

**STEREOTACTIC RADIOTHERAPY FOR
STAGE I NON-SMALL CELL LUNG CANCER
USING REAL-TIME TUMOR TRACKING**

Noëlle van der Voort van Zyp

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**Stereotactic Radiotherapy for Stage I Non-Small Cell
Lung Cancer using Real-Time Tumor Tracking**

**Stereotactische radiotherapie met
“real-time tumor tracking” voor het stadium I
niet-kleincellig longcarcinoom**

Proefschrift

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Promotor: Prof. dr. P.C. Levendag
Overige leden: Prof. B.J.M. Heijmen
Prof. dr. J.P. van Meerbeeck
Prof. dr. E.M. Noordijk
Copromotor: Dr. J.J. Nuyttens

Aan mijn ouders

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CHAPTER 1

INTRODUCTION

Introduction

Lung cancer is the most commonly diagnosed cancer world-wide (1.61 million; 12.7% of the total) and also the leading cause of cancer death (1.38 million; 18.2% of the total) (1). In the Netherlands, lung cancer was diagnosed in almost 11,000 patients in 2007 (website Netherlands Cancer Registry; www.ikcnet.nl). The majority of these patients (77%) have non-small cell lung cancer (NSCLC) and of these patients approximately 20% present with a resectable tumor (website Netherlands Cancer Registry; www.ikcnet.nl). Although surgery is the treatment of choice for patients with resectable tumors, many patients are inoperable due to smoking-related comorbidity. These patients were commonly treated with conventional radiotherapy (≥ 60 Gy in 2 Gy fractions), but the results were disappointing (51% local tumor control rate and a 15% survival rate at 5 years) (2, 3). Stereotactic body radiotherapy (SBRT) is an alternative treatment currently used for inoperable patients with stage I NSCLC. SBRT delivers a high radiation dose to the tumor in a small number of fractions over a short overall treatment time (typically 48-60 Gy in 3-6 fractions). Although the total dose may seem equal to that in conventional radiotherapy, the high dose per fraction of SBRT (20 Gy versus 2 Gy) is biologically more potent. Thus the biological effective dose (BED) is greater in SBRT than in conventional radiotherapy (BED >100 Gy versus 60 Gy).

Stereotactic body radiotherapy enables the delivery of high radiation doses to the tumor while restricting the dose to healthy tissues as 1) the radiation dose distribution conforms to the tumor shape and has a steep dose fall off and 2) geometric uncertainties in tumor targeting are reduced so that a smaller “safety” margin of healthy tissue is irradiated. In conventional radiotherapy a large safety margin of healthy tissue is typically irradiated to account for variations in patient set-up and tumor delineation, but also to account for tumor motion. Technical advances in SBRT have reduced geometrical uncertainties. The accuracy of patient set-up has been improved by the development of in-room imaging modalities such as stereoscopic x-ray systems or linac-integrated cone beam CT-scans (kV or MV). These modalities allow patient set-up to be based on images of the tumor position, or structures located near the tumor rather than on external skin-marks. Another challenging source of geometric uncertainty especially relevant to SBRT is tumor motion in the lung. Different approaches have been used to account for tumor motion including 1) the use of individualized margins to account for patient specific tumor motion, 2) breath-holding 3) abdominal compression 4) respiratory gating and 5) real-time tumor tracking. Breath-holding and abdominal compression both aim to reduce the extent of tumor motion. During respiratory

gating, radiation exposure is limited to a part of the breathing cycle. During real-time tumor tracking, the radiation beam follows the movement of the tumor and irradiates the tumor throughout the breathing cycle.

At the Erasmus Medical Center in Rotterdam the CyberKnife real-time tumor tracking system was used to treat patients with stage I NSCLC. The CyberKnife is a frameless stereotactic radiotherapy system that involves a light-weight 6 MV linear accelerator mounted on a highly mobile robotic arm and a real time image guidance system (Figure 1). The image guidance system consists of stereoscopic kV x-ray sources and a synchrony camera that records the motion of red-light emitting diodes attached to the patient's chest. The CyberKnife real-time tumor tracking system corrects for tumor motion by repositioning the radiation beam to the position of the moving tumor. As the tumor is not often directly visible during treatment, radio-opaque markers are inserted in or near the tumor and act as surrogates for tumor position. These markers can be placed via bronchoscopy, via the percutaneous

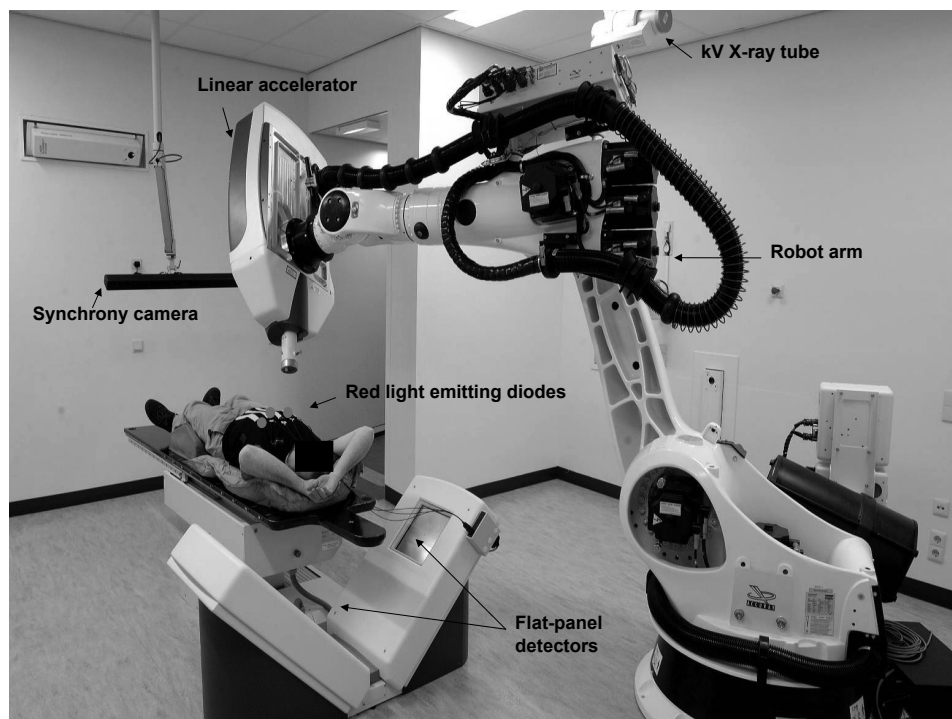


Figure 1. The CyberKnife real-time tumor tracking system.

intrapulmonary approach or via the vascular approach using embolisation coils. The location of these implanted markers is determined by a series of kV stereoscopic x-ray images taken during respiration. At the same time, motion of red-light emitting diodes on the patient's chest is registered and correlated to the location of the implanted markers. The resulting correspondence model is used to move the robot arm and direct the radiation beam at the moving tumor.

Aim of this thesis

As the position of radio-opaque markers are used to direct the radiation beam at the tumor, accurate delivery of radiation is only possible if the position of the markers relative to the tumor is stable. A concern regarding tumor localization is that markers may migrate from their initial position, or that the surrounding tissues may swell or deform during treatment. In **chapter 2** we determined the stability of markers placed in or near the lung tumor via the percutaneous intrapulmonary approach. In addition we assessed whether a change in distance between markers is a reliable check for displacement of the center of mass of the marker configuration relative to the tumor position.

In **chapter 3** we evaluated the clinical outcome of SBRT using real-time tumor tracking in stage I NSCLC patients. The local tumor control rate, overall survival, treatment related toxicity and toxicity related to marker placement were determined. These treatment outcomes were compared to those achieved using other SBRT techniques. **Chapter 4** focuses on the clinical outcome of SBRT in octogenarians with stage I NSCLC. As life expectancy increases, more octogenarians will present with stage I NSCLC. Merely carefully selected subsets of octogenarians are treated with surgery, and the postoperative morbidity and mortality are not negligible (4-6). Therefore it is of great interest to determine the outcome of SBRT in octogenarians.

Although local tumor control rates above 90% have been achieved in stage I NSCLC patients treated with SBRT (7-9), an equally important aim is to maintain or improve the patient's quality of life. Given the high level of comorbidity in many patients with NSCLC and the limited overall survival, we assessed the impact of SBRT on the patient's quality of life in **chapter 5**.

Lastly **chapter 6** considers the clinical implementation of the more accurate Monte Carlo dose calculation algorithm. Unlike the equivalent pathlength algorithm (EPL), Monte Carlo dose calculation accounts for decreased attenuation of the primary photon beam in low density lung tissue but also for the increased electron range. For this reason, doses to the planning target volume and organs at risk are lower for Monte Carlo than for EPL calculation. To enable treatment planning using the more accurate Monte Carlo dose calculation algorithm in the future, we compared dose distributions calculated with EPL and MC and proposed a MC prescription dose according to tumor size and location.

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CHAPTER 2

STABILITY OF MARKERS USED FOR REAL-TIME TUMOR TRACKING AFTER PERCUTANEOUS INTRA-PULMONARY PLACEMENT

NC van der Voort van Zyp, MS Hoogeman, S van de Water,
PC Levendag, B van der Holt, BJM Heijmen, JJ Nuytens

Abstract

Purpose

To determine the stability of markers used for real-time tumor tracking after percutaneous intrapulmonary placement.

Methods

Forty-two patients with 44 lesions, 111 markers and ≥ 2 repeat CT-scans were studied. The tumor in repeat CT-scans was registered to the tumor in the planning CT-scan. Next, the three-dimensional marker coordinates were determined on the planning CT-scan and the repeat CT-scans. Marker stability was analysed by the displacement of markers and the displacement of the center of mass (COM) of marker configurations. In addition, we assessed the reliability of using inter-marker distance as a check for displacements in the COM of the marker configurations.

Results

Median marker displacement was 1.3 mm (0.1-53.6 mm). Marker displacement exceeded 5 mm in 12% of markers and 10 mm in 5% of markers. Causes of marker displacement >5 mm were marker migration (2 of 13) and target volume changes (5 of 13). Non-synchronous tumor and marker movement during breathing may be responsible for displacements >5 mm in the other 6 of 13 markers. Median displacement in the COM of marker configurations was 1.0 mm (0.1-23.3 mm). Displacements in the COM of marker configurations ≥ 2.0 mm were detected by changes in the inter-marker distance of >1.5 mm in 96% of treatment-fractions.

Conclusion

The median marker displacement was small (1.3 mm). Nevertheless, displacements >5 mm occurred in 12% of the markers. Therefore, we recommend the implantation of multiple markers as multiple markers will enable a quick and reliable check for marker displacement by determining the change in the intermarker distance. A displacement in the COM of the marker configuration of ≥ 2.0 mm was almost always detected (96%) by a change in the distance between the markers of >1.5 mm. This enabled the displaced marker to be disabled, such that tumor localization was not compromised.

Introduction

Stereotactic body radiotherapy (SBRT) delivers escalated doses to the tumor using tight margins and a highly conformal dose distribution. As such, accurate tumor localization is required to prevent under dosage of the tumor or over dosage of the organs at risk. Several approaches can be used to localize the tumor during SBRT. These approaches include the use of cone-beam computed tomography (CBCT) imaging, electronic portal imaging and stereoscopic kilovoltage x-ray imaging. As electronic portal imaging and stereoscopic kilovoltage x-ray imaging rarely allow direct tumor localization, a surrogate is often required to determine the three-dimensional tumor location. Surrogates such as the bony anatomy or the position of anatomic landmarks (carina/diaphragm) can be used depending on the tumor site and location. The use of these surrogates to determine tumor position may however be inaccurate due to intra-fraction and inter-fraction variations in the relationship between surrogate structures and the tumor (1). A more direct way to detect tumor position is the use of markers implanted in or near the tumor.

At our institute, implanted markers are often used as a surrogate for the position of stage I non-small cell lung cancer (NSCLC) tumors during CyberKnife stereotactic radiotherapy. In order to accurately target the tumor, it is essential that the position of the implanted markers remains stable relative to the position of the tumor. Concerns regarding tumor localization based on implanted markers are that markers may migrate from their initial position, or that the surrounding tissues may swell or deform during treatment.

Two studies previously examined the stability of implanted markers during treatment. The first study assessed the stability of 1.5 mm gold markers implanted via bronchoscopy in 11 patients (2). These 11 patients had been selected from a total of 57 patients, and did not include those patients in whom markers were displaced after bronchoscopy but before the first fraction of radiotherapy. The second study examined the stability of a 2.0-cm long marker placed in the lung tumor via bronchoscopy in 8 patients and via the percutaneous intrapulmonary approach in 15 patients (3). Similar to this second study, we also placed markers via the percutaneous intrapulmonary approach. However, we used a smaller 4.0-mm long platinum marker and multiple markers were placed for the majority of tumors. The toxicity related to percutaneous implantation of the 4.0 mm platinum markers has been reported previously (4, 5). The aim of the present study was to determine the stability of the 4.0 mm platinum markers placed via the percutaneous intrapulmonary approach in 42 patients. In addition to

this, we assessed whether a change in distance between markers is a reliable check for the displacement of the COM of the marker configuration relative to the tumor.

Methods

Patient selection and marker placement

Patients were included in this study if markers were placed via the percutaneous intrapulmonary approach. Percutaneous intrapulmonary marker placement was performed under local anaesthesia by an experienced radiation oncologist or an intervention radiologist. An eighteen gauge needle was used to place markers in or near the tumor under fluoroscopic-, CT- or ultrasound guidance. Ideally three platinum markers were placed. The smooth markers were 4.0 mm long and had a diameter of 0.9 mm. Markers were manufactured in house using platinum-thread delivered by Drijfhout, Amsterdam. As percutaneous marker placement may be complicated by a pneumothorax or haemorrhage, two anteroposterior chest radiographs were made; one directly after the procedure, and one an hour later.

Approximately one week after marker placement, an exhale breath-hold treatment planning CT-scan was made. The planning CT-scan had a slice thickness and spacing of 1.5-2.0 mm. Details concerning treatment planning have been described previously (6). Briefly, the gross tumor volume (GTV) was contoured using lung window. Planning target volume (PTV) = GTV + 5 mm. Patients with peripheral tumors were treated with 3 x 20 Gy. Patients with central tumors (7) were treated with 6 x 8 Gy if the tumor was located near the oesophagus or 5 x 12 Gy for all other central tumors.

Registration of Repeat CT-scans

During the treatment course, repeat CT-scans were made using the same settings as the planning CT-scan (exhale breath-hold). Repeat CT-scans were made prior to each treatment fraction in patients with peripheral tumors (repeat CT-1, CT-2 and CT-3); and prior to the first, third and last treatment fraction (repeat CT-1, CT-2 and CT-3) in patients with central tumors. For the purpose of this study, we registered the tumor in the repeat CT-scans to the tumor in the planning CT-scan. A two step-approach was used for registration; first an automated registration was performed on a region of interest including the gross tumor volume (GTV) and a minimal volume of surrounding normal lung tissue. The cost function of the registration used the root-mean-square difference in grey values as a metric. The

registration included both translations and rotations (figure 1). The second step involved a visual check of each registration based on reference structures in or near the tumor (bronchial trees or pulmonary vessels). The uncertainty related to the registration of the CT-scans was expected to be approximately 0.75-2.0 mm. Once the CT-images had been registered, we determined the three-dimensional coordinate of each marker on the planning CT-scan and the corresponding marker coordinate on the repeat CT-scan.

