patients (91%) to make distinction between local disease progression and localized pulmonary fibrosis.[20,21] Acute and late toxicities were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Toxicity was classified as acute up to 3 months after SBRT.

The patient follow up time was defined as the period between the first day of Cyberknife treatment to the date of last visit or death.

TABLE 3. Dose-fractionation schemes

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%)

BED = mean biologically equivalent dose

Statistical analysis

Patient and lesion characteristics and toxicities were described in terms of means or medians (range) or in terms of numbers (%). A descriptive analysis was used to present patient and treatment characteristics and toxicity data. Local control (LC), overall survival (OS) and cause-specific survival (CSS) rates were estimated by the Kaplan-Meier method. The prognostic value of patient and tumor characteristics on LC was determined using uni- and multivariate Cox regression models. Results were considered to be statisticallysignificant at p-values ≤ 0.05. Statistical analysis was performed with the SAS version 9.3 software (SAS Institute, Cary, NC, USA).

Ethical considerations

This retrospective cohort study was approved by institutional review board.

Results

The mean and median follow up time (FUP) was 21 months (range 2–39) with only 8 cases (6.2%) with a follow-up of less than 6 months. Total dose and number of fractions was determined with consideration of tumor location and size. In some cases the initially planned dose was reduced and/or the fraction number was increased in order to better meet OAR constraints. The applied dose and fractionation schemes are described in Table 3.

Delivered dose varied from BED_{10Gy} = 72 Gy (40 Gy in 5 fractions) to BED_{10Gy} = 180 Gy (60 Gy in 3 fractions). The median dose for peripheral lesions was 3x 20Gy, whereas for central lesions the median was 3x 15Gy. Mean/median BED_{10Gy} for peripheral and central lesions were 170/180Gy and 102/112.5 Gy, respectively. Real-time tumor tracking was performed in 42% of treatments (n = 66) either using gold fiducial based (Synchrony) or direct fluoroscopic (Xsight Lung) methods.

Local control

For the whole cohort the actuarial 1-, 2-, and 3-year LC rates were 86%, 75%, and 62%, respectively.

In univariate Cox regression model, a higher BED_{10Gy} was associated with better LC (p = 0.008). Analysis of the different dose levels found a cut-off value between BED 112.5 Gy and 132 Gy. Treatments using doses higher than 112.5 Gy

showed a significant advantage in terms of LC, resulting 1-, 2-, and 3-year actuarial LC rates of 93% *vs* 73%, 80% *vs* 61%, and 63% *vs* 54%, respectively (p = 0.0061, HR = 0.384; Figure 1).

In univariate analysis there were no significant differences between primary (P), recurrent (R) and metastatic (M) lesions in terms of actuarial LC (p = 0.091). However in pairwise comparison primary tumors provided improved results compared to metastases: 1-, 2-, and 3-year LC rates were 89% *vs* 84%, 80% *vs* 59%, and 64% *vs* 53%, respectively (p = 0.035; Figure 2). Other factors such as tumor tracking (inclusive tracking modality), and histological confirmation of malignancy had no significant effect on LC.

During separate analysis of the primary tumor group there was no significant difference in LC according to T-stage. However, there was a a non-significant trend favoring LC in T1 compared to T2 (p = 0.063).

Local control was significantly higher for peripheral lesions, compared to central lesions (p = 0.025), resulting in 1-, 2-, and 3-year LC rates of 91% *vs* 74%, 79% *vs* 63%, and 60% *vs* 56%, respectively (Figure 3).

In univariate Cox regression model, larger GTV and PTV volumes were associated with a higher risk of local relapse (p = 0.0034 and p = 0.0013, respectively).

The variables tested in multivariate analysis were tumor type (primary/recurrent/metastasis), tracking (yes/no), confirmed histology (yes/no), location of lesions (central/peripheral), BED_{10Gy}, GTV, PTV, and PTV coverage. These variables were selected in order to determine treatment and tumor factors influencing LC. In multivariate analysis the metastatic origin of lesions (HR = 7.3; p < 0.0001), the histological confirmation of malignancy (HR = 4.1; p = 0.0052) and larger PTV (HR = 1.03; p < 0.0001) were associated with significantly lower LC rate.

