



Heike Peulen, José Belderbos, Maddalena Rossi, Jan-Jakob Sonke

Department of Radiation Oncology, The Netherlands Cancer Institute (NKI), Amsterdam,
The Netherlands

CHAPTER 3

Mid-ventilation based PTV margins in Stereotactic Body Radiotherapy (SBRT): A clinical evaluation

Radiother Oncol. 2014 Mar;110(3):511-6.

ABSTRACT

Purpose

Large tumor motion leads to large treatment volumes with an Internal Target Volume (ITV) based approach, whereas mid-ventilation (MidV) based Planning Target Volumes (PTV) margins typically lead to smaller treatment volumes. The purpose of this study was to evaluate the MidV approach on clinical outcome data of Stereotactic Body Radiotherapy (SBRT) in NSCLC.

Methods and materials

297 patients with 314 peripheral tumors treated from 2006-2012 were retrospectively analyzed. In all patients a 4D-CT was acquired and the MidV-CT-scan was selected. Tumor amplitudes were determined in left-right (LR), cranio-caudal (CC) and anterior-posterior (AP) direction, to calculate patient specific PTV margins.

Results

The median LR, CC and AP tumor amplitudes were 2 mm (0-16 mm), 4 mm (0-39 mm) and 3 mm (0-18 mm), respectively, yielding a median CTV-to-PTV margin of 8 mm. An ITV+5 mm based PTV margin would have been bigger in 47% of the patients. After a median follow up of 22 months, local recurrence occurred in six patients (2%). Two year LC and OS were 98% and 67% respectively.

Conclusions

Using the MidV approach combined with online image guidance an excellent LC of 98% was established with SBRT. This provides clinical support that incorporating respiratory motion into the PTV margin is a safe approach.

INTRODUCTION

Stereotactic Body Radiotherapy (SBRT) has become the standard of care in inoperable stage I non small cell lung cancer (NSCLC), resulting in three year local control rates of more than 90% and low toxicity [1-2]. Recently, equivalence to surgery was demonstrated in a systematic review [3]. State of the art in SBRT includes rigorous accounting for organ motion, such as abdominal compression, breath hold techniques and the acquisition of a four dimensional (4D) planning CT scan [4-7]. A common method is to generate an Internal Target Volume (ITV) from this 4D CT to account for respiratory motion during treatment delivery [8]. The ITV concept covers the entire tumor motion and therefore effectively treats all respiration motion as a systematic error. Although the reported high local control rates support this approach [9], patients with considerable tumor motion consequently have large margins to account for geometric uncertainty, resulting in an increased exposure of normal tissue to high doses. An alternative approach is to plan on the mid-ventilation (MidV) CT (frame of the 4D CT with the tumor closest to its time-weighted mean position) and use a Clinical Target Volume (CTV) to Planning Target Volume (PTV) expansion based on a margin recipe, to simultaneously account for respiratory motion and other geometrical uncertainties [10]. Wolthaus *et al.* compared different strategies to use 4D CT in treatment planning in 45 patients with a mean cranio-caudal tumor motion of 12 mm [11]. With an on-line set-up correction protocol the ITV approach led to a 33% relative volume increase of the PTV compared with the time averaged mean position approach. The purpose of this study was to evaluate the MidV approach on clinical outcome data.

MATERIALS AND METHODS

Patient population

Two hundred and ninety seven patients with 314 tumors treated with SBRT between June 2006 and May 2012 were analyzed. Patient characteristics are summarized in Table 1. All patients had peripherally localized lung tumors with a diameter <5 cm in accordance with RTOG criteria [12]. In patients with a contra-indication for a transthoracic puncture, an FDG PET-positive and growing lesion was accepted for treatment [13]. All patients were staged with a diagnostic FDG PET-CT scan. The majority of the patients had T1 tumors (83%), predominantly localized in the upper lobe (70%). Tumors were biopsy proven in 42%, with adenocarcinoma in 15%, squamous cell carcinoma in 14% and large cell carcinoma in 12%. At least 280 patients were diagnosed with stage I NSCLC. Seventeen patients had a synchronous or metachronous presentation of a second primary lung tumor or metastases (no differentiation possible). Of these patients, nine were treated simultaneously on both tumors and eight patients received SBRT with a median interval of 18 months (range 4-45 months).