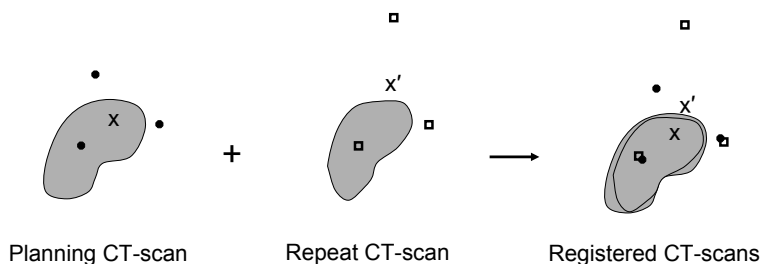


Figure 1. Registration of the planning CT-scan and the repeat CT-scan. The markers are represented by black dots in the planning CT-scan and open squares in the repeat CT-scan. The center of mass of the marker configuration is indicated by an X in the planning CT-scan and X' in the repeat CT-scan.

Marker stability assessment

Marker stability was first assessed by the displacement of individual markers. The displacement of an individual marker was defined by the vector connecting the marker coordinate in the planning CT-scan and the corresponding marker coordinate in the repeat CT-scan. If individual markers were displaced by >5.0 mm, we visually inspected the CT-registrations to examine the cause of marker displacement. Marker displacement was compared 1) for markers placed in the tumor versus outside the tumor, and 2) for markers of central tumors versus peripheral tumors. We also evaluated whether marker displacement was affected by the time between the planning CT-scan and the repeat CT-scans.

Next, marker stability was assessed by the displacement of the COM of the marker configuration. This was done because CyberKnife tumor localization is based on the COM of the marker configuration. First, the COM of the marker configuration was determined on the planning CT-scan and on the repeat CT-scans by calculating the average of the individual marker coordinates on these CT-scans. Next, the displacement of the COM coordinates of the marker configuration was determined by calculating the vector between the COM coordinates on the planning CT-scan and the repeat CT-scan.

Finally, we assessed whether a change in distance between markers could reliably detect a displacement of the marker configuration relative to the tumor. Patients with at least two markers were included in this analysis. As a quality assurance check, the CyberKnife tumor tracking system generates a warning if the distance between markers has deviated by >1.5 mm from the reference configuration in the planning CT-scan. This warning allows the physician to identify and disable the displaced marker or to increase the tolerated deviation from 1.5 mm to a maximum of 5.0 mm. We determined whether a relevant displacement in the COM of the marker configuration (≥ 2.0 mm) was accompanied by a change in the distance between markers of >1.5 mm. A displacement in the COM of the marker configuration of ≥ 2.0 mm was considered relevant. This value (≥ 2.0 mm) was chosen to account for the uncertainty related to the registration of the CT-scans. Marker COM displacements of ≥ 2.0 mm were also considered clinically relevant because 2.0 mm has been used for other uncertainties such as the respiratory tumor tracking uncertainty (determined largely by the correlation model error). The respiratory tumor tracking error was 1.2 mm (vector of the mean correlation model error) (8).

Statistical Analysis

Multi-level mixed-effects linear regression was used to evaluate the association between marker displacement and 1) the location of the marker (inside versus outside the tumor), 2) the location of the tumor (peripheral versus central) and 3) the time between the repeat CT-scan and the planning CT-scan. All p-values are two-sided, and a significance level $\alpha = 0.05$ was used.

Results

Patient selection

Thirty-eight patients with 40 tumors had three repeat CT-scans while four patients with four tumors had two repeat CT-scans. The average time between marker placement and the planning CT-scan was 9 ± 4 days (range: 3-26 days). The average time between the planning CT-scan and the repeat CT-scan was 8 ± 3 days for CT-1, 11 ± 3 days for CT-2 and 14 ± 4 days for CT-3. One-hundred and eleven markers were placed in total and 80% of the tumors (35/44) had two or more markers placed either in or near the tumor. None of the implanted markers were coughed-up between implantation and the planning CT-scan. Patient, tumor and marker characteristics are listed in table 1.

Table 1. Patient and tumor characteristics.

Gender	
Male	32
Female	10
Tumor size (cm)	
mean	4.2
range	1.0-10.5
Tumor location	
Right upper lobe	11 (25%)
Right middle lobe	5 (11%)
Right lower lobe	9 (20%)
Left upper lobe	13 (30%)
Left lower lobe	6 (14%)
Peripheral tumor location	31 (70%)
Central tumor location	13 (30%)
Markers detected on the planning CT-scan	111 (100%)
Number of markers per tumor	
1	9 (21%)
2	10 (23%)
3	18 (41%)
4	7 (16%)
Marker location	
Inside the tumor	58 (52%)
Outside the tumor	53 (48%)

Registration of Repeat CT-scans

The average rotational adjustment during automatic registration was $0.2 \pm 3^\circ$ (range: $-11-16^\circ$). In merely 4 of 44 tumours, manual adjustments were made after automated registration of one or more repeat CT-scans. Manual adjustments were made due to changes in tumor volume/shape.

Marker stability

The median displacement of markers was 1.1 mm on CT-1 (range: 0.2- 20.7 mm), 1.2 mm on CT-2 (range: 0.1- 25.4 mm) and 1.3 mm on CT-3 (range: 0.3- 53.6 mm) (figure 2). The displacement of markers along any anatomical axis is given in table 2. Marker displacement exceeded 5 mm in 13 of 111 markers (12%) placed in nine patients. Marker displacement exceeded 10 mm in 5 of 111 markers (4%) placed in four patients. These markers were displaced by more than 5 or 10 mm, in one or more repeat CT-scans.

Upon visual inspection of the CT-registration, the cause of marker displacement >5 mm was marker migration (2/111; 2%), tumor regression (4/111; 4%), tumor deformation (1/111; 1%)

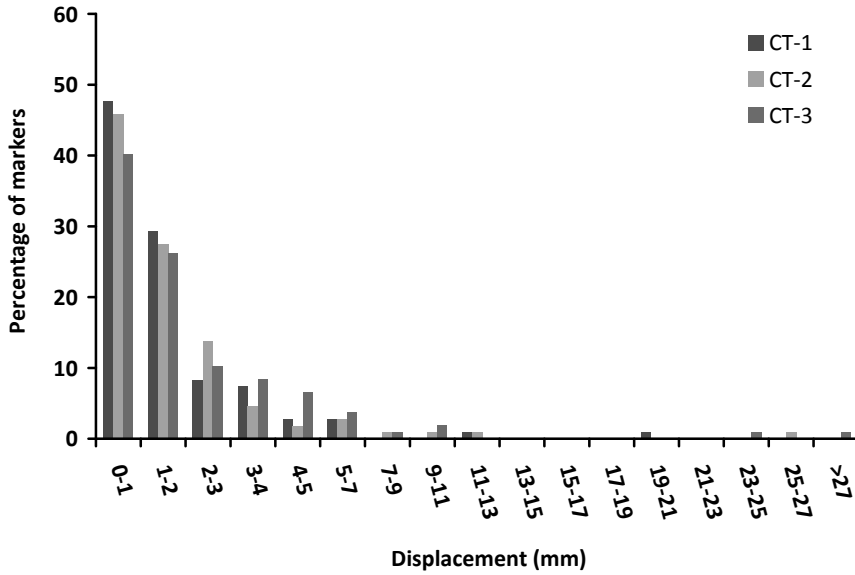


Figure 2. Displacement of individual markers in the repeat CT-scans.

Table 2. Displacement of individual markers (mm) in the repeat CT-scans.

	CT-1	CT-2	CT-3
Left-Right			
Average	-0.1	0	-0.1
SD	1.9	2.2	3.2
Range	-15.9 – 3.9	-20.1 – 4.5	-28.2 – 8.6
Cranio-caudal			
Average	-0.3	-0.2	-0.4
SD	1.9	2.2	3.2
Range	-13.1 – 3.8	-14.8 – 6.3	-22.7 – 4.5
Anterior-posterior			
Average	0	0.5	-0.2
SD	1.3	1.6	4.4
Range	-4.6 – 3.6	-3.0 – 7.2	-41.7 – 5.8
Average 3D- distance (SD)	1.9 (2.6)	2.0 (3.1)	2.8 (5.8)

SD: standard deviation; 3D: three-dimensional

and possibly non-synchronous tumor-marker motion (6/111; 5%). Two markers had migrated relative to the tumor and the surrounding structures in one patient. Four markers placed in three tumors were displaced due to tumor regression. Finally, one marker was displaced due to tumor deformation (this tumor had changed shape without a visually evident regression in tumor volume). For the remaining six markers, a clear cause of marker displacement >5 mm could not be identified. For five markers with a displacement >5 mm, the CT-registration showed an accurate tumor match, but also a slight respiratory phase difference (difference in the position of the ribs, diaphragm and vertebra). These markers may have moved non-synchronously to the tumor. The five markers were all placed furthest from the tumor compared to the other implanted markers (table 3). For the sixth marker, a respiratory phase difference was not evident between the planning CT-scan and the repeat CT-scan. We did however observe a pulmonary infiltrate on the repeat CT-scan, which may have influenced the motion of the marker but not that of the tumor.

Marker position (in or near the tumor) and tumor location (peripheral or central) did not significantly influence marker displacement. An increase in the time between the planning- and the repeat- CT-scan significantly increased the displacement of markers ($p < 0.01$). The magnitude of this effect was small (0.30 mm/day; 95% CI: 0.21-0.38 mm/day).

Table 3. Causes of marker displacement based on visual inspection of the CT-registration

Patient	Marker (location)	Displacement (mm)	Cause	Marker - Tumor Distance [§] (mm)	Tumor diameter (mm)
1	1 (O)	5.3	*	83.7	32.0
2	2 (O)	5.3	*	36.1	32.0
3	3 (O)	6.1	*	27.3	27.0
4	4 (O)	9.3	*	30.0	25.0
4	5 (O)	6.8	*	31.2	25.0
5	6 (O)	12.5	*	37.3	69.0
5	7 (I)	5.3	Tumor regression	26.0	69.0
6	8 (I)	10.4	Tumor regression	36.8	100.5
6	9 (I)	8.1	Tumor regression	35.0	100.5
7	10 (I)	10.9	Tumor regression	29.6	63.0
8	11 (O)	6.1	Tumor deformation	32.7	83.0
9	12 (I)	53.6	Migration	9.5	63.0
9	13 (I)	23.8	Migration	6.2	63.0

* Cause of displacement is uncertain. Marker may have been displaced by non-synchron tumor-marker motion.

[§]Marker- Tumor distance is the distance between the center of mass of the tumor and the center of the marker.

(O) located outside the tumor; (I) located inside the tumor

The median displacement of the COM of marker configurations was similar to the median displacement of individual markers (1.0 mm in all three CT-scans versus 1.1-1.3 mm). However, the maximum displacement of the COM of marker configurations was much smaller than the maximum displacement of individual markers: (7.4 mm versus 20.7 mm in CT-1, 8.2 mm versus 21.0 mm in CT-2, and 23.3 mm versus 53.6 mm in CT-3) (figure 3). The COM was displaced by >5 mm in 3 of 44 marker configurations (7%). These marker configurations were displaced by >5 mm in merely one CT-registration (n=2) or in all three CT-registrations (n=1). The COM of one marker configuration was displaced by more than 10 mm in one repeat CT-scan.

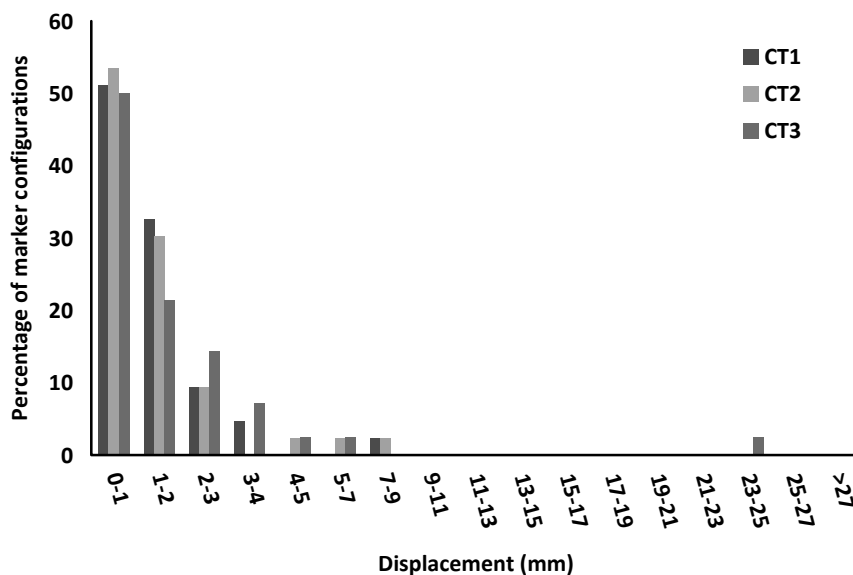


Figure 3. Displacement of the center of mass of the marker configurations in the repeat CT-scans.

Thirty-four patients with 35 tumors had at least two markers and were included in the analysis; “Is the change in distance between markers a reliable check for displacements in the COM of the marker configuration relative to the tumor position?”. One-hundred-and-two CT-scan registrations were available as 31 patients with 32 tumors had 3 repeat CT-scans (n= 96) while 3 patients with 3 tumors had 2 repeat CT-scans (n= 6). A displacement in the COM of the marker configuration of ≥ 2.0 mm was accompanied by a detectable change in the distance between markers of >1.5 mm in all but 4% of the CT-registrations (4/102). A displacement of the COM of the marker configuration of ≥ 3.0 mm was accompanied by

a detectable change in the distance between markers of >1.5 mm in all but 1% of the CT-registrations (1/102) (figure 4). In one CT-registration, the change in the COM of the marker configuration was 7 mm but the change in distance between markers was only 2 mm (figure 4). Despite this, an error in tumor targeting did not occur. The marker configuration was a mirror image of the original configuration; thus, the CyberKnife system could not recognize the original marker configuration on the stereoscopic x-ray images.

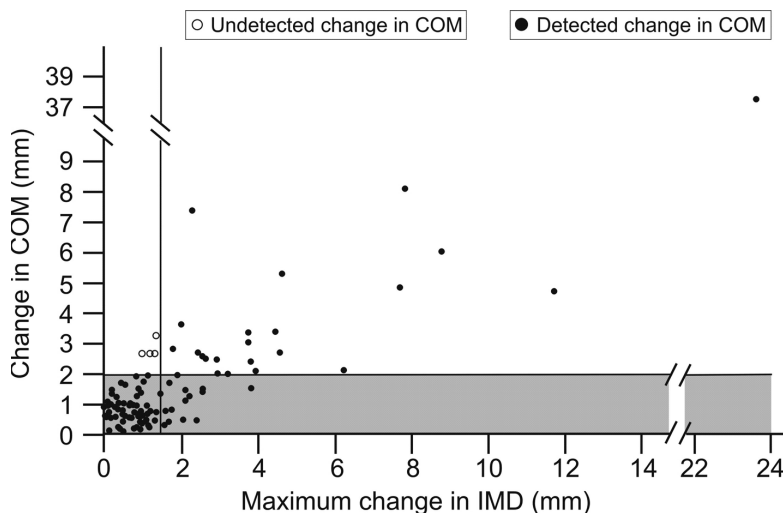


Figure 4. Change in the center of mass (COM) of the marker configurations and the corresponding maximum change in inter-marker distance (IMD). Changes in marker configuration COM of ≥ 2 mm were considered relevant (above the grey shaded area). Open circles represent undetected changes in the COM, while solid circles represent detected changes.

