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ORIGINAL ARTICLE

Risk-adapted robotic stereotactic body radiation therapy for inoperable early-stage non-small-cell lung cancer

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Abstract
Purpose To evaluate efficacy and toxicity of stereotactic body radiation therapy (SBRT) with CyberKnife® (Accuray, Sunnyvale, CA, USA) in a selected cohort of primary, medically inoperable early-stage non-small cell lung cancer (NSCLC) patients.
Methods From 2012 to 2016, 106 patients (median age 74 years, range 50–94 years) with primary NSCLC were treated with SBRT using CyberKnife®. Histologic confirmation was available in 87 patients (82%). For mediastinal staging, 92 patients (87%) underwent ^{18}F-fluorodeoxyglucose positron-emission tomography (18-FDG-PET) and/or endobronchial ultrasound (EBUS)-guided lymph node biopsy or mediastinoscopy. Tumor stage (UICC8, 2017) was IA/B (T1a-c, 1–3 cm) in 86 patients (81%) and IIA (T2a/b, 3–5 cm) in 20 patients (19%). Depending on tumor localization, three different fractionation schedules were used: 3 fractions of 17Gy, 5 fractions of 11Gy, or 8 fractions of 7.5 Gy. Tracking was based on fiducial implants in 13 patients (12%) and on image guidance without markers in 88%.
Results Median follow-up was 15 months (range 0.5–46 months). Acute side effects were mild (fatigue grade 1–2 in 20% and dyspnea grade 1–2 in 17%). Late effects were observed in 4 patients (4%): 3 patients developed pneumonitis requiring therapy (grade 2) and 1 patient suffered a rib fracture (grade 3). In total, 9/106 patients (8%) experienced a local recurrence, actuarial local control rates were 88% (95% confidence interval, CI, 80–96%) at 2 years and 77% (95%CI 56–98%) at 3 years. The median disease-free survival time was 27 months (95%CI 23–31 months). Overall survival was 77% (95%CI 65–85%) at 2 years and 56% (95%CI 39–73%) at 3 years.
Conclusion CyberKnife® lung SBRT which allows for real-time tumor tracking and risk-adapted fractionation achieves satisfactory local control and low toxicity rates in inoperable early-stage primary lung cancer patients.

Keywords Radiosurgery · Survival · Toxicity · Adverse effects · Fiducial markers

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Risikoadaptierte robotergestützte stereotaktische Strahlentherapie beim inoperablen nichtkleinzelligen Bronchialkarzinom im Frühstadium

Zusammenfassung
Zielsetzung Untersuchung von Wirkung und Toxizität einer stereotaktischen Bestrahlung (SBRT) bei Patienten

mit Frühstadien von medizinisch inoperablen primären nichtkleinzelligen Bronchialkarzinomen (NSCLC) am CyberKnife® (Accuray, Sunnyvale, CA, US).

Methoden Von 2012 bis 2016 wurden 106 Patienten (medianes Alter 74 Jahre, Spanne 50–94 Jahre) mit primärem NSCLC mittels SBRT am CyberKnife® behandelt. Bei 87 Patienten (82 %) war der Tumor histologisch gesichert. Zum Ausschluss mediastinaler Lymphknotenmetastasen erhielten 92 Patienten (87 %) eine ^{18}Fluorodeoxyglukose-Positronenemissionstomographie (^{18}FDG-PET) und/oder einen endobronchialen Ultraschall (EBUS) mit Lymphknotenbiopsie oder eine Mediastinoskopie. Das Tumorstadium (UICC8, 2017) war bei 86 Patienten IA/B (T1a–c, 1–3 cm) und bei 20 (19 %) IIA (T2a/b, 3–5 cm). Abhängig von der Tumorlokalisation wurden drei Fraktionierungsschemata verwendet: 3 × 17 Gy, 5 × 11 Gy, 8 × 7,5 Gy. Für das Tracking wurden 13 Patienten (12 %) Marker-Seeds implantiert, in 88 % erfolgte die Bestrahlung bildgesteuert ohne Marker.