Table 1. Patient characteristics

	N	%	Median (range)
Gender	297		
Male	162	52	
Female	135	43	
Age (y)			74 (42-91)
Tumors	314		
T1	262	83	
T2	52	17	
Biopsy proven			
Yes	132	42	
No	182	58	
Histology			
Adenocarcinoma	48	15	
Squamous cell	45	14	
Large cell	38	12	
NOS	2	1	
Volume (cm ³)			
GTV			5.6 (0.3-63)
PTV			34.8 (2.3-183)
Lobe			
LUL	100	32	
LLL	32	10	
RUL	120	38	
RML	9	3	
RLL	53	17	

NOS= not otherwise specified, GTV=Gross Tumor Volume, PTV=Planning Target Volume, LUL=left upper lobe, LLL=left lower lobe, RUL=right upper lobe, RML=right middle lobe, RLL=right lower lobe.

Acquisition of respiration-correlated 4D CT

Before treatment planning, a 4D CT was acquired for all patients. Patients were scanned during free breathing. The respiratory signal was registered using a thermocouple inserted into the entry of a regular oxygen mask, which measures temperature changes in the airflow during breathing. After tumor motion trajectory analysis, a single 3D CT-scan was reconstructed from the 4D CT data set, with the tumor closest to its time-weighted mean position for target definition and treatment planning. From August 2011 we replaced the MidV CT by the mid-position (MidP) CT because of better image quality [11]. The MidP concept is a refinement of the MidV concept, which generates a motion compensated CT scan from

the 4D CT data set and comprises all the internal structures in their time-weighted mean position over the respiratory motion. The tumor peak-to-peak amplitude was measured in left-right (LR), cranio-caudal (CC) and anterior-posterior (AP) direction. From these data an amplitude vector length was calculated, that we from now on refer to as “amplitude vector” in our analysis.

Tumor delineation and margins

The GTV was delineated on the MidV or MidP scan in lung window level setting. There was no additional margin for CTV. Expansions from CTV to PTV were based on the margin recipe of van Herk et al. [14] and have previously been described in detail by our group [15]. In brief, margins consist of two components: a margin for treatment preparation (systematic) errors and a margin to compensate for the blurring of the cumulative dose due to treatment execution (random) variation (set-up, breathing). The former component is larger than the latter. Moreover, errors are summed up quadratically and not linearly as opposed to the ITV approach. With this recipe, margins were calculated and tabulated in LR, CC and AP directions and applied according to the patient specific individual tumor amplitudes. Generally margins were in the order of 8 mm in CC and LR direction and 9 mm in AP direction (Figure 1), the latter being slightly larger than the CC margin due to more intrafraction variability. A schematic overview of an example patient is given in Figure 2.

Treatment planning and delivery

All patients were scanned and treated frameless in supine position using an arm and knee support. Treatment plans were optimized in Pinnacle version 7.4-9.2 (Philips, Best, The Netherlands) and consisted of static Intensity Modulated Radiotherapy (IMRT) using a predefined class solution of in total 15 coplanar and non-coplanar beams. The prescription isodose line encompassed 95% of the PTV and dose inhomogeneity with a maximum of 165% of the prescribed dose was allowed. From 2010 onwards patients were treated with Volumetric Modulated Arc Therapy (VMAT) using a dual arc technique. All tumors were treated with 3x18 Gy with a maximal overall treatment time of eight to ten days. Patient set up was verified using a 3D or 4D Cone Beam CT (CBCT), the latter being applied in case the tumor amplitude on the planning CT-scan was ≥ 8 mm. Tumor alignment started with a bone match and was followed by a tumor match. Couch shifts were verified with a second CBCT. Intrafraction tumor motion was monitored at first with a post treatment CBCT or (starting from September 2010) an inline CBCT concurrent with VMAT delivery.