Overall survival and cause-specific survival

One-, two-, and three-year actuarial rates of OS were 85%, 74% and 62%, respetively, whereas the respective rates of CSS were 93%, 90%, and 80%.

Early and late toxicities

Treatment related Grade (G) 3 or higher acute and late toxicities were observed at 3 (2%) and 6 patients (5%), respectively. Acute toxicities included 2 cases (1.5%) of G3 pneumonitis and a single case (0.8%) of

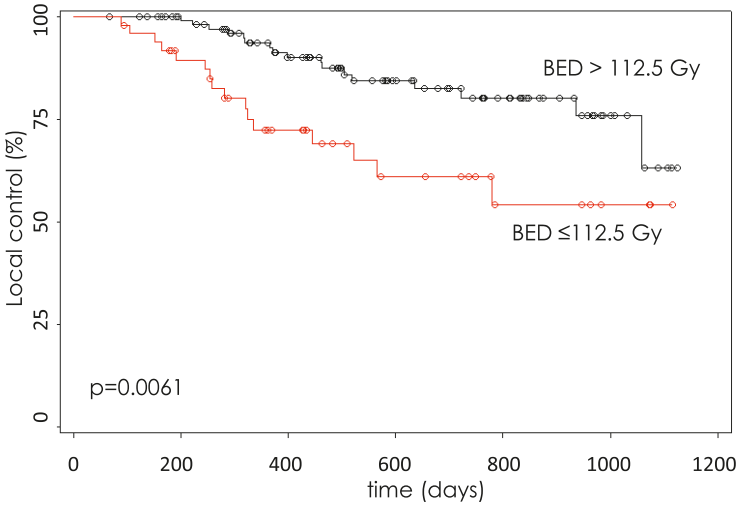

FIGURE 1. Probabilty of local control according to dose (BED ≤ 112.5 Gy *vs.* higher).

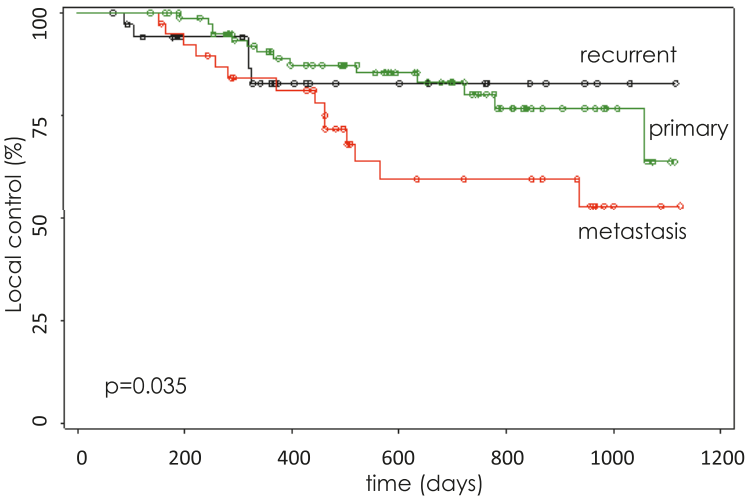

FIGURE 2. Probability of local control for primary (n = 86), recurrent (n = 35) and metastatic (n = 39) lesions.

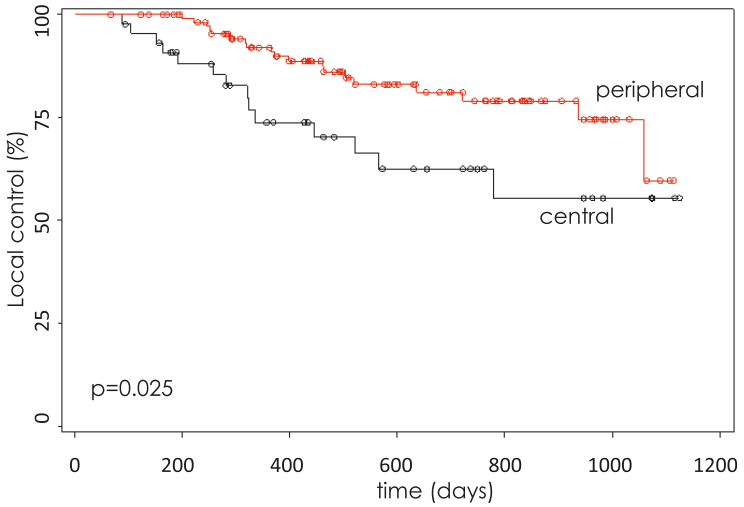

FIGURE 3. Probability of local control for peripheral (n = 113) and central (n = 47) lesions.