Ergebnisse Das mediane Follow-up betrug 15 Monate (Spanne 0,5–46 Monate). Akute Nebenwirkungen waren mild (Fatigue Grad 1–2 in 20 %, Atemnot Grad 1–2 in 17 %). Spättoxizitäten zeigten sich bei 4 Patienten (4 %): 3-mal eine Pneumonitis (Grad 2),1-mal eine Rippenfraktur (Grad 3). Bei 9/106 Patienten (8 %) trat ein Lokalrezidiv auf, die lokale Kontrollrate betrug 88 % (95 %-Konfidenzintervall [KI] 80–96 %) nach 2 und 77 % (95 %-KI 56–98 %) nach 3 Jahren. Das mediane krankheitsfreie Überleben war 27 Monate (95 %-KI 23–31 Monate). Das Gesamtüberleben betrug 77 % (95 %-KI 65–85 %) nach 2 und 56 % (95 %-KI 39–73 %) nach 3 Jahren.

Schlussfolgerung Durch Tumor-Tracking in Echtzeit und risikoadaptierte Fraktionierung führt die CyberKnife®-SBRT der Lunge bei inoperablen primären NSCLC-Patienten im Frühstadium zu einer guten lokalen Kontrolle bei niedrigen Toxizitätsraten.

Schlüsselwörter Radiochirurgie · Überleben · Toxizität · Nebenwirkungen · Marker

For patients with early stage non-small cell lung cancer (NSCLC), stereotactic body radiotherapy (SBRT) has been established as a curative treatment option during recent years, as local control and survival rates approach those observed after surgery [1–3]. In consequence, elderly patients and those with cardiovascular and respiratory comorbidities who are either high-risk candidates for surgery or even definitely inoperable are nowadays less likely to undergo surgical resection and can be offered SBRT as a reasonable alternative [4, 5].

In general, SBRT techniques include some kind of motion management, e. g., four-dimensional computed tomography (CT) used for internal treatment volume (ITV) definition or respiratory gating, combined with intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) [6]. An advanced set of techniques is available with CyberKnife® (Accuray, Sunnyvale, CA, USA), which allows highly conformal, non-isocentric irradiation of a moving target using non-coplanar beams and real-time tumor tracking [7].

We retrospectively analyzed the clinical outcome and toxicity in a selected series of patients with primary stage I NSCLC treated with CyberKnife® (rel. 9.5) SBRT at our institution. As fractionation schemes and the applicability of the linear quadratic model for single doses >10 Gy are still matters of debate, and because single fraction protocols carry the risk of severe adverse effects, particularly in large and/or centrally located tumors, three fractionation schedules considering the patient's individual risk were adopted from a major institution where they had been developed for conventional linear accelerator (LINAC)-based lung SBRT [8].

Materials and methods

Between April 2012 and December 2015, 182 patients with stage I NSCLC underwent definitive CyberKnife® SBRT at our institution. This cohort included 106 patients who had their first diagnosis of NSCLC, 62 patients who had been treated for lung cancer before, and 14 patients who received SBRT as primary treatment for their lung tumors but had a history of successfully treated oligometastatic disease. Those with the primary tumors were analyzed retrospectively. Patients were referred to the Radiotherapy Department by two community hospitals or by the Departments of Thoracic Surgery or Pneumology. In all cases, the decision to treat the patient with stereotactic irradiation was made by an institutional tumor board. All patients were deemed medically inoperable, mostly due to age, comorbidities, or reduced pulmonary function as measured by FEV1 (forced expiratory volume < 1 sec) or DLCO (diffusion capacity of lung for carbon monoxide). Therefore, the Charlson comorbidity index [9] was computed for every patient.

Histopathological proof of malignancy was achieved by biopsy of the primary tumor whenever possible. In cases where tumors were inaccessible or biopsy carried a high risk, malignancy was assumed in case of tumor growth on repeated CT scans and/or the presence of a well demarcated enhancing lesion on combined ^{18}F-fluorodeoxyglucose positron-emission tomography/X-ray CT (18-FDG-PET/CT) according to established criteria [10]. Mediastinal lymph node staging was performed by either CT and/or 18-FDG-PET/CT and/or endobronchial ultrasound (EBUS)-guided transbronchial biopsy or mediastinoscopy, see Table 1. In some cases, nodal staging was performed by the

Table 1 Patient characteristics (n = 106)