Follow up

Patients were followed up according to a standardized scheme, with the first CT-thorax four months after SBRT, thereafter every six months during two years, followed by a yearly CT-thorax up to five years. In case of suspicion of a local recurrence an FDG PET-CT scan was performed and if indicated and judged feasible, pathological confirmation was obtained.

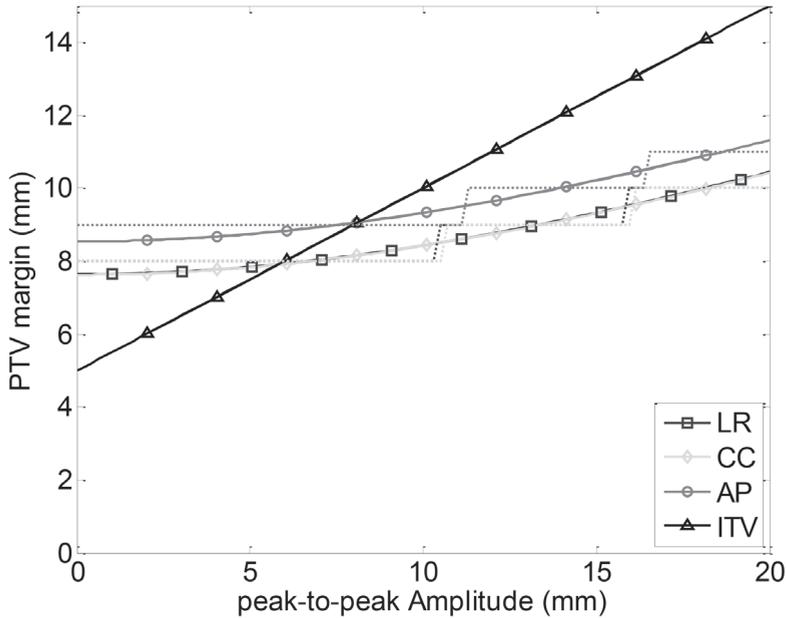


Figure 1. Mid-ventilation based PTV margins in left-right (LR), cranio-caudal (CC) and anterior-posterior (AP) direction. In solid the calculated margin and in dashed the applied margin (rounded to the nearest mm) for SBRT in lung cancer. Note that CC en LR margins are nearly identical. The ITV based PTV margin is estimated by a 5 mm margin + 50% of the tumor amplitude. The MidV based PTV is only modestly influenced by respiratory amplitude.

Definition of local recurrence

The definition of local recurrence after SBRT is not straightforward. Although any in lobe failures in most surgical series are considered local recurrences, it seems counter intuitive to score a small nodule detected during follow up with e.g. a distance of 7 cm from the former GTV, as a “true” local recurrence. Therefore, we choose to apply a more specific description of local recurrence: a growing mass in the same lobe within 3 cm distance of the GTV on CT-scan. In addition, if pathological proof could not be obtained pathological increased FDG PET uptake should be present.

Statistical analysis

Follow up was calculated starting from the first day of treatment until the last day of follow up or death, with a minimal follow up of six months. Overall survival and local recurrence free survival were calculated using the Kaplan Meier method. Since 17 patients had metachronous or synchronous disease, overall survival was analyzed per patient using the start date of the first treatment as entry point. Local recurrence free survival was analyzed per tumor and censored by last date of CT-thorax or X-thorax. Differences between GTV and amplitude vector in tumors with or without local recurrences were calculated using the Mann-Whitney