Discussion

Our results have shown that the median displacement of markers placed via the percutaneous intrapulmonary approach is 1.3 mm during treatment. However, marker displacements >5 mm occurred in 12% of markers (13/111). Visual inspection revealed that displacements >5 mm did not necessarily reflect marker migration.

Large marker displacements were also caused by tumor regression and deformation, and perhaps by non-synchronous tumor-marker motion. Although lung tumors frequently regress

during conventional radiotherapy (9, 10), previous stereotactic radiotherapy studies merely observed slow tumor regression (11, 12). In our study, only a minority of tumors significantly changed in volume/shape (4/44; 9%). In these tumors, the short onset of regression was perhaps related to tumor-specific characteristics and/or the delivery of 3-5 high fraction doses within one week. None of the reductions in tumor volume were related to the disappearance of atelectasis. Besides tumor regression/deformation, large marker displacements may have been caused by non-synchronous tumor-marker movement. In six of 13 markers, a definite cause for marker displacements >5 mm could not be identified. These markers may have migrated. A plausible alternative is that these markers moved non-synchronously to the tumor. The six markers were the most distal markers from the tumors (2.7 – 8.4 cm away from the center of the tumor). As such, the risk of non-synchronous tumor-marker motion may be related to the distance between the marker and the tumor. However, further research using four-dimensional respiratory correlated CT-scans is required to 1) determine the extent of non-synchronous tumor- marker motion during respiration, and 2) assess whether a greater tumor-marker distance increases the risk of non-synchronous tumor-marker motion.

As large marker displacements may occur, a reliable check for marker displacement is required in order to reduce the risk of inaccurate tumor localization. The CyberKnife real-time tumor tracking system localizes the tumor based on the COM of the marker configuration. Large COM displacements were however observed in some fractions (up to 23.3 mm; median 1.0 mm). Therefore we recommend a reliable check for displacements in the marker configuration COM prior to each treatment fraction. Our results have shown that the change in distance between markers is a reliable check for displacements in the COM of the marker configuration relative to the tumor. Displacements in the COM of the marker configuration of ≥ 2.0 mm were almost always accompanied by a change in the distance between markers of >1.5 mm. As the CyberKnife tumor tracking system generates a warning if the distance between markers deviates by >1.5 mm from the reference configuration, marker configuration COM displacements of ≥ 2.0 mm will be detected in the majority of cases. Thus, the displaced markers can be identified and the tumor can be localized using the remaining stable markers. Displacements smaller than 2.0 mm can be accounted for by the 5-mm GTV-PTV margin. We do not advise increasing the margin such that for all or nearly all patients the tumor is covered adequately even with the occurrence of large marker migration. Instead, it is our policy to disable the displaced marker.

A previous study reported the fixation rate of 1.5 mm gold markers after bronchoscopic placement in 57 patients with peripheral lung cancer (2). Merely 122 of the 154 implanted markers (79%) could be detected at treatment planning compared with 100% in our study (table 1). The rate of marker fixation was higher for peripheral tumors than for central tumors. Imura et al. hypothesized that the rate of marker fixation depended on the diameter of the marker in relation to the bronchus (2). Perhaps the fixation rate was higher in our study as larger markers (4.0 mm versus 1.5 mm) were used in mostly peripheral tumors (smaller bronchi diameter). Imura et al. also studied the stability of markers during treatment in 11 of the 57 patients (2). The change in distance between markers was much smaller than in our study (≤ 2.0 mm in 95% of cases versus ≤ 6.2 mm in 95% of cases). However, the analysis did not include those patients in whom a marker migrated after treatment planning (7/122 markers, 6%). In addition to this, the stability of markers during treatment was assessed in a small number of patients (n=11). The number of markers placed in these 11 patients was not mentioned (2).

The average displacement of the markers used in our study is similar to the displacement of a 2.0 cm-long marker placed in lung tumors via the percutaneous intrapulmonary approach (n=15 markers) or via the bronchoscopic approach (n=8 markers) (3). The average displacement of the 2.0 cm-long marker was 2.6 mm compared with 2.8 mm in our study. The maximum displacement was however much lower than in our study (5.4 mm versus 53.6 mm). The authors stated that marker displacements >5.4 mm were probably not observed because the 2.0 cm-long marker is more likely to get wedged in the lung than smaller markers. We clearly observed migration in two markers, and possibly in another 6 markers, for which the cause of displacement was unclear (n=2-8/111). Although the 4.0 mm-long markers used in our study may be more susceptible to migration than the 2.0 cm-long markers, this cannot be concluded based solely on the present results. In our study, non-synchronous tumor-marker motion may have caused displacements ≥ 5 mm in 6 markers. Non-synchronous tumor-marker motion was probably not an issue for the 2.0 cm-long marker as this marker was placed into or directly bordering the tumor. In addition, it should be noted that the sample size of the 2.0 cm-long marker study is much smaller than our sample size (23 markers versus 111 markers). Thus the lower migration rate of the 2.0 cm-long marker may be coincidental.

It is debated whether a single or multiple markers should be used for stereoscopic x-ray guided radiotherapy (13). Based on our results, we recommend the use of multiple markers. An advantage of using multiple markers is that marker displacements can be easily

detected on x-ray images through changes in the marker configuration. This is not possible if a single marker is used. Displacements of a single marker may remain undetected and cause systematic localization errors. Some may argue that large marker displacements are rare. We observed displacements >5 mm in 12% of markers. The incidence of marker displacement may be high in our study due to non-synchronous tumor-marker motion (as some markers were located >2 cm from the tumor). On the other hand, the largest displacements occurred when markers were placed inside the tumor. These displacements were not only limited to the first week after implantation; a time interval considered sufficient for fixation/fibrosis of the marker. Implantation of multiple markers also enables the detection of changes in tumor volume and shape. Although tumor volume and shape changes are less relevant in small lung tumors, it is possible to adapt the treatment plan in those cases where large target volume changes occur.

An argument against the use of multiple markers is the higher risk of a pneumothorax when multiple markers are implanted. The risk of pneumothorax after marker placement is not negligible (ranging from 17-53%) (3, 5). The development of transbronchial, trans-oesophageal and vascular marker placement techniques has however reduced the risk of pneumothorax (14-16). In the absence of these alternative techniques, one should consider, per patient, whether the higher risk of pneumothorax still justifies the use of multiple markers. If this risk is unacceptable, then four-dimensional respiratory-correlated CT-scans should be made prior to each treatment fraction in order to assure that the single marker remains stable relative to the tumor. At our institute, markers are frequently placed via the intravascular approach. An interesting question is whether marker displacement depends on the technique of implantation. Although we have not yet examined this, marker coils placed via the intravascular approach are probably more stable. These coils have been used extensively in neurosurgical clipping of aneurysms, and migration of endovascular coils has not been described (17).

A limitation of our study is the accuracy of localizing the markers. Identification of the center of the marker is limited by the slice thickness and spacing of the CT-scan. In our study the CT-scan slice spacing was 1.5-2.0 mm. Therefore the uncertainty in the CT-measurement was at best 0.75-1.0 mm. As such, the actual displacement of individual markers may be smaller than the median displacement of 1.3 mm stated in our “Results” section.

Conclusion

Intrapulmonary markers are generally stable as the median marker displacement was small (1.3 mm). However, marker displacements >5 mm occurred in 12% of markers. To reduce the impact of marker displacement on tumor localization, we recommend the implantation of multiple markers. Multiple markers enable a quick and reliable check for displacement in the COM of the marker configuration by determining the change in inter-marker distance. In the majority of cases (96%), a displacement in the COM of the marker configuration of ≥ 2.0 mm, is detected by a change in the distance between markers of >1.5 mm. This allows displaced markers to be disabled such that tumor localization is not compromised.

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CHAPTER 3

STEREOTACTIC RADIOTHERAPY WITH REAL-TIME TUMOR TRACKING FOR NON-SMALL CELL LUNG CANCER: CLINICAL OUTCOME

NC van der Voort van Zyp, J-B Prevost, MS Hoogeman,
J Praag, B van der Holt, PC Levendag, RJ van Klaveren,
P Pattynama, JJ Nuyttens

Abstract

Purpose

To report the clinical outcome of treatment using real-time tumor tracking for 70 patients with inoperable stage I non-small cell lung cancer (NSCLC).

Methods

Seventy inoperable patients with peripherally located early stage NSCLC were treated with 45 or 60 Gy in 3 fractions using the CyberKnife. Pathology was available in 51% of patients. Thirty-nine patients had a T1-tumor and thirty-one had a T2-tumor. Markers were placed using the vascular, percutaneous intra-, or extra-pulmonary approach, depending on the risk of pneumothorax.

Results

The actuarial 2-year local control rate for patients treated with 60 Gy was 96%, compared to 78% for patients treated with a total dose of 45 Gy ($p=0.197$). All local recurrences ($n=4$) occurred in patients with T2-tumors. Overall survival for the whole group at two years was 62% and the cause specific survival was 85%. The median follow-up was 15 months. Grade 3 toxicity occurred in two patients (3%) after marker placement. Treatment-related late grade 3 toxicity occurred in 7 patients (10%). No grade 4 or 5 toxicity occurred.

Conclusion

Excellent local control of 96% at 1- and 2-years was achieved using 60 Gy in 3 fractions for NSCLC patients treated with the real-time tumor tracking. Toxicity was low.

Introduction

Tumors of the lung are prone to motion which affects both intra- and inter-fractional radiation delivery. This motion is largely caused by respiratory breathing. The degree of motion tends to be small in tumors located in the upper lobe and those attached to the chest wall, but larger in small peripheral tumors. These tumors often move more than 1 cm and sometimes as much as 3 cm during deep in- or expiration (1). To accommodate this range of motion, conventional radiotherapy has typically used safety margins in the order of 1-2 cm. These margins decrease the risk of missing the tumor, at the cost of irradiating a larger volume of healthy lung tissue. The necessity for large safety margins in conventional radiotherapy limits dose escalation. This is the main reason for the poor local tumor control (LC) rates in patients with early-stage NSCLC (51%) (2).

High local control rates exceeding 90% have been reported for early-stage NSCLC patients treated with stereotactic radiotherapy (SRT) (3-5). This technique not only precisely targets and delivers radiation, but also reduces the effects of tumor motion. These characteristics of SRT allow reduction of safety margins surrounding the tumor volume. Consequently, treatment volumes are reduced and treatment doses can be escalated. The following methods have been applied to reduce the impact of respiratory tumor motion: 1) Patient-specific treatment volumes based on tumor motion observed during planning CT scans , 2) forced shallow breathing with abdominal compression, 3) breath-hold methods, 4) respiratory gating methods and 5) real-time tumor tracking (6).

Real time tumor tracking corrects for tumor motion during respiration by repositioning the radiation beam to the position of the moving tumor. This technique is applied by the Synchrony Respiratory Tracking System (RTS). The tracking system is part of the CyberKnife Robotic Radiosurgery treatment unit (Accuray Inc. Sunnyvale, USA) and requires the insertion of radio-opaque markers. The Synchrony RTS targets the tumor by moving the linear accelerator by means of a robotic manipulator. Synchrony RTS was implemented in 2004.

Few clinical results have been published for the treatment of lung cancer with real-time tumor tracking using the Synchrony RTS (7, 8). In each of these studies no more than 30 NSCLC patients were included. Clinical results of patients treated prior to 2004 were reported however these patients were not treated with real-time tumor tracking (9, 10). These studies used the breath-holding technique to account for tumor motion.

The purpose of this study is to report and compare the results of 70 patients treated with real-time tumor tracking, of whom 59 were treated with 60 Gy and 11 were treated with 45 Gy in three fractions. In addition, we will also address the question whether marker placement is feasible in patients with poor lung function.

Methods

Patients were eligible for treatment if they had inoperable T1-T2N0M0 NSCLC, refused surgery and if there was a peripheral tumor location. A peripheral tumor was located ≥ 2 cm from the trachea and main bronchus on the CT-scan. Patients were considered inoperable in the presence of severe co-morbidity or when tumors were deemed irresectable. Pathological confirmation was highly recommended. Comorbidity was registered using the Charlson comorbidity index and the cumulative illness ranking score (11, 12).

Prior to treatment, markers were placed in or near the tumor. Depending on the risk of pneumothorax, markers were placed via the percutaneous intra- or extra-pulmonary approach or via the vascular approach (13, 14). Briefly, percutaneous marker placement required fluoroscopy or CT-guidance to place platinum markers into or near the tumor (intrapulmonary approach) or in the thoracic wall against the ribs (extrapulmonary approach). The vascular approach involved the insertion of embolisation coils into small subsegmental end branches of the pulmonary artery near the tumor using a transcatheter. Ideally a minimum of 3 markers have been implanted to allow for correction of translational and rotational target motion.

A planning CT-scan of the chest with slice thickness and spacing of 1.5-2 mm was obtained 4-7 days after marker placement. The gross tumor volume (GTV) defined as visible tumor, was contoured using lung window. We added a 5 mm margin to the GTV to account for microscopic tumor extension and residual inaccuracy of the Synchrony RTS (~ 1.5 mm) (15, 16). Patients were initially treated with 3 fractions of 12 Gy ($n=1$) or 15 Gy ($n=10$). The dose was escalated to 3 fractions of 20 Gy ($n=59$). The dose was prescribed to the 70-85% isodose line, covering at least 95% of the PTV. The maximum dose was defined by the 100% isodose line.

Treatment consisted of approximately 130 non-coplanar beams using one or two circular collimator cones sizes (20-60 mm). Median treatment time was 1h40min (range 47min-3h30min) at a dose rate of 400 MU/min. Treatment planning was carried out with the On

Target treatment planning system, version 3.4.1, Accuray Inc., Sunnyvale, CA. The equivalent path-length method was used for correction of tissue inhomogeneity. Dose constraints are listed in table 1.

Table 1. Dosis constraints for critical structures

Organ	Volume	Dose (Gy)
Spinal Cord	Any point	8 Gy per fraction
Esophagus	Any point	7 Gy per fraction
Trachea and main bronchus	Any point	10 Gy per fraction
Plexus Brachialis	Any point	8 Gy per fraction
Liver	Any point	20 Gy per fraction
Lung	<31% of the total volume	4.5 Gy per fraction

All patients were treated with real-time tumor tracking. A detailed description of the CyberKnife Synchrony RTS has been reported previously (13-15). Briefly, motion of red light-emitting diodes attached to the patients' chest was registered and correlated to the location of implanted markers, as determined by a series of orthogonal x-ray images taken during respiration. The correlation model directed the robot arm and targeted the tumor with the 6 MV radiation beam. During treatment the correlation model was validated and updated.