Characteristics		Number (%/range)
Age, median (years; range)	–	74 (50–94)
Gender	Male/female	48/58 (45%/55%)
Tumor diameter, median (cm; range)	–	2.3 (0.8–6.6)[a]
Stage (UICC8, 2017)	I/IIA	86/20 (81%/19%)
Pathological confirmation	Yes/no	87/19 (82%/18%)
Mediastinal staging	CT only	14 (13%)
	CT + PET	51 (48%)
	CT + EBUS	18 (17%)
	CT + EBUS + PET	19 (18%)
	CT + mediastinoscopy	3
	CT + PET + mediastinoscopy	1
Histology	Adenocarcinoma	33 (31%)
	Squamous cell	42 (40%)
	Other	12 (11%)
	Unknown	19 (18%)
Tumor location	Peripheral	101 (95%)
	Central	5 (5%)
Fractionation scheme	1 × 25 Gy	6 (6%)
	3 × 20 Gy (3 × 17 Gy)	44 (41%)
	5 × 12 Gy (5 × 11 Gy)	39 (37%)
	8 × 7.5 Gy	17 (16%)
Tracking mode	Fiducials	13 (12%)
	XSight Lung[b]	93 (88%)
Charlson morbidity index	2	7 (7%)
	3	31 (29%)
	4	21 (17%)
	5	24 (20%)
	6	13 (12%)
	7	4 (4%)
	8	4 (4%)
	9–11	2 (2%)

CT computed tomography, *UICC* Union for International Cancer Control, *PET* positon-emission tomography, *EBUS* endobronchial ultrasound

[a]1 patient > 5 cm

[b]Accuray, Sunnyvale, CA, USA

referring hospitals in advance of the decision for radiotherapy. If these patients had received EBUS with biopsy or mediastinoscopy, additional PET/CT was not performed before SBRT.

Patients were treated with the CyberKnife® stereotactic radiation therapy system. Real-time tumor tracking was accomplished with fiducial-based target tracking (Synchrony®, Accuray) in 13 patients (12%) or image-guidance with direct tracking of the tumor contour (XSight Lung®, Accuray) in 92 patients (88%). The decision to use fiducials was usually based on the diagnostic CT where tumors with diameters less than 1.5 cm, low density, or position along the CyberKnife® X-ray projection line through the heart or spine where selected for marker implantation. In these cases, 1–5 gold markers were placed in or near the tumor under CT guidance (n = 7) or by navigated bronchoscopy (n = 6). For planning and treatment, patients were immobilized in supine position using an individually fitted vacuum pillow. Planning CT imaging was performed using 1-mm continuous slices, 7–10 days following fiducial placement. The gross tumor volume (GTV) was contoured on the planning CT using a typical lung center/width setting. For the planning target volume (PTV), the GTV was expanded by 3–4 mm. Critical structures included ipsi- and contralateral lungs, ribs adjacent to the PTV, and mediastinal structures.

As suggested by the Amsterdam University group [8], a risk-adapted fractionation scheme was applied. In peripheral T1 tumors (<3 cm) [11] without broad contact to the chest wall, 3 fractions of 20 Gy were used. In T1 tumors with broad contact to the chest wall and in T2 tumors (3–5 cm) [11], 5 fractions of 12 Gy were given. Near-central or true central tumors were treated with 8 fractions of 7.5 Gy. Initially, a pencil beam dose calculation algorithm was used (Accuray Multiplan® 4.5, Ray Tracing). From 2012 on, a Monte Carlo algorithm (Multiplan^R 4.5) [12] was applied and fractionation schedules for peripheral tumors were adapted (3 × 17 Gy instead of 3 × 20 Gy, 5 × 11 Gy instead of 5 × 12 Gy). Occasionally, very small tumors (<1.5 cm) were irradiated with a single fraction of 25 Gy. Dose prescription was to the 65–70% encompassing isodose for all fractionation schemes.

Clinical and radiological follow-up was scheduled at 3 and 6 months after radiotherapy and every 6 months thereafter. CT scans were performed at each visit. A local recurrence was assumed if the irradiated lesion showed a solid core that increased by at least 25% in the sum of diameters [13] compared to the last follow-up and exhibited further growth. Local fibrosis was diagnosed in lesions with a solid or ring-shaped structure that became smaller during follow-up. In cases where a growing lesion could not be differentiated from fibrosis, a FDG-PET/CT scan or a biopsy was performed.