Schematic overview of mid-ventilation based PTV margins of an example patient

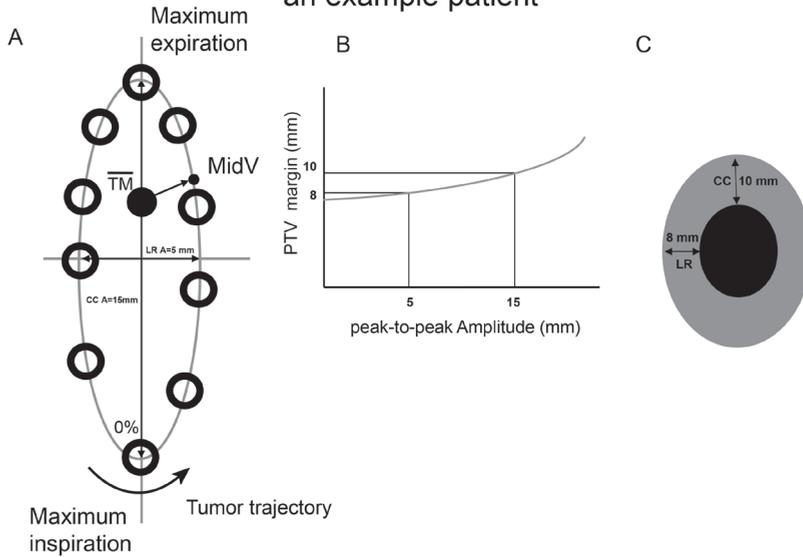


Figure 2. A: Peak-to-peak tumor amplitude (A) is measured in left-right (LR), crano-caudal (CC) and anterior-posterior (AP) direction (latter not shown). Selection of the single appropriate CT-scan of the 4D CT, closest to the time weighted mean position of the tumor (= TM). B: (anisotropic) Margin using the margin recipe taken into account the peak-to-peak tumor amplitude (A) in LR, CC, AP direction (latter not shown). C: GTV= black PTV=grey using MidV based margins.

test. A Cox-regression univariate analysis was performed to test if GTV and amplitude vector were predictive for local failure as continuous variables. Amplitude vector was further explored with a cut-off point based on ROC-analysis. The level of (two-tailed) statistical significance was set at 0.05.

RESULTS

After a median follow up of 21.9 months local recurrence occurred in six patients (2%) with a range of 4-39 months post SBRT. Local control was assessed by CT-thorax in 280 patients (89%), CT-PET in 8 patients (3%) and X-thorax in 26 patients (8%), with the latter occurring most frequently in the early cohort. Eight patients (3%) were lost to follow up. In two patients pathological confirmation of a recurrence was obtained. In four patients a growing mass on CT-scan was suspicious for a local recurrence and in two of these patients an additional FDG PET-CT was performed showing maximum Standardized Uptake Values (SUVmax) of 4.4 and 10.9. Pathological proof of recurrence was not obtained in these four patients due to poor pulmonary function or poor performance score and hence lack of treatment consequences.

Five patients had a recurrence within the same lobe, with at least 5 cm distance from the former GTV. These patients were therefore scored as a regional instead of local failure and thus not included in the subsequent analysis. Isolated regional lymph node failure occurred in six patients (2%). Two year local control was 98% (1 standard error (SE) = 1%). One and two year overall survival were 85% (1SE=2%) and 67% (1SE=3%) respectively. For all tumors the median LR, CC and AP amplitudes were 2 mm (range 0-16 mm), 4 mm (range 0-39 mm) and 3 mm (range 0-18 mm), respectively. The median amplitude vector was 6.5 mm (range 0-39 mm) for all tumors as well as for the locally controlled tumors. In case of local recurrence, the median amplitude vector was significantly *smaller*: 3.0 mm (range 1-8.1 mm) ($p=0.04$). In patients with a local recurrence the median GTV was significantly larger with a volume of 16.0 cm^3 (range $2.1\text{-}57.6 \text{ cm}^3$) ($p=0.04$). In univariate continuous Cox-regression analysis GTV was predictive for local recurrence ($p<0.001$ and $HR=1.08$). Amplitude vector was borderline significant ($p=0.08$ and $HR=0.77$). ROC analysis revealed an optimal cut-off for amplitude vector of 3.5 mm. Additional Cox-regression was significant for LR ($p=0.02$ $HR=0.13$).

In Figure 3 and 4 the local control and overall survival curves are split according to tumor amplitude vector with a cut-off point at 6.5 mm. Two year local control rates for amplitude vector <6.5 mm were 96% (SE=2%) and 99% (SE=1%) for amplitude vector ≥ 6.5 mm. Values for two year overall survival were 68% (SE=5%) and 65% (SE=4%) respectively. Due to the low number of events a non-inferiority test was not performed.