The first clinical examination was performed three weeks after SRT. Clinical visits and CT-scans were performed 2-3, 6, 9, 12, 18, 24 and 30 months thereafter. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 3.0 (17). Toxicity was acute if it occurred within 4 months and late if it occurred thereafter.

The primary objective was to evaluate the efficacy of radiotherapy in terms of local control. Local control was calculated from the first day of treatment until diagnosis of a local recurrence. Patients without a local recurrence were censored on the last day of contact. In the absence of pathological confirmation of malignancy, local recurrence was defined as a 20% increased CT-tumor dimension compared to the previous CT-scan. In addition a corresponding avid lesion on the PET-scan was required. Overall survival was measured from the start of radiotherapy until death of any cause. Cause-specific survival was measured from the start of radiotherapy until death of lung cancer. Patients alive at the last date of contact were censored.

Local control and overall survival were estimated by the Kaplan-Meier method, and 95% confidence intervals (95% CIs) were constructed. Cox regression analysis was used to

evaluate the prognostic value of patient and tumor characteristics on survival endpoints. Differences between subgroups were illustrated and compared with Kaplan-Meier curves and the log-rank test. All P-values are two-sided. A significance level $\alpha = 0.05$ was used.

Results

Seventy patients with stage I NSCLC were treated using real-time tumor tracking from August 2005- October 2007. Patient and tumor characteristics are summarized in table 2. Patient comorbidity scores were high (table 2). Sixty-five patients (93%) were inoperable and 5 patients (7%) refused surgery. Thirty-nine patients had T1-tumors and 31 had T2-tumors. Histology was obtained in thirty-six (51%) of the seventy lung tumors. All thirty-four patients (49%) without histology had PET scans, as did 93% of the study population. In 63 patients activity on the PET scan was limited to the primary tumor site. The other two patients had a synchronous tumor located in the breast and head & neck region.

Table 2. Patient and tumor characteristics

Median age (years, range)	76 (54-90)
Charlson comorbidity score	
>4	5 (7%)
3-4	31 (44%)
1-2	32 (46%)
0	2 (3%)
Cumulative Illness score	
>6	23 (33%)
5-6	16 (23%)
0-4	31 (44%)
Histology	36 (51%)
Large cell carcinoma	16 (44%)
Squamous cell carcinoma	11 (31%)
Adenocarcinoma	7 (19%)
Undifferentiated carcinoma	2 (6%)
No biopsy or inconclusive biopsy	34 (49%)
Forced expiratory volume in 1 second (FEV1) (L)	
Median (Range)	1.38 (0.81-3.81)
Gross tumor volume (cc)	
Median (Range)	11.8 (0.7-176.5)
Planning target volume (cc)	
Median (Range)	35.0 (4.9-254.0)
Tumor diameter (cm)	
Median (Range)	2.7 (1.0-10.0)

Two-hundred-twenty-five markers were placed. One-hundred forty-three markers (43%) were placed with the vascular approach in 43 patients. Seventy-two markers (32%) were placed with the intrapulmonary approach in 25 patients and ten markers (4%) were placed using the extra-pulmonary approach in two patients. A median of 3 markers have been placed per patient (range 1-5). Grade 3 toxicity occurred in two patients (3%). One had a pneumothorax requiring a chest drain; another had cardiac arrhythmia after intravascular coil placement and required a pacemaker. Grade 2 toxicity occurred in one patient who was observed at the hospital for a pneumothorax but required no chest drain. Six patients had grade 1 toxicity consisting of minor dyspnea (n=1), pneumothorax without clinical symptoms (n=2) and self-limiting pulmonary haemorrhage (n=3).

The estimated local control rate was 96% (95% CI=84-99%) at 2-years for 59 patients treated with 60 Gy compared to 78% (95% CI=37-94%) for 11 patients treated with 45 Gy (figure 1A; p=0.197). After treatment with 60 Gy, T1 tumors had 100% local control at 2-years compared to 89% (95% CI=76-100%) for T2 tumors (figure 1B; p=0.085). Characteristics of patients with a local recurrence (n=4) are stated in table 3. All local recurrences were seen in patients with T2 tumors. No significant difference in local control was seen for patients with or without pathology. Three patients had regional (4%) and seven patients had distant metastases (10%). Five patients had both distant and regional recurrences (7%).

The estimated overall survival was 83% (95% CI=71-90%) at one year and 62% (95% CI=45-75%) at two years. Patient-, tumor- and treatment characteristics and presence/absence of pathology, had no influence on survival (figure 1C; p=0.64). Nineteen patients died during follow-up; six died of metastatic NSCLC (32%), 13 died of intercurrent disease (68%). Causes of intercurrent death are summarized in table 4. The cause-specific survival was 94% at one year and 86% at two years.

No grade 4 or 5 toxicity occurred after treatment. Acute Grade 1-2 toxicity occurred in 32 patients, consisting mostly of fatigue, dyspnoea and cough. One patient had acute grade 3 toxicity, requiring morphine for severe thoracic pain. Late grade 3 toxicity was observed in 7 patients (10%). Three patients had radiation pneumonitis treated with antibiotics and corticosteroids. Four patients had thoracic pain requiring morphine. They all had a tumor near the chestwall. A rib fracture was found in one of these patients.

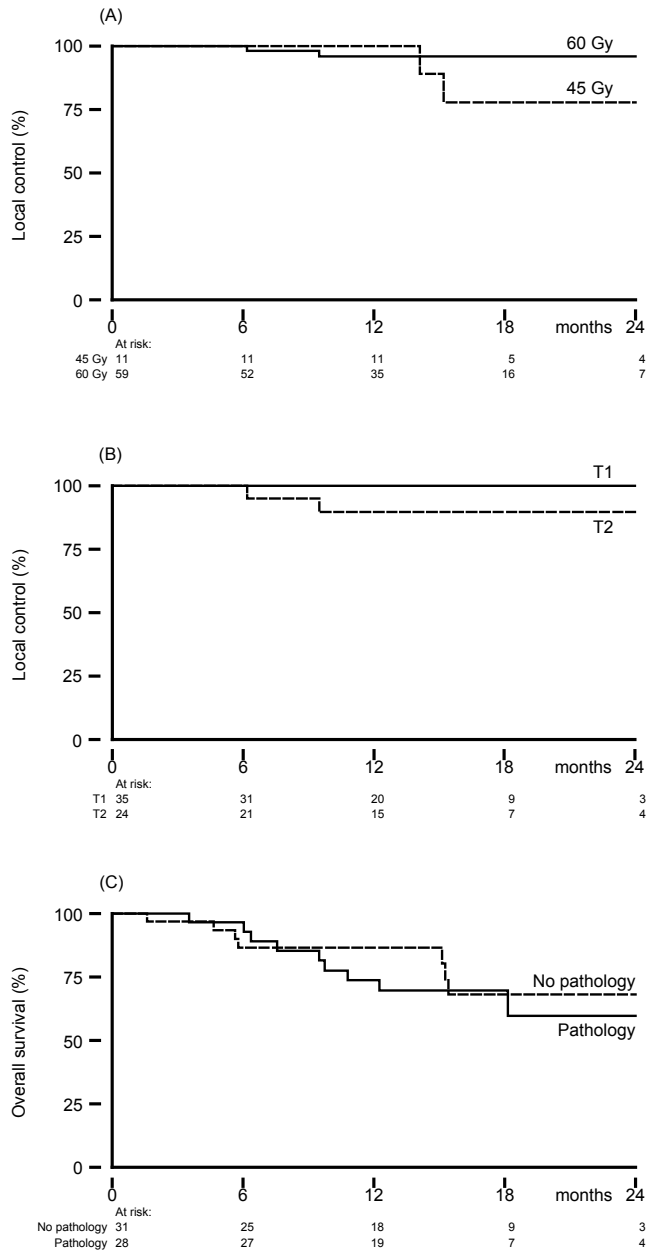


Figure 1(A). Local control rates of patients treated with 45 Gy and 60 Gy ($p=0.197$).
Figure 1(B). Local control rates of patients with T1 and T2 tumors treated with 60 Gy ($p=0.085$).
Figure 1(C). Overall survival of patients with and without pathology treated with 60 Gy ($p=0.64$).

Table 3. Characteristics of patients with a local recurrence

Patient	Total dose (Gy)	Pathology	Gross tumor volume (cc)	Planning target volume (cc)	Months to local relapse
1	45	Large cell	10	37	14
2	45	SCC	177	254	15
3	60	No PA	15	39	6
4	60	SCC	26	61	10

Table 4. Characteristics of patients who died during follow-up

Sex (Age)	Charlson score	Cummulative Illness Ranking	Cause of death
Male (78)	4	6	Sudden death
Male (75)	3	4	Sudden death
Female (83)	0	3	Myocardial infarction
Female (73)	1	2	Myocardial infarction
Male (85)	1	7	General deterioration
Male (90)	4	4	General deterioration
Male (69)	7	16	Cardiac decompensation after dialysis
Male (77)	7	14	Haemorrhage from a leiomyoma of the oesofagus
Male (80)	3	7	Cardiac decompensation
Female (61)	3	9	Haemorrhage of the digestive tract
Male (76)	3	3	Cerebrovascular bleeding
Male (83)	3	4	Cerebrovascular infarction
Male (76)	3	6	Unknown

Discussion

In our study, estimated local control of 59 NSCLC patients treated with 60 Gy in 3 fractions was 96% at two years. Estimated two-year local control was 78% in 11 patients treated with 45 Gy in 3 fractions. Clinical results after treatment with real-time tumor tracking are sparse (7, 8). The two studies available included patients with NSCLC as well as pulmonary metastases. The first study treated 51 patients with 60 Gy in 3 fractions, only 26 patients had NSCLC. After a median follow-up of 11 months the crude local control for the NSCLC patients was 85% (7). The second study treated patients with 45-60 Gy in 3 fractions and included 15 stage I NSCLC patients. Crude local control was 100% after a median follow-up of 12 months (8). This local control rate appears superior to ours, but the sample size was

small. In addition only small lung tumors were treated (median GTV of 8 cc; range 1-14 cc). In our study the median GTV was 11.8 cc but the largest tumor was 176.5 cc. All the T1-tumors in our study also had 100% local control.

Similar local control rates are reported by studies using patient-specific treatment volumes and abdominal compression. Crude local control of 97% at 12 months was reported in 206 patients treated using patient specific treatment volumes (18). Local control rates after treatment with abdominal compression are also comparable to our study. At 3 years, crude local control was 80-98% after treatment with 45 Gy in 3-4 fractions (3, 19). Variation in local control may be related to the proportion of T2-tumors treated. Local control was 98% after treating mainly T1-tumors, and 80% after treating mainly T2-tumors.

Clinical results are limited after breath-hold or respiratory gated treatment. In addition, study sizes are small. Despite this, similar local control rates were reported after breath-holding. Crude local control at a median follow-up of 13 months was 94% in 35 stage I NSCLC patients treated with 60 Gy in ten fractions (4). Ng et al. treated 20 patients with 45-54 Gy in 3-4 fractions; only five patients were treated using the deep inspiration breath hold technique. Local control was 94% at 2 years for the whole group (5). Despite these results, breath holding may be poorly tolerated by patients with mediocre lung function and active patient and therapist participation is often required (20).

Local control rates after respiratory gated treatment are lower in studies using lower doses but comparable when a similar dose is delivered. Local control was 73% at two years and 57% at three years in 41 NSCLC patients treated with 40-48 Gy in 4 fractions (21). Local control was significantly higher with greater radiation doses ($p=0.0059$) and in T1 tumors compared with T2 tumors ($p=0.0059$). In another study, 27 of 59 lung tumors were treated with respiratory gating; the respiratory cycle was too irregular in 9 patients and tumor motion was <10 mm in 23 patients. Local control was 83% at 2 years after treatment with a single fraction of ≥ 30 Gy, compared with 52% after treatment with ≤ 30 Gy (22). This study demonstrates a benefit of higher radiation dose on local control. It also demonstrates that not all patients are suitable for respiratory gating despite the indication.

In our study a somewhat lower local control rate (89% at 2 years) was seen in T2-tumors, even when treated with 60 Gy in 3 fractions ($p=0.085$). The number of local recurrences are

however too small (n=4) to make conclusions about the influence of dose and tumor stage on local control. Despite this our results do not contradict previously published results.

The studies above all used methods to regulate tumor motion, aimed at reducing irradiation of healthy tissue and escalating the dose to the target while maintaining toxicity at an acceptable level. To safely reduce treatment volume it is not sufficient to consider intra-fractional tumor motion alone. Shifts in the base-line position of the tumor between fractions forms a larger source of error (23). Even when margins are not reduced, these variations can cause the tumor to be situated outside the treatment field. In-room imaging prior to each treatment fraction can minimize this error if the imaging technique allows direct visualization of the tumor, or visualization of surrogate markers implanted near the tumor. CyberKnife uses the surrogate marker technique and localizes the tumor trajectory prior and during each treatment fraction.

Despite the achievement of excellent local control, the overall survival was 62% at two years. Others have reported two-year overall survival rates of 64-83% (4, 18). The cause-specific survival rate of 86% at two years, was similar to that reported by others (78% at 2 years) (5, 21). Presumably patient selection plays a role in the variation of overall survival. In our study $\geq 90\%$ of patients were medically inoperable and 56% of patients had a cumulative illness ranking score of ≥ 5 . Given the high comorbidity, the 11 intercurrent deaths were not completely unexpected. The cause of intercurrent death is unknown in three patients. These patients were all free of treatment related symptoms and had no evidence of a local recurrence on the CT-scan made 1-2 months prior to their death. All three patients had a history of severe pulmonary, cardiac or cerebrovascular disease.

Late grade 3 toxicity occurred in 7 patients (10%) after a median follow-up of 15 months. Others report late toxicity in 3-8% of patients (8, 18, 24). With increasing follow-up our incidence of toxicity may rise. Despite this, toxicity seems comparable to that reported by others with 12 months of follow-up (8, 18). Difficulties to distinguish between treatment-related symptoms and the natural course of COPD may cause variation in reported toxicity. Two of our patients with radiation pneumonitis had a history of COPD and the CT-scans showed only slight ground-glass effects. The symptoms may have resulted from a COPD exacerbation. On the other hand SRT may render patients more susceptible to COPD exacerbations. The incidence of pain syndromes and rib fractures was similar to that reported previously (18).

The use of implanted markers required for real-time tumor tracking is a major concern due to the risk of pneumothorax after percutaneous intrapulmonary placement. The risk is approximately 17-53% with 4-40% requiring treatment (25, 26). Only one patient in this series required treatment after percutaneous intrapulmonary marker placement. The incidence of pneumothorax was low due to the available alternative methods of marker placement (vascular and extra-pulmonary approach). The vascular approach was complicated by grade 3 toxicity in one patient. This patient, with a pre-existent conduction abnormality, required pacemaker implantation for a complete third degree atrioventricular block.