Treatment outcomes for local control (LC), disease-free survival (DFS), and overall survival (OS) were assessed by the Kaplan–Meier method. For the calculation of overall survival probability, the period from the first day of radiotherapy to the day of death from any cause was used. For the assessment of LC, the period from the date of radiotherapy to the date of an initially confirmed recurrence was used, and patients who died of any cause without local

recurrence were censored. Any new tumor manifestations (local recurrence, new lung lesions distant from the PTV, lymph node metastases, other distant metastasis) and death due to any cause were counted for the calculation of DFS. Univariate analysis was performed using the log-rank test with *p*-values of 0.05 (two-sided) in order to investigate the prognostic value of gender, age, tumor size, histology, fractionation scheme, and Charlson Comorbidity Index. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Toxicities were evaluated using the Common Toxicity Criteria for Adverse Events version 4.0 (U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2009).

Results

A total of 106 patients with primary NSCLC were analyzed. The median follow-up was 15 months (range 0.5–46 months). Patient characteristics are summarized in Table 1. Of note, 82% had pathological confirmation of malignancy, only 5% had central tumors, and tracking without fiducials was used in 88%. None of the analyzed patients who had fiducial placement (n = 13) suffered a pneumothorax. We did not observe any loss of fiducials between placement and planning CT, but in 4/13 cases, some fiducials migrated between fractions, requiring selective disregard during tracking or re-planning. Acute side events were usually mild and were dominated by fatigue (grade 1–2) in 20% and dyspnea (grade 1–2) in 17% of the patients (Table 2). Infectious pneumonia 5–22 months after irradiation was suffered by 3 patients, probably unrelated to therapy.

In total, 9/106 patients (8%) developed local recurrence according to the abovementioned criteria. Actuarial LC rates were 88% (95% confidence interval, CI, 80–96%) at 2 years and 77% (95%CI 56–98%) at 3 years, (Fig. 1).

Table 2 Acute and late side effects after CyberKnife® (Accuray, Sunnyvale, CA, USA) lung stereotactic body radiation therapy

Effect	Grade: number (%)
Acute	
Fatigue	G1–2: 21/106 (20%)
Dyspnea	G1–2: 18/106 (17%)
Pain	G1: 5/106 (5%)
Late	
Focal consolidation/fibrosis (pneumonitis G1)	29/106 (27%)
Symptomatic pneumonitis (pneumonitis G2)	3/106 (3%)
Chest wall pain (G1)	2/106
Rib fractures (G3)	1/106

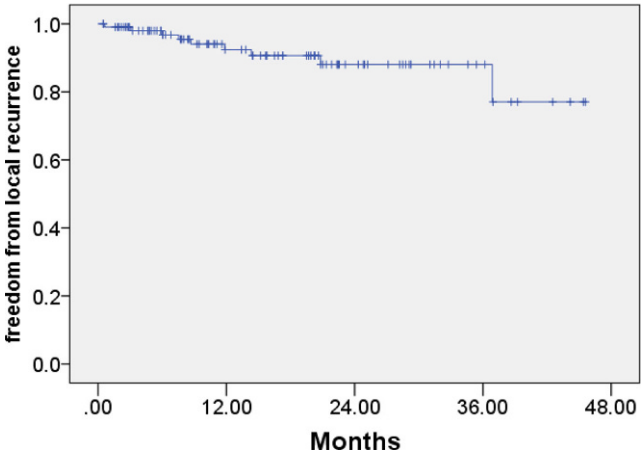

Fig. 1 Local control (freedom from local recurrence) in n = 106 patients with primary inoperable stage I/IIA (UICC8) non-small cell lung cancer treated with CyberKnife® (Accuray, Sunnyvale, CA, USA) stereotactic radiotherapy. Patients who deceased without manifested recurrence were censored

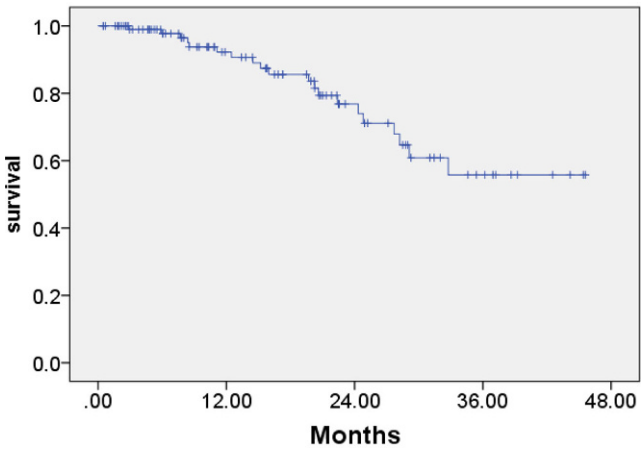

Fig. 2 Overall survival in n = 106 patients with primary inoperable stage I/IIA (UICC8) non-small cell lung cancer treated with CyberKnife® (Accuray, Sunnyvale, CA, USA) stereotactic radiotherapy

Seven recurrences were detected based on CT criteria only, 1 patient had a PET/CT [14], and 1 patient showed early progression during CyberKnife® SBRT. None of the factors tumor stage, histology, fractionation scheme, or mode of tracking had a significant influence on local tumor control (log-rank test $p \geq 0.05$ for all factors).