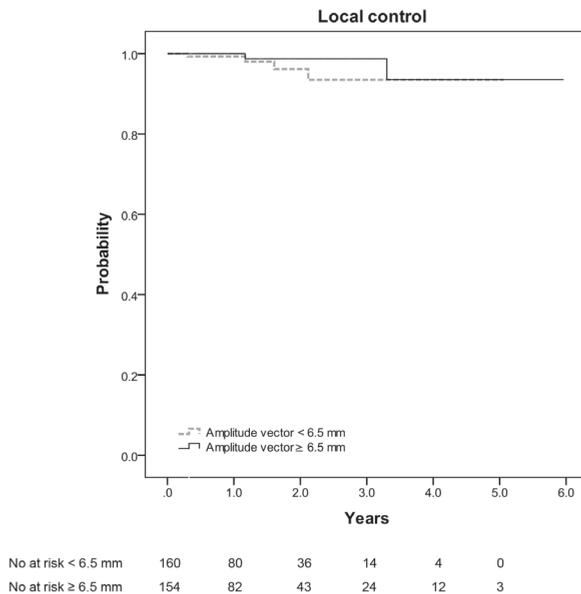


Figure 3. Local control analyzed per tumor according to respiratory tumor amplitude vector.

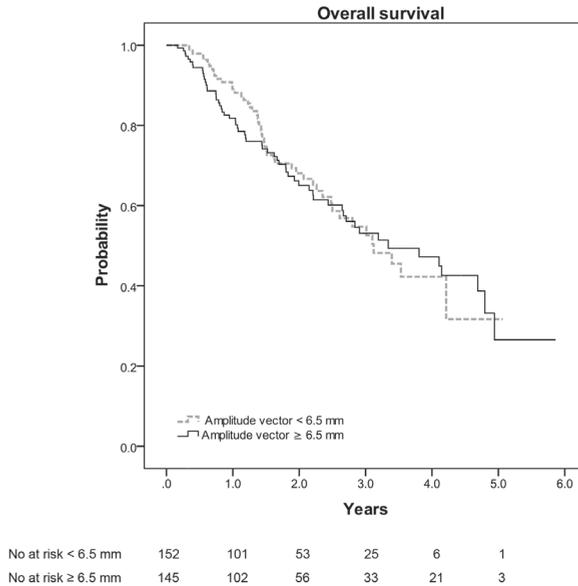


Figure 4. Overall survival analyzed per patient according to respiratory tumor amplitude vector.

DISCUSSION

In this large patient cohort, we reported an excellent local control of 98% using the MidV based PTV margin approach combined with online image guided SBRT in early stage lung cancer.

Our data showed that there were more local recurrences if the vector amplitude was smaller than 3.5 mm. However, we do not have a good explanation for this counter-intuitive observation.

The median tumor amplitude vector of 6.5 mm roughly reflects the cut-off point from which the ITV approach results in larger PTV margins compared with our MidV based approach (Figure1). Assuming that 50% of the tumors were “potentially at risk” of developing a local recurrence, smaller margins did not influence local control and overall survival if the tumor amplitude vector was ≥ 6.5 mm. However, since this study was a retrospective analysis and not designed as an equivalence study, p-values of the subgroup analysis in Figure 3 and 4 were precluded and conclusions should be drawn with caution.

Note that our “baseline” margins at 0 mm respiratory amplitude were somewhat larger than those frequently used with an ITV based approach. Consequently, in 47% of the cases studied

in this paper an ITV based PTV margin would be bigger than the MidV approach in at least one direction (assuming an ITV-to-PTV margin of 5 mm).

Our reported local control rate is high with a median follow up of 22 months, but not exceptional compared to others that reported two year local control rates in the range of 90-97% [1,9,16]. Since local recurrences may occur beyond five years of follow up, our local control rate may decrease with longer follow up [17].