TABLE 4. Comparative table of relevant published data and own results

Study	Technic	Histological confirmation %	No. of pts/ lesions	dose (Gy)/fx	BED_{10Gy} (Gray)	Median FUP (month)	Local Control	Overall Survival
PRIMARY								
Chen VJ (26)	CK	100	40	median 48 (42-60)/3 fx	124.8	44	91%@3y	75%@3y
van der Voort van Zyp (27)	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 (28)	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 (29)	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 (30)	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 (31)	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 (32)	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	

BED = mean biologically equivalent dose; CK = Cyberknife; fx = fractions; LINAC = linear accelerator, Met = metastases; Prim = primary tumour; Y = year

G5 pulmonary haemorrhage. This latter elderly (85 years old) patient had a fatal ipsilateral pulmonary haemorrhage 1 month after the completion of his SBRT (45 Gy in 5 fractions) for a right sided central tumor recurrence, and was classified as a possible treatment related adverse event. The patient had already been treated with chemotherapy 4 years earlier for his primary lung tumor, and 1 year earlier by Cyberknife for a contralateral upper lobe relapse without progression until the time of death.

Late toxicities were G3 dyspnea (n = 3; 2.3%, all presenting with chronic obstructive pulmonary disease [COPD] Global Initiative for Chronic Obstructive Lung Disease [GOLD] III prior to SBRT), G3 sick sinus syndrome (n = 1; 0.8%) requiring pacemaker implantation 8 months after SBRT, G3 pain due to a rib fracture requiring major analgesic (n = 1; 0.8%). One patient (0.8%) suffered a fatal haemorrhage (G5) 7 months after SBRT for a centrally located recurrent tumor mass, which invaded vascular structures already at the time of detection, and had shown progression after Cyberknife treatment (40 Gy in 5 fracions). This case was encoded as a treatment related adverse event, although local tumor progression could not be formally excluded.

Grade 2 late toxicities were also recorded such as asymptomatic or moderately painful rib fractures (n = 5; 3.8%), recurrent laryngeal nerve palsy (n = 1; 0.8%), late radiation pneumonitis (n = 14; 10.8%) and pneumothorax (n = 6; 4.6%) after transthoracic marker placement requiring tube placement for a few days.

Discussion

High (86%, 75%, and 62% at 1, 2, and 3 years) actuarial LC rates were observed at the first 130 consecutive patients treated with lung SBRT in our institution. Our results are comparable with published data from other lung SBRT series (Table 4).[4-5,7-9, 22-28] Bahig *et al.* reported their results on 150 patients treated with Cyberknife with a median dose of 60

Gy in 3 fractions leading to exellent LC rates of 96% at 2 years. This cohort, including peripheral and central tumors, consisted of purely stage T1-2 primary NSCLC.[4] In our study favorable LC was observed for primary tumors compared to metastatic lesions. The same finding was reported by Duncken-Rohr[32], while Guckenberger *et al.*[31]n = 41; Stage IA, n = 13; Stage IB, n = 19; T3N0, n = 9 showed comparable 3-year results for primary and metastatic lesions treated with SBRT between the two groups at 3 years. In a comparative study of primary and metastatic lung tumors by Yamamoto *et al.*[33] tumor diameter and metastatic origin were associated with significantly lower LC rates, which is congruent with our findings.

Location of the target in lung SBRT has an important role in defining maximum deliverable doses in function of their proximity to adjacent radiosensitive OARS. In our analysis, LC rates at 1-, 2-, and 3-years are significantly different between central and peripheral lesions. The same observation was reported by van der Voort van Zyp *et al.* with LC of 96 % *vs.*78% LC at 2 years for peripheral *vs.* central T1-2 NSCLC lung tumors treated with 60 Gy or 45 Gy in 3 fractions, respectively.[27]

The question of optimal dose of SBRT for central lesions remains unclear however, careful and appropriate dose-fractionation can lead to high tumor control with low rate of severe toxicities even in this population. In our series the overall mean BED_{10Gy} was 151 Gy with a range between 72–180 Gy. As the total dose and the number of fractions was determined by the location and the size of the target lesion, the same treatment schedules were applied for primary, recurrent and metastatic lesions. Central lesions were treated with a mean / median BED_{10Gy} of 102/112.5 Gy, the corresponding doses for peripheral lesions were 170/180 Gy, respectively. Obviously, the above seen better local control rates for peripheral tumors were linked to higher deliverable dose.