Another limitation of our study is the absence of pathologic confirmation of malignancy in 49% of the patient population. This limitation is not uncommon in radiotherapy trials treating patients with poor pulmonary function as the risk of trans-thoracic biopsies are frequently too high (18, 19). According to the malignancy prediction model of Swensen et al. the risk for malignancy is very high in our older patient population of whom the majority have smoked (27). The additional requirement of PET scanning added to the prediction model of Swensen et al. further minimizes the risk of treating a benign lesion (28). The specificity of PET to differentiate between benign and malignant nodules is 70%-95% (29). Although the PET scan can not give certainty that all the lesions treated in this study were malignant, it was ensuring to find similar local control and overall survival rates in patients with and without pathological confirmation of disease.

Conclusion

Excellent local control of 96% at 2 years was achieved for NSCLC patients treated with 60 Gy using real-time tumor tracking. These results were obtained while adapting a tight 5 mm margin and allowing patients to breathe freely. The cause-specific survival rate of 86% at 2 years was comparable to that reported by other SRT studies. Treatment related toxicity was low as was toxicity after marker placement. As various marker placement techniques were available even patients with a poor lung function could be treated safely.

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CHAPTER 4

STEREOTACTIC BODY RADIOTHERAPY USING REAL-TIME TUMOR TRACKING IN OCTOGENARIANS WITH NON-SMALL CELL LUNG CANCER

NC van der Voort van Zyp, B van der Holt, RJ van Klaveren,
P Pattynama, A Maat, JJ Nuyttens

Abstract

As the incidence of stage I non-small cell lung cancer (NSCLC) increases among octogenarians and only selected patients are surgical candidates, an alternative treatment is necessary. This manuscript evaluates the overall survival, local tumor control rate, and treatment related toxicity after stereotactic body radiotherapy (SBRT) in 38 octogenarians with stage I NSCLC. Treatment consisted of 45 Gy (n=4) or 60 Gy (n=25) in 3 fractions for patients with peripheral tumors. A risk adaptive schedule of 45-60 Gy in 3-6 fractions was used for central (n=7) or large peripheral tumors (n=2). An overall survival rate of 65% at one year and 44% at two years was achieved in octogenarians after SBRT. The local tumor control rate was excellent (100% at two years) and no grade 4 or 5 treatment related toxicity occurred. Despite the high incidence of comorbidity in these octogenarians (Charlson score ≥ 5 in 16% of patients), an approach that merely provides supportive care cannot always be justified. SBRT offers octogenarians with stage I NSCLC a good treatment alternative.

Introduction

As life expectancy increases, more octogenarians will present with stage I non-small lung cancer (NSCLC). The treatment of these patients with potentially resectable lung cancer is challenging. Although treatment decisions are often based on prospective randomized trials, elderly patients are highly underrepresented in these trials due to their age or stringent inclusion criteria. As a result these trials cannot guide treatment decisions in elderly patients (1, 2). Other concerns are patient frailty and the assumption that life-expectancy is limited. Treatment is therefore often primarily aimed at avoiding side effects, and preserving quality of life while curation is of secondary concern.

The trend for more conservative management of NSCLC in elderly (3, 4) may deprive elderly patients of both quantity and quality of life. A nihilistic approach in elderly with NSCLC cannot be justified as more than 50% of patients die due to their cancer (5). In addition the projected life expectancy of octogenarians is on average >7 years (6, 7). Although 5-year survival rates after surgery in octogenarians are encouraging (34-57%) (8-11), careful patient selection is essential and postoperative morbidity and mortality are not negligible (10, 12, 13). An alternative to surgery currently used to treat patients with inoperable stage I NSCLC is stereotactic body radiotherapy (SBRT).

SBRT precisely targets and delivers radiation to the tumor even when the tumor moves during respiration. The methods used to account for respiratory tumor motion include 1) patient specific treatment volumes based on tumor motion, 2) forced shallow breathing with abdominal compression, 3) breath-holding during irradiation, 4) respiratory-gated radiotherapy and 5) real-time tumor tracking. As a result of the precise targeting, stereotactic radiotherapy can deliver a higher dose per fraction and thus higher biological effective doses than conventional radiotherapy. SBRT in the general population achieves local tumor control rates similar to those after surgery (92%) and the overall survival rates range from 26-83% at 2-5 years (14-18).

In this study we determined the overall survival, the rate of death due to cancer progression and intercurrent disease, and the local tumor control rate after SBRT in octogenarians with stage I NSCLC. SBRT was delivered using real-time tumor tracking. Complications after marker placement and treatment-related toxicity were also evaluated.

Methods

A review of our prospective database identified 38 octogenarians with cT1-2N0M0 NSCLC who were treated with SBRT from August 2005 to July 2008. Pathologic confirmation of malignancy was obtained in 22/38 patients (58%) and a PET-scan was obtained in 34/38 patients (89%). Those patients without pathology had a growing lesion on the computer tomography (CT) scan and an avid lesion on the positron emission tomography (PET) scan. Hilar or mediastinal nodes with a short axis <1 cm on CT and no abnormal hilar or mediastinal uptake on PET were considered N0. Activity on the PET-scan was limited to the primary tumor in all patients. Comorbidity was scored using the Charlson comorbidity index (table 1) and the cumulative illness ranking score (19, 20). Patient and tumor characteristics are listed in table 2.

Table 1. The Charlson comorbidity scale

Comorbidity	Points
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes (without complications)	1
Diabetes with end-organ damage	2
Hemiplegia	2
Moderate or severe renal disease	2
Second solid tumor (non-metastatic)	2
Leukemia	2
Lymphoma, multiple myeloma	2
Moderate or severe liver disease	3
Second metastatic solid tumor	6
Acquired immunodeficiency syndrome	6

Patients were treated with SBRT using the CyberKnife. CyberKnife accurately targets and radiates the tumor using the synchrony respiratory tracking system (RTS). This system requires insertion of radio-opaque markers near the tumor, and enables the CyberKnife to compensate for tumor motion. It does this by continuously repositioning the radiation beam

Table 2. Patient and tumor characteristics

Median age (range)	82 (80-90)
Medically inoperable	34 (89%)
Refused surgery	4 (11%)
Charlson comorbidity score	
0	1 (3%)
1-2	14 (37%)
3-4	17 (45%)
>5	6 (16%)
Cumulative Illness score	
0-4	9 (24%)
5-6	9 (24%)
>7	20 (53%)
T1	12 (32%)
T2	26 (68%)
Peripheral tumor location	32 (84%)
Central tumor location	6 (16%)
Histology	22 (58%)
Large Cell carcinoma	8 (36%)
Squamous cell carcinoma	7 (32%)
Adenocarcinoma	4 (18%)
Undifferentiated carcinoma	4 (18%)
No biopsy or inconclusive biopsy	16 (42%)
Forced expiratory volume in 1 second (FEV1) (L)	
Median (Range)	1.57 (0.79-3.08)
Gross tumor volume (cc)	
Median (Range)	18.2 (2.4-376.5)
Planning target volume (cc)	
Median (Range)	46.2 (14.8-609.5)
Tumor diameter (cm)	
Median (Range)	3.5 (1.6-10.5)

to the position of the moving tumor. Details on marker placement and the RTS have been published previously (21, 22). Briefly, markers were placed via the vascular, percutaneous intrapulmonary or percutaneous extrapulmonary approach. Seventy-four markers were placed via the vascular approach in 22 patients, 46 markers were placed via the percutaneous intrapulmonary approach in 15 patients and 5 markers were placed via the percutaneous extrapulmonary approach in one patient. On average 3 markers (range 1-5 markers) were placed per patient to allow for correction of translational and rotational motion. A planning CT-scan was obtained 4-7 days after marker placement. The gross tumor volume (GTV) was delineated using the lung window setting. The planning target volume (PTV) was obtained by adding a 5 mm margin to the GTV. This margin accounts for microscopic tumor extension and inaccuracy of the synchrony RTS (23, 24).

In the treatment room, the location of the implanted markers was determined by a series of orthogonal x-ray images taken during respiration. At the same time, motion of red light-emitting diodes on the patients' chest was registered and correlated to the location of the implanted markers. The resulting correspondence model was used to move the robot arm and direct the radiation beam at the tumor. Treatment of peripheral tumors (located ≥ 2 cm from the trachea and main bronchus) initially consisted of 45 Gy in 3 fractions (n=4) but was escalated to 60 Gy in 3 fractions (n=25). The dose was escalated to 60 Gy in 3 fractions as it was demonstrated that this was a safe and effective dose (25, 26). Two large peripheral tumors could not be treated with this dose due to normal tissue constraints. Instead they received 50-60 Gy in 5 fractions. Central tumors were treated with 6 x 8 Gy if they were located near the oesophagus. Otherwise they received 5 x 9-12 Gy (n=4). Dose was prescribed to the 78-87% isodose line, covering at least 95% of the PTV. Maximum dose was defined by the 100% isodose line. The equivalent pathlength algorithm was used to correct for tissue inhomogeneity. The dose constraints to organs at risk are given in table 3.

Table 3. Dose constraints for the organs at risk

Organ	Volume	Schedule 3 x 20 Gy Dose per frac. (Gy)	Schedule 6 x 8 Gy Dose per frac. (Gy)	Schedule 5 x 12 Gy Dose per frac. (Gy)
Spinal Cord	Any point	8	4.5	5.5
Esophagus	Any point	7	6	7
Heart	Any point	12	8	10
Trachea and main bronchus	Any point	10	8	10
Plexus brachialis	Any point	8	5	6
Lung	V ₂₀ (EQD2)	<31%	<31%	<31%

Clinical visits and CT-scans were performed every 3 months during the first year, and every 6 months thereafter. A local recurrence was defined as a 20% increased tumor diameter compared to the diameter on the previous CT-scan. In addition, a corresponding avid lesion was required on the PET-scan. Local tumor control was calculated from the day of treatment until a local recurrence was diagnosed or until the last day of contact for patients without a recurrence. Overall survival was measured from the first day of radiotherapy until death from any cause. Patients alive on the last date of contact were censored. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 3.0 (27).

Statistical considerations

Kaplan-Meier analysis was used to estimate the local tumor control rate and overall survival and to determine 95% confidence intervals (CIs). The rate of death due to cancer progression and intercurrent disease were also determined using competing risk analysis. The prognostic value of tumor stage on overall survival was determined using the logrank test. The influence of tumor stage on death due to cancer progression and death due to intercurrent disease were also evaluated. The cox-regression analysis was used to evaluate the impact of the Charlson comorbidity score on intercurrent death. P values <0.05 were considered statistically significant.

Results

The overall survival was 65% (95% CI = 47-78%) at one year and 44% (95% CI = 27-61%) at two years. Death due to cancer progression was 18% and death due to intercurrent disease was 38% at two years (figure 1). Surviving patients had a median follow-up of 23 months. The two-year overall survival was 81% for T1 and 29% for T2 tumors ($p < 0.01$, figure 2). No statistically significant difference was seen in the overall survival at two-years for tumor location (50% for peripheral versus 17% for central tumors, $p = 0.07$) or treatment dose (52% for patients treated with 3 fractions of 20 Gy versus 31% for patients treated with a lower dose, $p = 0.53$). The median survival was 20 months. Death due to disease progression was 10% in T1 tumors and 21% in T2 tumors at two years ($p = 0.06$). At two years, death due to intercurrent disease was 8% in T1 tumors and 51% in T2 tumors ($p = 0.02$). The mean Charlson comorbidity score (CCS) and cumulative illness ranking score (CIRS) were not significantly different for patients with T1 or T2 tumors (CCS = 2 for T1 vs 3 for T2, $p = 0.28$; CIRS = 6 for T1 vs 7 for T2, $p = 0.32$). Table 4 summarizes the cause of death for patients with T1 and T2 tumors and the time of death. Twenty-one patients died; seven died due to disease progression and fourteen died due to intercurrent disease. The cause of death was unknown in one patient with a sudden death. Of the fourteen patients with intercurrent death, ten patients died in the first year after treatment. In the patients who died of a cardiac cause ($n = 5$), general deterioration ($n = 3$) or due to a sudden death ($n = 1$), the median of the maximum heart dose was 1.2 Gy (range: 0.1-4.4 Gy). The patients who died of pneumonia ($n = 1$), general deterioration ($n = 3$) or a sudden death ($n = 1$) all had a V20 (EQD2) well below the constraint of 31% (median 15%). The Charlson comorbidity score had no significant influence on intercurrent death.

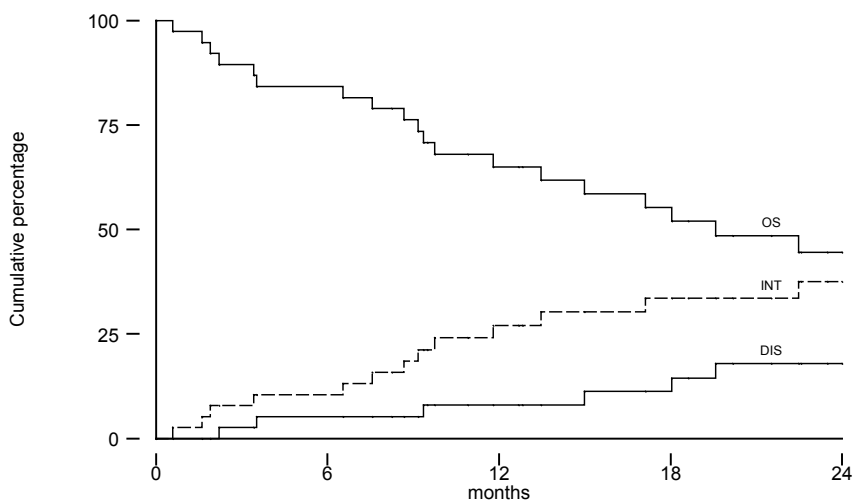


Figure 1. Overall survival (OS), death due to cancer progression (DIS) and death due to intercurrent disease (INT).

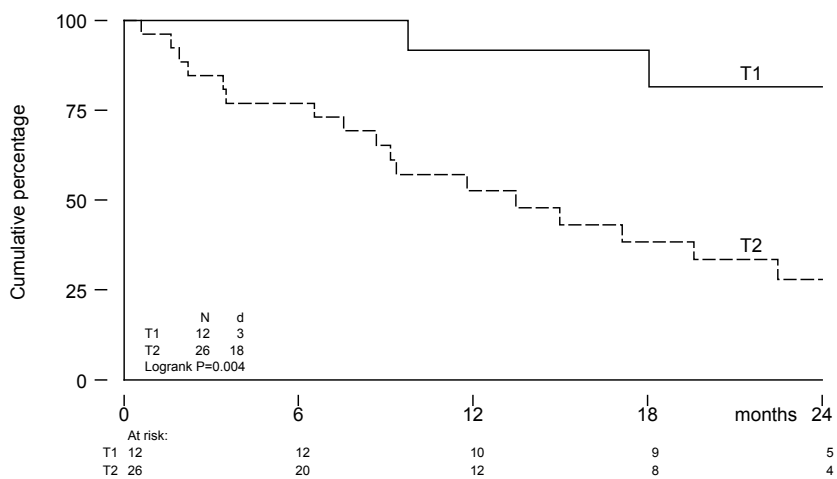


Figure 2. Overall survival for T1 and T2 tumors treated with SBRT ($p=0.01$).