Regional or distant progression outside the PTV was observed in 15 patients (14%). The median DFS time was 27 months (95%CI 23–31 months). When recording the first event, 6 patients (5%) developed new lung lesions (secondary lung cancer in the same lobe 8 cm distant from the PTV in 1 patient, secondary lung cancer in the contralateral lobe in 2 patients, multiple metastatic lung lesions in 2 patients, malignant pleural effusion in 1 patient) and 5 patients (5%) had mediastinal lymph node metastases.

In 4 patients (4%), other distant metastases (brain, bone, liver, adrenal gland) were diagnosed. Actuarial disease-free survival was 63% (95%CI 51–74%) at 2 years and 38% (95%CI 23–54%) at 3 years. OS is depicted in Fig. 2. It amounted to 77% (95%CI 65–85%) at 2 years and 56% (95%CI 39–73%) at 3 years. Neither gender, histology, tumor stage, fractionation scheme, tracking mode, nor Charlson index had a significant influence on OS (log-rank test $p > 0.05$ for all factors).

Late toxicities are shown in Table 2. Asymptomatic focal consolidation (up to local fibrosis) of uninvolved lung tissue was observed in 29 patients (27%) after 9 (4–21) months following SBRT and was graded as pneumonitis grade 1. Another 3 patients (3%) developed symptomatic pneumonitis after 12 (5–33) months requiring cortisone therapy (pneumonitis grade 2). Some amount of late chest wall pain was found in 2 patients and 1 patient suffered a rib fracture (grade 3) in the vicinity of the PTV 15 months after irradiation.

Discussion

We report herein on oncologic outcome and acute and late toxicity of a selected patient cohort with primary, inoperable stage I NSCLC treated with CyberKnife® SBRT at a single institution. With the limitation of a median follow-up of only 15 months, treatment proved to be effective in this selected group of patients with a high comorbidity rate, achieving a LC rate of 88% at 2 years, an OS of 77% at 2 years, with an overall severe late toxicity rate (grade 2–3) of 4% (4/106 patients).

While (LINAC)-based stereotactic irradiation techniques have been used in early lung cancer for many years and have been reviewed comprehensively [15–18], results of CyberKnife® SBRT in a significant number of patients have only been reported recently (Table 3; [19–24]). It seems that fractionation schemes in the range of 3 × 18–20 Gy for peripheral tumors and 4 × 12 or 5 × 8–10 Gy for central tumors or those approaching the chest wall, which were mainly developed in the LINAC-based setting, are also frequently used for CyberKnife® SBRT. The choice of these fractionation schemes is based on the observations that a biologic effective dose (BED) of more than 100–105 Gy [25–27], which these regimes achieve, have LC rates of about 90%, and that risk-adapted hypofractionation results in acceptable toxicity rates.

Compared to LINAC-based stereotactic techniques, CyberKnife® technology allows for real-time tumor tracking and highly conformal target coverage by non-isocentric, non-coplanar beam settings, thus making the use of an ITV and techniques for reducing tumor movement obsolete. Potentially, this could translate to an increased therapeutic ratio. However, it has been shown that tumor control rates depend mainly on BED, and that recurrences may continue to develop even after more than 3 years [26]. As shown in Table 3, recent results for LC rates after CyberKnife® SBRT and those of the present report are well in the range of those observed for conventional stereotactic radiotherapy [26]. Thus, with regard to LC, there is currently no evidence that CyberKnife® lung SBRT is superior to other

Table 3 CyberKnife® (Accuray, Sunnyvale, CA, USA) radiotherapy for early stage non-small cell lung cancer. Compilation of recent reports comprising more than 50 patients. The proportion of patients with centrally located tumors and the associated dose/fractionation scheme is specified where available