Diagnosis of a local relapse is challenging and pathological proof of recurrence was obtained in only two out of six patients. Computed tomography based anatomic assessment is known to overestimate local recurrence [18-19]. Tools are being developed to distinguish local recurrence from fibrosis in salvage candidates [20-21]. A strong point of this analysis is that local control was assessed by CT-scan or PET-scan in more than 90% of the patients. In some patients only a recent X-thorax was available, which was mostly performed in referring hospitals. Fifty % of the patients had a follow up of at least 22 months and only eight patients (3%) were lost to follow up, diminishing the chance of potential miss of events.

Since only six patients experienced a local recurrence, the statistical power was low to detect potential predictive factors. Not surprisingly, GTV was found to be predictive for local recurrence [1,22]. In literature another predictor for local recurrence is the biological effective dose (BED) with a threshold dose of ≥ 100 Gy [16,22]. Since all patients in this study cohort were treated with 3x18 Gy corresponding to a BED_{10} of 151 Gy, our local control rate was not influenced by treatment dose.

In case of large tumor motion use of the ITV margin results in a significantly larger PTV compared to our MidV based PTV margin, provided that other geometrical uncertainties are accounted for in a similar way [11]. Other strategies to limit the PTV, such as gating, breath hold techniques and abdominal compression [5,7,23], have the disadvantage of being technically challenging and introducing patient discomfort during treatment, especially for medically inoperable lung cancer patients with compromised pulmonary function. Our method is very easy to use in the clinic, however the method to derive the MidV or MidP scan is unfortunately not yet commercially available.

Reduction of the PTV translates into less normal tissue exposure to high doses, potentially leading to decreased toxicity. Generally, toxicity in lung SBRT is low [22]. Therefore, a clinical relevant decrease in toxicity for small peripheral tumors is questionable. However, this effect may be more pronounced in “high risk” treatments that are currently being investigated, such as larger tumor volumes, tumors closely related to mediastinal structures or reirradiations. Another potential gain of margin reduction is the increase of the number of patients eligible for SBRT, who would have been otherwise declined due to normal tissue constraints. Currently

we are treating patients with SBRT on peripheral tumors larger than 5 cm in a mean-lung dose escalation trial, called the “VOLUMES trial” (NCT01543672).

The margins we describe in this manuscript are about 2 mm larger than the originally published paper by Sonke et al. [15]. The currently applied margins were based on an early subgroup analysis with more variation than the large cohort described in this paper. Margins were not decreased at that time, because of the low incidence of toxicity. However with a local control rate of 98%, we updated our margins based on the cohort in this paper. This revealed a decrease of margin in CC and LR with 3 mm and AP with 4 mm, resulting in a baseline margin of 5 mm in all directions. We will adopt these margins in clinic soon.

Limitations of this study are that we did not describe our toxicity results. This has been reported previously in a collaborative analysis [22], with overall low toxicity. Moreover, about 60% of our patient did not have pathological proof of disease. Instead, a growing mass on CT-scan or X-thorax and pathological increased FDG PET uptake was used [13], which has shown not to influence locoregional control and survival outcomes [22,24].

Our BED_{10} largely exceeds 100 Gy and one could argue that our high dose compensates for the small margins in patients with large amplitudes. If smaller margins are used to account for geometrical uncertainties, such as set-up error, intra- and interfraction variability and delineation variability, there is a higher risk of tumor miss. We do not know whether the same local control would hold true for treatment schedules with lower BED. Due to the low toxicity profile of our treatment schedule [22], our strategy of optimizing the trade-off between tumor control probability (TCP) and normal tissue complication probability (NTCP) in “high risk” treatments would be to first decrease margins as described above and second consider decreasing fraction size in the context of a clinical trial.

The high local control and thus low number of events limit the statistical power of this study. Although it therefore does not provide a rigorous statistical prove of the validity of the MidV approach, it comprises a clinical demonstration of the safety of this approach for a widely adopted SBRT fractionation scheme.