Local tumor control was 100% at one and two years. Complications after marker placement occurred in 2 patients (5%). One had a pneumothorax after intrapulmonary marker placement and required a thorax drain. The other patient required a pacemaker after vascular coil placement. This patient had pre-existent atrioventricular conduction abnormalities.

Table 4. Cause of death

	Number of deaths	Time till death (months)	Tumor category
Disease progression	7		
Lung metastases	2	18, 20	T1 = 1, T2 = 1
Leptomeningeal metastases	1	2	T2
Brain metastases	1	32	T2
Brain & liver metastases	1	4	T2
Lymphangitis carcinomatosa	1	9	T2
Carcinomatous pleuritis	1	15	T2
Intercurrent disease	14		
Abdominal aneurysm	1	7	T2
Sepsis (toe infection)	1	1	T2
Cerebral haemorrhage	1	2	T2
Haemoptysis*	1	13	T2
Cardiac death	5	2, 3, 8, 17, 30	T1 = 1, T2 = 4
COPD/pneumonia	1	9	T2
General deterioration	3	9, 10, 12	T1 = 1, T2 = 2
Sudden death/unknown	1	22	T2

* Haemoptysis as a result of anticoagulant therapy

Treatment-related grade ≥ 4 toxicity did not occur. Two patients had acute grade 3 toxicity (5%). One had self-limiting chest pain 3-8 weeks after treatment and temporarily required pain medication. The other patient was admitted to the hospital for chest pain and dyspnoe. The pain was attributed to an exacerbation of chronic obstructive pulmonary disease (COPD) and resolved with antibiotics and prednisone. Dyspnoe remained severe. Although late toxicity could not be evaluated in all patients due to limited follow-up, 32 patients were followed ≥ 6 months and 22 patients were followed ≥ 12 months. Of these patients, five (16%) had late grade 3 or higher toxicity including: dyspnoe related to severe COPD (n=2), thoracic pain (n=2) and grade 3 radiation pneumonitis six months after treatment (n=1). The patient with acute grade 3 dyspnoe related to COPD also had late grade 3 dyspnoe related to severe COPD. The patients presenting with thoracic pain (at 9 and 12 months) had mild or no pain at the following out-patient visit.

Discussion

An overall survival of 65% at one year and 44% at two years were achieved after SBRT in octogenarians with stage I NSCLC, while the rate of cancer progression was 18% at two years. Local tumor control was excellent (100%) and toxicity was low after marker placement (5%) and radiation treatment (5% acute and 16% late grade 3 toxicity). The overall survival rate was significantly higher in T1 than T2 tumors. Although the rate of death due to disease progression was higher in T2 tumors than in T1 tumors (21% versus 10%), this difference was not statistically significant. It should be noted that this difference may not be statistically significant as a result of the small number of patients that died of progressive disease.

While the survival rate after SBRT in our study was merely 44% at two years, five-year survival rates of 34-79% are reported after surgery in octogenarians with stage I NSCLC (8-10). The largest surgical study included 196 patients with stage I NSCLC. Overall survival for stage 1A disease was 90% at one year and 48% at five years. For stage 1B disease it was 83% at one year and 39% at five years (9). Surgical series emphasize careful selection of physically fit octogenarians (10, 28-30). Overall survival after surgery was worse in octogenarians with ≥ 2 comorbidities than for those with less comorbidity (31). The extent of selection in some surgical series is high: curative resections in octogenarians with stage I-II NSCLC accounted for merely 4-6% of the total number of curative lung resections performed at two centers (8, 10). In our study comorbidity was severe. Fourteen patients (16%) had a Charlson comorbidity score ≥ 5 . This score is associated with an increased risk of mortality (19, 32). Mortality due to intercurrent disease occurred in fourteen patients (T1 N=2, T2 N=12). As the mean comorbidity scores were not significantly different for patients with T1 and T2 tumors, this does not explain the higher rate of intercurrent death in patients with T2 tumors. Despite this, the higher intercurrent death rate in patients with T2 tumors may well be coincidental. Death due to an abdominal aneurysm, sepsis from a toe infection and cerebral hemorrhage could well have happened in either patients with T1 or T2 tumors and are not related to the tumor stage or treatment. The other intercurrent deaths in patients with T1 and T2 tumors (cardiac death n= 5, pneumonia n=1, general deterioration n=3, and sudden death n=1) were also not the result of treatment related toxicity. The patients that died due to cardiac disease, general deterioration and an unknown cause all had treatment plans in which the maximum dose to the heart was <5 Gy (median 1.2 Gy, range 0.1-4.4 Gy). As the maximum dose to the heart in these patients was well below the dose constraint, these deaths

were not the result of cardiac toxicity related to SBRT. The V20 (EQD2) was also well below the constraint for the patients that died of pneumonia, general deterioration or sudden death. Besides the high incidence of comorbidity, another factor that may contribute to the lower survival in our study is the absence of surgical staging. Patients treated with SBRT may have been under-staged. This may lower overall survival after SBRT. Lastly, some surgical series have excluded postoperative deaths from their overall survival analysis in order to evaluate factors that influence long-term survival (8, 9). By doing this, overall survival after surgery appears higher.

Although the survival in our study is merely 44% at 2 years (median survival of 20 months), the estimated survival of untreated early stage NSCLC is poor (5, 13, 33). Knowledge of the natural course of untreated stage I NSCLC in octogenarians is limited. For patients aged 54-84, the median survival was 14 months in untreated patients versus 46 months following surgery (5, 33). In a second study, the median survival for a general population with untreated stage I-II NSCLC was 13 months (overall survival of 58% at one year and 8% at two years) (7). Survival rates are poor after a best-supportive care approach. Therefore best supportive care should be replaced by active treatment even in octogenarians. Many octogenarians will be unsuitable for surgery due to the high probability of severe comorbidity (29, 31, 34). In addition, the physiologically reduced lung function in octogenarians can lead to significant morbidity after surgery. Prior to the wide-spread availability of SBRT, patients with stage I NSCLC were treated with dose escalated conventional radiotherapy in an attempt to improve outcomes compared with conventional radiotherapy. Radiation doses up to 94.5 Gy in 42 fractions could be safely given to patients with small-volume lung tumors and were associated with better treatment outcomes (35, 36). Patients with stage I-III NSCLC had an overall survival of 44% at two years and 28% at five years after treatment with >92 Gy (36). A direct comparison with our SBRT study is however hampered as this study included patients younger than 80 years with a performance status of 0-2. An advantage of SBRT over dose escalated conventional radiotherapy is that SBRT allows for hypofractionated radiotherapy, thereby shortening the overall treatment time while high doses can be delivered due to the accurate targeting of the tumor.

At our institute, SBRT in 38 octogenarians achieved excellent local tumor control. Similar local tumor control has been reported by the largest multi-institutional SBRT study including 245 Japanese early-stage NSCLC patients. Patients were 35-92 years old, the majority had a World Health Organisation (WHO) performance score of 0-1 and 65% were inoperable due

to COPD, other chronic illnesses or advanced age. At 5 years, local control was 92% and overall survival was 47% (90% for operable patients) (14). Although Japanese and western patients differ, these results suggest that SBRT is a good alternative to surgery, and that survival rates for operable patients may be similar. The role of SBRT in operable early stage NSCLC patients is currently examined by a randomized trial in the Netherlands (the ROSEL trial) and by an international randomized trial (the STARS- trial).

Treatment related morbidity and mortality are also important in making treatment decisions for octogenarians with stage I NSCLC. Grade 3 treatment-related morbidity occurred in 6 patients (one within 4 months, four thereafter, and one persisting after 4 months). Although the incidence of late toxicity may increase with longer follow-up, 32 patients were followed >6 months and 22 patients were followed >12 months. All toxicity was self-limiting and treatment-related mortality did not occur despite severe comorbidity in our patients before treatment.

Morbidity and mortality has been drastically reduced after surgery owing to strict pre- and postoperative measures and advances in surgical techniques including the introduction of less invasive lung preserving operations. Despite these advances, 11-30% of octogenarians treated with surgery had major morbidity (mainly cardiopulmonary) (8, 13). Mortality rates in octogenarians have been reduced from 30% in the sixties (37) to current rates just below 2% for limited pulmonary resections (38). Despite this, the risk of mortality still increases with each decade of life (33, 38, 39) and reported rates of mortality in octogenarians still vary enormously (0-15%) (8, 10, 12, 13, 38). Variation in these mortality rates are caused by small study sizes, differences in hospital treatment volumes and the extent of lung surgery. High volume academic centers generally do better than community based centers (39) and the mortality risk in the general population after a pneumonectomy is higher than after a wedge resection (7.2% versus 0.6%) (34). Although limited resections are preferable due to the lower complication risk, not all octogenarians will have a tumor suitable for limited resection as tumors may be >2.5 cm or located centrally in the lung. And even after limited resections using video-assisted thoracoscopy, mortality rates remained 10% in patients with an impaired performance status (33). As such, treatment with stereotactic radiotherapy may be a safer alternative for octogenarians with early-stage NSCLC.

Although toxicity is low and hospital admission is not needed, a disadvantage of treatment using the CyberKnife is the necessity of markers for tumor tracking. In a significant portion

of patients the risk of a pneumothorax after intrapulmonary marker placement was too high. In these cases, bronchoscopic or intravascular marker placement provides a solution. Our complication rate after marker placement was acceptably low (5%) even when compared to complications in younger populations (16-28%) (40, 41). Treatment was also tolerated well by octogenarians despite treatment times of approximately 90 minutes. Improved CyberKnife technology allows treatment in less than 60 minutes. Low toxicity and excellent local tumor control are obtained with CyberKnife treatment. Similar results could be obtained with the various other SBRT methods mentioned in the introduction.

A drawback of our study is the absence of pathological confirmation of malignancy in 58% of patients while it is confirmed in all patients treated with surgery. The absence of pathology is a common problem in radiotherapy trials as the risk of trans-thoracic biopsies is often too high due to poor pulmonary function (16, 42). Despite this, the risk of malignancy in elderly patients who have smoked is very high according to Swensen's malignancy prediction model (43). The risk of treating a benign lesion is further reduced by the PET-scan, which has a specificity of 70-95% to differentiate between malignant and benign lesions (44). Although our study is non-randomized and has potentially introduced a selection bias of relatively healthy octogenarians, the high rate of comorbidity suggests that even octogenarians with multiple comorbidities can be safely treated with SBRT.

Conclusion

Stereotactic radiotherapy in octogenarians with stage I NSCLC achieved an overall survival rate of 65% at one year and 44% at two years, and the rate of cancer progression was 18% at two years. The local tumor control rate was excellent (100%) and the marker placement complication rate (5%) and treatment related toxicity were low (5% acute grade 3 toxicity and 16% late grade 3 toxicity).

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CHAPTER 5

QUALITY OF LIFE AFTER STEREOTACTIC RADIOTHERAPY IN STAGE I NON-SMALL CELL LUNG CANCER

NC van der Voort van Zyp, J-B Prévost, B van der Holt,
C Braat, RJ van Klaveren, PM Pattynama, PC Levendag,
JJ Nuytens

Abstract

Purpose

To determine the impact of stereotactic radiotherapy (SRT) on the quality of life (QoL) of inoperable patients with early-stage non-small cell lung cancer (NSCLC). Overall survival, local tumor control and toxicity were also evaluated in this prospective study.

Methods

From January 2006 to February 2008 quality of life, overall survival and local tumor control were assessed in 39 patients with pathologically confirmed T1-2N0M0 NSCLC. These patients were treated with SRT. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the lung cancer specific questionnaire (QLQ-LC13) were used to investigate changes in QoL. Assessments were done before treatment, at 3 weeks, and 2, 4, 6, 9 and 12 months after treatment until death or progressive disease. Toxicity was evaluated using the common terminology criteria for adverse events version 3.0.

Results

Emotional functioning improved significantly after treatment. Other functional scores, QLQ-C30 and QLQ-LC13 lung symptoms (as dyspnea and coughing) showed no significant changes. Overall two-year survival was 62%. After a median follow up of 17 months one patient had a local recurrence (3%). No grade 4 or 5 treatment related toxicity occurred. Grade 3 toxicity consisted of thoracic pain and occurred in one patient within four months of treatment while it occurred thereafter in two patients.

Conclusion

Quality of life was maintained and emotional functioning improved significantly after stereotactic radiotherapy for stage I NSCLC while survival was acceptable, local tumor control was high and toxicity was low.

Introduction

Stereotactic radiotherapy (SRT) is an important treatment modality in patients with inoperable stage I non-small cell lung cancer (NSCLC). Although surgery is the treatment of choice, many patients are medically inoperable due to smoking-related comorbidity. For these patients stereotactic radiotherapy is a good alternative treatment, achieving local tumor control rates above 90% (1-3) and 5-year overall survival rates of 47% (4). An equally important aim of any cancer treatment is to maintain or improve the patients' quality of life. Given the high level of comorbidity in many patients with NSCLC and the limited overall survival, it is of great interest to assess the impact of treatment on the patients' quality of life. Although quality of life has been evaluated after conventional radiotherapy in patients with NSCLC, reports of quality of life after stereotactic radiotherapy are sparse. The aim of this prospective study is to assess the impact of stereotactic radiotherapy on the quality of life of inoperable patients with NSCLC using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30 and the lung cancer specific supplementary questionnaire QLQ-LC13. In addition the overall survival, local tumor control rate, and treatment related toxicity were evaluated.

Methods

Patients

From January 2006 to February 2008, 43 patients with pathologically confirmed T1-2N0M0 NSCLC entered our prospective phase II trial and were treated with real-time tumor tracking using the CyberKnife. Patients were eligible for the trial if they refused surgery or had an inoperable tumor. The trial was approved by the Medical Ethical Committee of the Erasmus MC and was in accordance with the Declaration of Helsinki. Four patients were excluded from quality of life analysis; two due to a lacking pre-treatment assessment, one due to progressive disease shortly after the first follow-up assessment at 3 weeks, and one patient declined to participate in the quality of life study after inclusion. Pathological confirmation of malignancy was obtained in all patients. Diagnostic staging included a CT-scan in all patients and a PET-scan in all but four patients. Comorbidity was registered using the Charlson comorbidity index and the cumulative illness ranking score (5, 6). Patient characteristics are listed in table 1. One patient had a T2 tumor at the time of inclusion but a T3 tumor at the time of treatment. This patient is included in this analysis.

Table 1. Patient and tumor characteristics

Median age (years, range)	77 (55-87)
Medically inoperable	33 (85%)
Refused surgery	6 (15%)
Charlson comorbidity index	
0-2	20 (51%)
3-4	13 (33%)
>4	6 (15%)
Median cumulative illness ranking (range)	6 (2-16)
Incidence of COPD	22 (56%)
Tumor location	
Peripheral	33 (85%)
Central	6 (15%)
T-classification	
T1	17 (44%)
T2	21 (54%)
T3	1 (3%)
Histology	
Squamous cell carcinoma	14 (36%)
Large cell carcinoma	13 (33%)
Adenocarcinoma	8 (21%)
Other	4 (10%)
Planning target volume (PTV) median (range)	46 cc (7-609 cc)

Treatment

All patients were treated with real-time tumor tracking using the synchrony respiratory tracking system of the CyberKnife. This system requires the insertion of radio-opaque markers and enables the radiation beam to reposition to the location of the moving tumor. Details on the marker placement techniques and the synchrony tumor tracking system have been published previously (7-9).