Author	No. of patients	Stage/tumor localization	Dose/ fractionation	Fiducials (%)	Local control	Overall survival	Toxicity
Bahig 2015 (Montreal) [19]	150	T1-2 N0 (74% peripheral, 26% central)	3 × 20/5 × 12 Gy 4 × 12.5/5 × 8–10 Gy	44	96%/2 years	87%/2 years	5/150 pneumonitis G3-5 8/150 chest wall pain 5/150 rib fractures
Heal 2015 (Philadelphia) [22]	100	T1-2 N0 73% peripheral: 27% central:	3 × 18–20 Gy 4 × 12.5/5 × 10 Gy	48	94%/2 years 84%/3 years	60%/2 years 37%/3 years	2/100 pneumonitis
Factor 2014 (New York) [21]	74	T1-2 N0 (44% peripheral, 56% central)	3 × 15–20 Gy 4 × 12 Gy	100	87%/2 years 78%/3 years	68%/2 years 48%/3 years	1/78 pneumonitis G2
Van Zyp 2009 (Rotterdam) [24]	70	T1-2 N0	3 × 15 Gy 3 × 20 Gy	100	78–96%/ 2 years	62%/2 years	3/70 pneumonitis 4/70 chest wall pain
Kelley 2015 (Huntington) [23]	67	Stage I	4 × 12 Gy	50	61%/2 years 50%/3 years	70%/2 years 60%/3 years	None
Bibault 2012 (Lille) [20]	51	T1-2 N0	3 × 20 Gy 4 × 15 Gy	0	86%/2 years	80%/2 years	6% pneumonitis G1

irradiation techniques, but a direct comparison is hampered by the variety of definitions for tumor recurrence (lesion size increase in CT only, additional PET confirmation, additional pathological confirmation, new lesions in the same lobe counting as local recurrence).

With CyberKnife® SBRT, lung toxicity (≥grade 2) usually seems not to exceed 5%. This could be a consequence of the target definition concept. While GTV–PTV margins of 5 mm (transversal) and 10 mm (craniocaudal) have been used in recent trials for LINAC-based lung SBRT [28–30], smaller margins of 3–8 mm are typical for CyberKnife® series [19–24]. In a North American phase II study on LINAC-based lung SBRT using 3 fractions of 18 Gy, the abovementioned margins resulted in a substantial number of lung toxicities (24% grade 2, 16% grade 3–4)[29]. The Radiation Therapy Oncology Group (RTOG) 0915 study [30] compared 1 × 34 Gy to 4 × 12 Gy in patients with peripheral tumors <5 cm using the same GTV–PTV margins or an ITV–PTV margin of 5 mm and observed grade 3 protocol-specific lung toxicities in 10–13%. The SPACE-trial [28] compared SBRT with 3 × 22Gy to three-dimensional conformal radiotherapy with 35 × 2Gy. In the SBRT arm, margins of 5 mm (transversal) and 10 mm (craniocaudal) were again used. SBRT led to lung fibrosis in 50% (42% grade 1, 8% grade 2) of the patients and to pneumonitis in 19% (15% grade 1, 4% grade 2). The rates of local lung fibrosis and pneumonitis of any grade are well below these figures in the present analysis and other recent CyberKnife® series and may reflect the use of smaller margins.

Another issue is the use of fiducial implants, which is more or less specific for CyberKnife® lung SBRT. The rate of fiducial use varies substantially, with ranges between 0 and 100%. This may reflect the different experiences and complication rates after fiducial implantation in different institutions [31, 32]. In the present report, only 12% of the patients had fiducials, but local tumor control did not depend on tracking mode. This is in accordance with the results of other groups who have treated 50–100% of their patients fiducial-free without compromising outcome [20, 22, 23], and who reported 2-year LC and OS rates between 64–98%.

Conclusion

In our series, we presented the results of CyberKnife® radiosurgery in early stage primary inoperable NSCLC with the adoption of a risk-based dose/fractionation scheme and demonstrated that this a safe and oncologically effective procedure which provides the chance of long-term survival without considerable treatment-related toxicity.

Compliance with ethical guidelines

Conflict of interest S. Temming, M. Kocher, E. Stoelben, L. Hagmeyer, D.-H. Chang, K. Frank, K. Hekmat, J. Wolf, W.W. Baus, R. Semrau, C. Baues, and S. Marnitz declare that they have no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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