In conclusion, with the MidV approach combined with online image guidance an excellent 2 year local control of 98% using SBRT in early stage lung cancer was established. This provides clinical support to incorporate respiratory motion directly into the PTV instead of using an ITV concept, leading to a margin reduction in case of large tumor motion with potential toxicity reduction and increasing the numbers of patients eligible for SBRT. Further research is warranted to support this conclusion.

Acknowledgments

This work is supported by a research grant from the Dutch Cancer Society (NKI 2009-4568). We thank Wilma Heemsbergen for her support with the statistical analysis.

REFERENCES

- [1] Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290-3296.
- [2] Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010;28:5153-5159.
- [3] Solda F, Lodge M, Ashley S, Whittington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; Systematic review and comparison with a surgical cohort. *Radiother Oncol* 2013;109:1-7.
- [4] Ford EC, Mageras GS, Yorke E, Ling CC. Respiration-correlated spiral CT: a method of measuring respiratory-induced anatomic motion for radiation treatment planning. *Med Phys* 2003;30:88-97.
- [5] Lax I, Blomgren H, Naslund I, Svanstrom R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* 1994;33:677-683.
- [6] Onishi H, Kuriyama K, Komiyama T, et al. Clinical outcomes of stereotactic radiotherapy for stage I non-small cell lung cancer using a novel irradiation technique: patient self-controlled breath-hold and beam switching using a combination of linear accelerator and CT scanner. *Lung Cancer* 2004;45:45-55.
- [7] Wulf J, Hadinger U, Oppitz U, Olshausen B, Flentje M. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. *Radiother Oncol* 2000;57:225-236.
- [8] Rietzel E, Liu AK, Doppke KP, et al. Design of 4D treatment planning target volumes. *Int J Radiat Oncol Biol Phys* 2006;66:287-295.
- [9] Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;70:685-692.
- [10] Wolthaus JW, Schneider C, Sonke JJ, et al. Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. *Int J Radiat Oncol Biol Phys* 2006;65:1560-1571.
- [11] Wolthaus JW, Sonke JJ, van Herk M, Damen EM. Reconstruction of a time-averaged midposition CT scan for radiotherapy planning of lung cancer patients using deformable registration. *Med Phys* 2008;35:3998-4011.
- [12] Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833-4839.
- [13] Herder GJ, van Tinteren H, Golding RP, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. *Chest* 2005;128:2490-2496.

- [14] van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47:1121-1135.
- [15] Sonke JJ, Rossi M, Wolthaus J, van Herk M, Damen E, Belderbos J. Frameless stereotactic body radiotherapy for lung cancer using four-dimensional cone beam CT guidance. *Int J Radiat Oncol Biol Phys* 2009;74:567-574.
- [16] Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94-100.
- [17] Matsuo Y, Shibuya K, Nagata Y, et al. Preliminary report of late recurrences, at 5 years or more, after stereotactic body radiation therapy for non-small cell lung cancer. *J Thorac Oncol* 2012;7:453-456.
- [18] Matsuo Y, Nagata Y, Mizowaki T, et al. Evaluation of mass-like consolidation after stereotactic body radiation therapy for lung tumors. *Int J Clin Oncol* 2007;12:356-362.
- [19] Takeda A, Kunieda E, Takeda T, et al. Possible misinterpretation of demarcated solid patterns of radiation fibrosis on CT scans as tumor recurrence in patients receiving hypofractionated stereotactic radiotherapy for lung cancer. *Int J Radiat Oncol Biol Phys* 2008;70:1057-1065.
- [20] Huang K, Dahele M, Senan S, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR)—can we distinguish recurrence from fibrosis? A systematic review of the literature. *Radiother Oncol* 2012;102:335-342.
- [21] Huang K, Senthil S, Palma DA, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. *Radiother Oncol* 2013;109:51-57.
- [22] Grills IS, Hope AJ, Guckenberger M, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. *J Thorac Oncol* 2012;7:1382-1393.
- [23] Keall P. 4-dimensional computed tomography imaging and treatment planning. *Semin Radiat Oncol* 2004;14:81-90.
- [24] Verstegen NE, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. *Radiother Oncol* 2011;101:250-254.