Markers were placed via the vascular approach in 24 patients, the percutaneous transthoracic approach in 14 patients and the bronchoscopic approach in 1 patient. On average 3 markers (range 1-5 markers) were placed per patient to allow for correction of translational and rotational motion. Four to seven days after marker placement a planning CT-scan with slice thickness and spacing of 1.5-2 mm was obtained. The visible tumor (gross tumor volume, GTV) was delineated using the lung window setting. We added a 5 mm margin to the GTV to account for microscopic tumor extension and residual inaccuracy of the synchrony RTS (approximately 1.5 mm) (9-11).

In the treatment room, motion of red light-emitting diodes attached to the patients' chest was registered. This motion was correlated to the location of the implanted markers, determined

by a series of orthogonal x-ray images taken during the respiratory cycle. This correspondence model was used to direct the radiation beam at the tumor. During treatment the correlation model was validated and updated.

Treatment consisted of 60 Gy in 3 fractions for 30 patients. A risk-adaptive treatment schedule consisting of 48-50 Gy in 5-6 fractions was used to treat six patients with central tumors and one patient with a large T2 tumor. Two patients were treated with 45 Gy in 3 fractions by choice of the treating physician. Treatment dose was prescribed to the 78-87% isodose line, covering at least 95% of the PTV. The maximum dose was defined by the 100% isodose line. Treatment was carried out with 2 circular collimator cone sizes (20-60mm) and approximately 130 non-coplanar beams. Treatment planning was done with the On Target treatment planning system, version 3.4.1, Accuray Inc., Sunnyvale, CA. Tissue inhomogeneity was corrected for using the equivalent path-length method. Dose constraints can be found in table 2. None of the patients were treated with chemotherapy prior to treatment or in adjuvant setting.

Table 2. Dose constraints for critical structures

Organ	Volume	Dose (Gy)
Spinal Cord	Any point	6 Gy per fraction
Esophagus	Any point	7 Gy per fraction
Trachea and main bronchus	Any point	10 Gy per fraction
Plexus Brachialis	Any point	8 Gy per fraction
Lung	<31% of the total volume	4.5 Gy per fraction

Quality of Life Instruments

Quality of life assessments were performed before treatment, at 3 weeks and at 2, 4, 6, 9 and 12 months. As the peak incidence of acute toxicity (including radiation pneumonitis) occurs within 6 -12 months of treatment and rarely thereafter (12), QoL was assessed over 12 months, thus allowing the influence of acute toxicity on the QoL to be examined. Patients with evidence of progressive disease were excluded from further analysis to prevent bias caused by disease progression or by the treatment of progressive disease. Quality of life was evaluated by means of the European Organization for Research and Treatment of Cancer quality of life core questionnaire (EORTC QLQ-C30) and the supplementary lung cancer specific module, the QLQ-LC13. The QLQ-C30 (version 3.0) is a 30-item questionnaire composed of five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, pain and nausea and vomiting), a global health status/quality of life

scale and six single items. The single items assess additional symptoms commonly reported by cancer patients including dyspnea, constipation, diarrhea, sleep disturbance, loss of appetite and the financial impact of the disease and treatment. All of the scales and single items have a score in the range of 0 to 100. A high score for the functional and QoL scale represents a high level of functioning/high quality of life, whereas a high symptom score represents a high level of symptoms. The QLQ-C30 questionnaire has been validated in a sample of lung cancer patients in 13 countries (13). The lung cancer module is designed for patients with varying disease stages treated with chemotherapy and/or radiotherapy. It comprises of 13 questions assessing lung cancer associated symptoms (cough, hemoptoe, dyspnea and site specific pain), treatment related side effects (sore mouth, dysphagia, peripheral neuropathy and hair loss) and pain medication. The scoring approach is identical to that of the single items in the QLQ-C30 questionnaire. Both questionnaires have been translated and validated for use in a Dutch population.

Follow-up and toxicity scoring

The first clinical examination was performed three weeks after SRT. Clinical follow-up was performed every three months and a CT-scan was performed 2, 4, 6, 9 and 12 months after treatment. Toxicity was scored at each out-patient visit by the patients' physician using the common terminology criteria for adverse events version 3.0 (CTCAEv3.0) (14). Toxicity was acute if it occurred within 4 months and late if it occurred thereafter.

Statistics

Changes in the mean QoL and symptom scores over time were evaluated with a multilevel mixed-effects linear regression model using 'xtmixed' in Stata version 10.1. The method of restricted maximum likelihood was used to estimate the parameters of the model. Wald tests were used for testing main effects of time. Overall survival was measured from the start of radiotherapy until death of any cause. Patients still alive at the date of last contact were censored. Local tumor control was calculated from the first day of treatment until the diagnosis of a local recurrence. Patients without a local recurrence were censored on the last day of contact. In the absence of biopsy-confirmed viable carcinoma, local recurrence was defined as a 20% increased longest tumor dimension on the CT-scan compared to the previous CT-scan. In addition a corresponding avid lesion on the PET-scan was required. All P-values were two-sided, and a significance level = 0.05 was used.

Results

Compliance of Quality of Life Assessments

Quality of life was assessed in thirty-nine patients. Compliance was 90% at 3 weeks (35 forms of 39 patients still alive without progression), 95% at 2 months, (35/37), 95% at four months (35/37), 100% at 6 months (33/33), 96% at nine months (27/28) and 95% at 12 months (18/19).

Quality of Life and baseline symptoms

Global health status and respiratory symptoms did not deteriorate after CyberKnife treatment as the changes in mean score over time were small and not significant. The size of the PTV and the tumor location (central vs peripheral) did not significantly influence changes in global health status and respiratory symptoms. The only significant change observed in the quality of life scores at every time interval was an improvement of the emotional functioning score; $p=0.02$). None of the other functional scores or symptom scores changed significantly. Changes in the QLQ-C30 mean global health status and functional scores are depicted in figure 1. Changes in QLQ-LC13 symptom scores are depicted in figure 2. The QLQ-LC13 score for dyspnea increased by 6 points at 6 months. At 12 months dyspnea decreased almost to baseline. These changes were not significant. The QLQ-LC 13 score for coughing also did not change over time.

The most frequently reported baseline respiratory symptoms were dyspnoea in 90% of patients and coughing in 67% of patients. Fatigue was the most frequent general symptom affecting 87% of patients. Symptoms at baseline are listed in table 3.

Overall survival and local tumor control

Overall survival was 75% (95% CI=58-86%) at one year and 62% (95% CI=42-77%) at two years. Twelve patients died; six died of metastatic disease and six patients died of intercurrent disease. Causes of intercurrent death were: cardiac failure ($n=3$), mortality during surgery for an aneurysm of the abdominal aorta ($n=1$), sudden death of unknown cause ($n=1$) and general deterioration in an 85-year-old patient ($n=1$). Local tumor control was 97% (95% CI=78-99%) at one and two years. One patient had a local recurrence and eleven patients had distant metastases. Of the eleven patients with distant metastases, five patients had mediastinal lymph nodes. The median follow-up was 17 months (6-31 months).

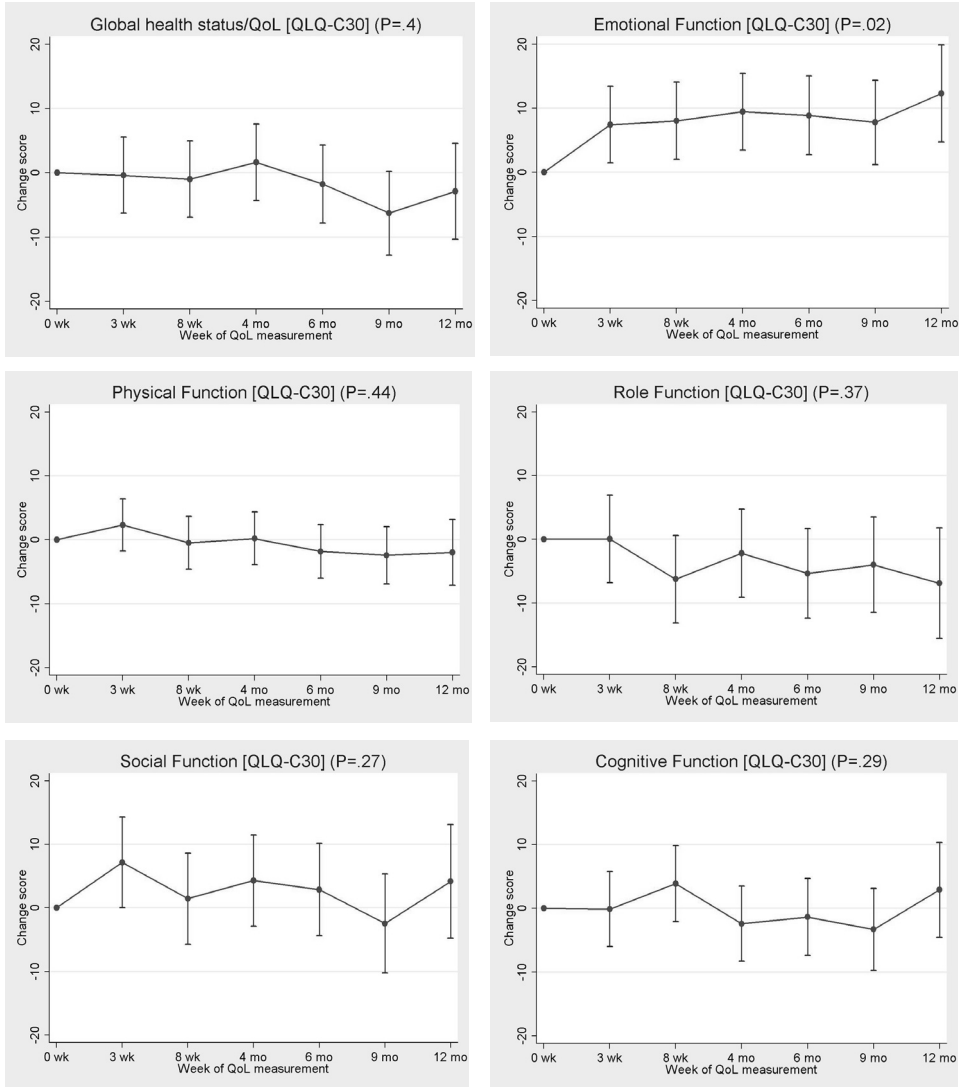


Figure 1. Change in mean global health and functional scores during follow-up

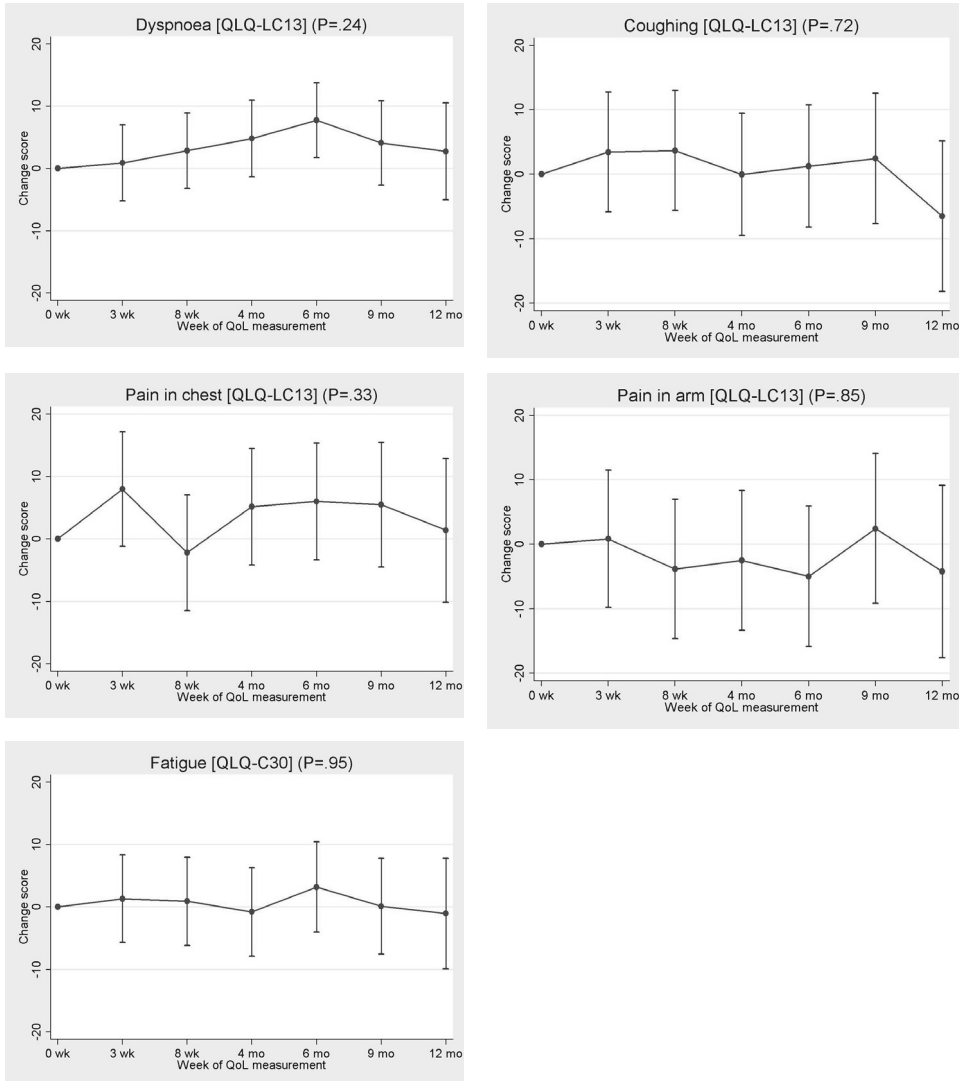


Figure 2. Change in mean QLQ-LC13 symptom score (dyspnea, coughing, chest pain, pain in the arm, and fatigue score) during follow-up.

Table 3. Symptoms at baseline

	Patients with symptoms (%)	Mean score (SD)
Symptoms (QLQ-LC13)		
Dyspnea	90	36 (26)
Fatigue	85	39 (29)
Coughing	67	35 (31)
Pain	51	23 (30)
Insomnia	46	24 (31)
Pain arm/shoulder	39	23 (33)
Pain elsewhere	39	23 (35)
Appetite loss	31	13 (21)
Pain chest wall	26	14 (25)
Hemoptysis	8	3 (9)
Functioning scales (QLQ-C30)		
Global health status	NA	62 (21)
Physical functioning	NA	62 (24)
Role functioning	NA	64 (35)
Emotional functioning	NA	69 (27)
Cognitive functioning	NA	79 (26)
Social functioning	NA	78 (30)

SD: standard deviation NA: not applicable

QLQ-LC 13: Lung cancer-specific quality of life questionnaire

QLQ-C30: Quality of Life Questionnaire C30

Toxicity

No grade 4 or 5 toxicity was observed. Twelve patients had no acute side effects at all. The most common grade 1 and 2 toxicities were fatigue and dyspnea. Acute grade 3 toxicity occurred in one patient (2.6%) who required morphine for thoracic pain. Late grade 3 toxicity occurred in two patients (5.1%) with thoracic pain. None of the patients developed grade ≥ 3 radiation pneumonitis (table 4).