In a recent systematic review of central tumors Senthi *et al.*[34] have found that LC rates ≥ 85 % can be achieved with low rates of complications when prescribed BED on the tumor is ≥ 100Gy, and at the same time the biologically equivalent normal tissue dose does not exceed 210 Gy. In a recent multicentric analysis of linac based central lung SBRT for NSCLC in German and Austrian institutions,the authors show similar LC rates to ours with 76%, 64% and 52% at 1, 2, and 3 years with a delivered median BED_{10} of 72 Gy (range 43–180 Gy).[35]

In series reporting results of purely peripheral, T1-2 NSCLC treated with similar technology and doses to ours, LC rates as high as 83.8–100% were achieved at 2 years.[26,29,36-38]

A subgroup analysis of primary lung cancer patients in our cohort yielded actuarial 1-, 2-, and 3-year LC of 89%, 80%, and 64 %, respectively. These results are similar to the findings of a recent, large scale publication on data of the RSSearch® Patient Registry of Radiosurgery Society reporting the clinical outcome of 723 patients with early stage, node negative NSCLC treated with various SBRT techniques achieving 88% and 76% LC rates at 1 and 2 years, respectively.[5]

For metastatic and recurrent patient groups we observed 1-, 2-, and 3-year LC rates of 84%, 59%, 53% and 83%, 83%, 83%, respectively. Inoue *et al.*[8] reported comparable results (3-year LC rate of 80%) in a large cohort study of central and peripheral metastases of 87 pts (189 lesions).

Although the distribition of patient numbers at the different dose-levels was particularly inbalanced in our cohort, analysis was performed on effect of BED_{10Gy} on LC. A clear correlation between the applied dose and the actuarial local control rates were found with a cut-off at BED_{10Gy} of 112.5 Gy, where lower doses were associated with higher rates of local recurrence. Local control rates at 1, 2, and 3 years were 93% *vs* 73%, 80% *vs* 61%, and 63% *vs* 54%, for the higher and lower dose groups, respectively ($p = 0.0061$, HR = 0.384). These results are coherent with the findings of others, however dose cut-off was found to be somewhat lower in the literature. Onishi *et al.*[12] and Olsen *et al.*[39] has shown that SBRT with a $BED_{10Gy} \geq 100$ Gy was associated with significantly better LC rates than those with lower doses. In a large cohort study of 505 patients treated for NSCLC $BED_{10Gy} < 105$ Gy predicted higher local recurrence rates of 15% *vs* 4% in the low dose and high dose group, respectively.[40] In contrast, in a cohort of 94 NSCLC Stephans *et al.*[41] did not observe a significant difference in 12 months actuarial LC between fractionation schemes of 5x10 Gy *vs* 3x20 Gy (BED_{10Gy} = 100 Gy *vs* 180Gy).

The limitations of our findings concerning the optimal BED_{10Gy} include the inbalanced distribution of patients in different dose-level groups, the possible selection bias and the non-randomized nature of this cohort study.

The incidence of G3 or higher toxities in our study was coherent with the literature with 2% of acute and 5% of late complications.[8,38] Two patients out of 130 (1.5%) has died because of pulmonary haemorrhage. Grade 5 toxicities are rare, but existing complications of SBRT, occuring predominant-

ly in centrally located tumors with an incidence of 0–2% in the literature.[4,35] This low incidence of treatment realted deaths can reasonably be considered as acceptable, given the lack of treatment alternatives for this population.

Conclusions

Stereotactic ablative radiotherapy using the CybeKnife system for the treatment of primary, recurrent and metastatic lung lesions seems to be a safe and effective treatment option for medically inoperable patients. A clear dose-response relationship was confirmed with a significantly improved local control with BED_{10Gy} over 112.5 Gy. More firm data from prospective trials are needed to validate findings of this study.

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