Table 4. Treatment-related toxicity

Grade	No. of patients with indicated score (% of total)
Acute grade 4 or 5	0
Acute grade 3	1 (3)
No Acute toxicity	12 (31)
Late grade 4 or 5	0
Late grade 3	2 (5)
No late toxicity	16 (41)

Discussion

Quality of life and respiratory symptoms did not deteriorate after stereotactic radiotherapy and emotional functioning was significantly improved. The two year survival rate of 62% and the local tumor control rate of 97% were achieved without detrimental effects on the quality of life. The low rate of treatment related toxicity observed during follow-up is in line with the finding that quality of life did not deteriorate.

Studies reporting the impact of conventional high dose radiotherapy on quality of life in stage I NSCLC patients are sparse. One study reported the outcome of 46 stage I NSCLC patients who were treated with 70 Gy in 2 Gy fractions (15). Although the global quality of life did not deteriorate, dyspnea and fatigue gradually worsened, emotional functioning did not improve, and the overall survival was 39% at two years as compared with 62% in our study. The worsening of dyspnea and fatigue was attributed to the natural progressive nature of COPD and the late sequelae of conventional radiotherapy. A worsening of respiratory symptoms was not observed in our study while the incidence of COPD (56% in our study vs 48%) and the duration of follow-up were similar (17 months in our study vs 19 months). Although the duration of follow-up was slightly shorter in our study, it was long enough to observe radiation pneumonitis, which is likely to worsen respiratory symptoms. Functional and symptom scores at baseline also could not account for the difference in outcome as these scores were slightly worse in our study. Although the incidence of toxicity is not mentioned by Langendijk, the low incidence of toxicity after stereotactic radiotherapy may be the reason why symptom scores did not increase in our study. The risk of late toxicity is small (2-8%) after treating patients with stereotactic radiotherapy as treatment volumes are generally small (4, 12, 16). On the other hand, the risk of toxicity after stereotactic irradiation of central tumors is not negligible (17) and may influence the patient's quality of life. In our study no severe toxicity was observed in central tumors (n=6). The reason for this may be the use of the risk-adaptive treatment schedule for central tumors; on the other hand, the number of central tumors was small.

Publications concerning the influence of stereotactic radiotherapy on quality of life in cancer patients are also sparse. The impact of stereotactic radiotherapy on the quality of life has been reported for primary and metastatic liver tumors. A prospective phase I/II study examined the impact of stereotactic treatment on the quality of life in 28 patients with metastatic liver tumors treated mostly with three fractions of 12.5 Gy. Three quality of life instruments were used, among which the EORTC QLQ-C30 (18). High local tumor control was achieved after SRT

and no detrimental changes were observed on the quality of life. These results are similar to those seen in our study. Perhaps the highly localized and non-invasive nature of stereotactic radiotherapy is the reason that treatment was well-tolerated. The increased emotional functioning in our study may be the result of the excellent local tumor control achieved after SRT, giving patients a brighter outlook on their future, while they do not have treatment related side effects.

Although surgery is the treatment of choice in patients with stage I NSCLC and overall 5 year survival rates are as high as 67% (19), the influence of surgery on quality of life is still controversial. Several studies have reported only a temporary decline in the quality of life after surgical treatment, with symptom and functional scores returning to baseline at 3 months after treatment (20, 21), while others state that recovery is not complete (22-25). A prospective study including 159 NSCLC patients, found that physical functioning, dyspnea and pain remained significantly impaired even up to 24 months after surgery. Patients who underwent a pneumonectomy had significantly worse quality of life than those who had a limited resection (22). Although an irreversible detrimental effect of surgery on the quality of life is not consistently reported, the effect of extensive lung parenchyma resection on long-term quality of life seems less controversial. After pneumonectomy, functional and symptom scales did not return to baseline during the 12 months of follow-up, while after lobectomy and wedge-resections, functional and symptom scores returned to baseline after 3 months, indicating a good recovery (23). Although pneumonectomy holds a high risk of worsening a patient's quality of life, this procedure is necessary when tumors are located centrally in the lung. In our study the number of patients with central tumors was low (n=6, 15%) and as reported by Timmerman, the risk of toxicity in these patients is higher than in peripheral tumors (17). The patients with central tumors in our study did not have a large and statistically significant change in quality of life after treatment but the number of patients with central tumors is too small to detect moderate but perhaps clinically relevant changes in quality of life. The impact of the size of the planning target volume on the quality of life is also of great interest as the treatment of larger volumes may increase the risk of worsening quality of life, as is the case for pneumonectomies. Although no large change in quality of life was observed, the small sample size is once again a limitation to detect moderate but perhaps clinically relevant changes. In our study no deterioration is seen in quality of life after SRT, even though the majority of patients were inoperable due to comorbidity. In comparison, even after lobectomy there was at least a temporary decline in quality of life. Survival after stereotactic radiotherapy in our study was 62% at 2 years while it was as high as 67% at five years after surgery (19). The difference in survival may be explained by the different rates

of comorbidity. As the patient populations differ, a randomized trial is evidently necessary to compare the effect of surgery and stereotactic radiotherapy on treatment related changes in quality of life and survival.

Although statistical analysis can identify differences in quality of life scores before and after treatment, interpretation of these changes and their impact on clinical decision making are important, yet complex. Defining the minimum clinically important difference in mean scores is challenging. Treatment may give improvement in one dimension of quality of life at the cost of another dimension. As such, determining the clinical relevance of changes in mean scores after treatment requires consideration of the different dimensions of quality of life but also endpoints such as overall survival and local tumor control. The definition of a clinically relevant difference is subjective as both patients and clinicians are individuals with subjective values. A small change in quality of life may be of great value to a severely disabled patient while it is of little value to a relatively healthy patient. King et al. considered a difference in the mean global quality of life score of 15 points as a relatively large clinical difference and a change in score of 5 points as a relatively small clinical difference (26). This guideline is supported by Osoba et al. who evaluated the impact of changes in EORTC-QLQ mean scores on the way the treated patients experienced these changes (27). Using a subjective significance questionnaire, this study was able to detect changes in mean EORTC-QLQ scores that were perceived as important by patients. When patients indicated moderate changes in perceived quality of life, the mean EORTC-QLQ score changed by 10-20 points. For large perceived changes, the mean EORTC-QLQ score changed by >20 points. As can be seen in figure 1, none of the mean EORTC-QLQ scores in our study changed by ≥ 10 points for more than one of the six time points except emotional functioning. Although our study is non-randomized and small changes in quality of life scores may not be detectable in our study due to population size ($n=39$), the lack of >10 point changes suggests that there are no moderate or large perceived changes in quality of life scores.

Conclusions

The level of quality of life prior to treatment was maintained after treatment with stereotactic radiotherapy and emotional functioning improved significantly. While maintaining the quality of life, stereotactic radiotherapy achieved acceptable overall survival (62% at 2 years), local tumor control (97% at 2 years) and low treatment related toxicity.

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CHAPTER 6

CLINICAL INTRODUCTION OF MONTE CARLO TREATMENT PLANNING; A DIFFERENT PRESCRIPTION DOSE FOR NON-SMALL CELL LUNG CANCER ACCORDING TO TUMOR LOCATION AND SIZE

NC van der Voort van Zyp, MS Hoogeman, S van de Water,
PC Levendag, B van der Holt, B Heijmen, JJ Nuyttens

Abstract

Purpose

To provide a prescription dose for Monte Carlo (MC) treatment planning in patients with non-small-cell lung cancer according to tumor size and location.

Methods

Fifty-three stereotactic radiotherapy plans designed using the equivalent path-length (EPL) algorithm were recalculated using MC. Plans were compared by the minimum dose to 95% of the PTV (D95), the heterogeneity index (HI) and the mean dose to organs at risk (OARs). Based on changes in D95, the prescription dose was converted from EPL to MC. Based on changes in the HI, we examined the feasibility of MC dose prescription to plans recalculated but not re-optimized with MC.

Results

The MC fraction dose for peripheral tumors is 16-18 Gy depending on tumor size. For central tumors the MC dose was reduced less than for peripheral tumors. The HI decreased on average by 4-9% in peripheral tumors and by 3-5% in central tumors. The mean dose to OARs was lower for MC than EPL, and correlated strongly ($R^2 = 0.98-0.99$).

Conclusion

For the conversion from EPL to MC we recommend a separate prescription dose according to tumor size. MC optimization is not required if a HI $\geq 70\%$ is accepted. Dose constraints to OARs can be easily converted due to the high EPL-MC correlation.

Introduction

Stereotactic radiotherapy (SRT) accurately targets and delivers radiation to early stage non-small cell lung cancer (NSCLC), achieving local tumor control rates above 90% (1, 2). Despite these promising results, large deviations in planned and delivered dose are found when treatment planning is based on dose calculation using simple heterogeneity correction algorithms (3-6). Due to the sigmoidal dependence of tumor control and normal tissue toxicity on radiation dose, uncertainties in dose calculation along the steep gradient of the dose-response curve may lower the probability of tumor control or increase toxicity (7).

Simple heterogeneity correction algorithms, such as the equivalent pathlength algorithm (EPL), consistently underestimate the penumbra width in low density regions and overestimate dose to the planning target volume (PTV) (4, 8). These errors occur because the simple algorithms merely account for decreased attenuation of the primary photon beam in low density lung tissue, while increased electron range is not accounted for. Monte Carlo dose calculation (MC) on the other hand explicitly accounts for these effects. It is the most accurate dose calculation algorithm currently available (8-10) as it transports photons and electrons individually through the patient volume. MC can now be used in clinical practice as calculation times have been reduced by high performance computers and variance reduction techniques.

The clinical introduction of MC however requires an adjustment of the currently used EPL prescription dose. Without this adjustment, the risk of normal tissue complications will increase as EPL systematically overestimates the dose delivered to the PTV while MC does not. Furthermore, it is not possible to simply convert the prescription dose from EPL to MC. This is because the magnitude of dose difference between EPL and MC are highly dependent on several factors including beam arrangements, field size, beam energy, and tumor size and location (7). A previous study compared EPL and MC plans for tomotherapy treatment (4). The aim of this study is to 1) compare dose distributions calculated with EPL and MC for CyberKnife treatment, 2) propose a MC prescription dose for NSCLC patients according to tumor size and location and 3) examine the feasibility of MC prescription to EPL plans recalculated with MC, but not re-optimized with MC.

Methods

Treatment plan selection

The treatment plans used in this study were derived from early-stage NSCLC patients previously treated with SRT using the CyberKnife (Accuray Inc., Sunnyvale, CA) (2, 11). Treatment plans were selected to include a range of tumor sizes and locations (central or peripheral) (12). Fifty-three treatment plans were evaluated. Tumor characteristics are listed in table 1.

Table 1. Tumor characteristics

	Peripheral Tumors	Central Tumors	Total group
Total	33	20	53
Tumor Size			
<3 cm	12 (36%)	-	12 (23%)
3-5 cm	12 (36%)	8 (40%)	20 (38%)
>5 cm	8 (24%)	6 (30%)	14 (26%)
>7 cm	1 (3%)	6 (30%)	7 (13%)
Tumor diameter (cm)			
Median	3.8	5.4	4.3
Range	0.9 - 8.0	3.3 - 12.2	0.9 - 12.2
Gross tumor volume (cm ³)			
Median	13.5	47.7	19.6
Range	0.7 - 83.3	4.9 - 370	0.7-370
Planning target volume (cm ³)			
Median	37	97.4	52.6
Range	4.9 - 149	19.1 - 528	4.9 - 528

Treatment planning

An exhale treatment planning CT-scan was made of the entire thorax, with slice thickness and spacing of 1.5-2 mm. The gross tumor volume (GTV) was delineated using lung window setting. The PTV = GTV + 5 mm (2). Organs at risk (OARs) were contoured and defined according to the RTOG 0236 protocol (12). The lungs and spinal cord were contoured in all treatment plans while the heart, oesophagus, bronchus and ribs were contoured if they received ≥ 4 Gy per fraction. Ribs were contoured in bone window setting if any part of the rib received ≥ 4 Gy per fraction. Treatment consisted of 3 x 20 Gy in peripheral tumors, 6 x 8 Gy in central tumors located near the oesophagus and 5 x 12 Gy in all other central tumors. Dose was prescribed to the isodose line covering at least 95% of the PTV (usually the 80% isodose line; range 75-87%). The maximum dose was defined by the 100% isodose line. Dose constraints to OARs have been described previously (13). Treatment plans were gener-

ated using the On Target treatment planning system (version 3.4.1, Accuray Inc., Sunnyvale, CA.). The plans were optimized using EPL dose calculation. This process has been described previously (14).

Recalculation of treatment plans in Multiplan

For the purpose of this study, all treatment plans were transferred from On Target to the Multiplan treatment planning system (version 2.2.0, Accuray Inc, Sunnyvale, CA). Multiplan has implemented both EPL and MC dose calculation. The MC dose calculation algorithm has been validated at our institute (15). It is based on MC particle transport and incorporates ideas from previously developed algorithms (16-19). The treatment plans in Multiplan were first recalculated with EPL, and then with MC. This was done to eliminate subtle differences between the On Target and Multiplan treatment planning systems. A high-resolution grid (256^2) was used for the EPL and MC calculations and the variance in MC calculation was set to 2%. MC computation time was approximately 5-10 minutes. We verified that a variance of 2% yielded similar dose volume parameters as a variance of 1%. As the plan recalculated with MC was the same as the EPL plan, the number of beams and monitor units were the same.

Comparison of EPL and MC re-calculated plans (first aim)

We compared the EPL and MC re-calculated plans by: 1) the minimum dose to 95% of the PTV (D95), 2) the minimum dose to 99% of the PTV (D99), 3) the mean PTV dose, 4) the percentage of PTV receiving the prescribed dose, and 5) the PTV heterogeneity index (HI), defined as the ratio of D95 and D1 (the minimum dose to 1% of the PTV). Although the HI is usually defined as the ratio of D95 and the maximum dose, we chose D95/D1 because the maximum dose is a less reliable dose metric in MC dose calculation (due to statistical uncertainties) (20). Differences in dose parameters were reported as the percentage of dose difference from the EPL plan. Treatment plans were evaluated separately according to a central or peripheral tumor location but also according to tumor size (<3 cm, 3-5 cm and >5 cm). Tumor size and location were taken into account as these parameters are expected to influence the magnitude of dose difference between EPL and MC calculated plans. The tumor size groups were chosen in accordance to the size criteria used by the 7th TNM classification for T1, T2a and T2b/T3 tumors (21). The mean and maximum doses to OARs were also compared.

Monte Carlo Dose prescription

The second aim of our study was to propose a MC prescription dose for NSCLC patients according to tumor size and location. The EPL prescription dose was converted to a MC prescription dose based on the median difference in D95 in EPL and MC recalculated plans. In agreement to recommendations by the AAPM task force, we prescribed the MC prescription dose to an isodose surface rather than to a single point (20).

We prescribed the MC prescription dose to the plans re-calculated with MC. Plans were not optimized with MC as the generation of MC optimized plans requires three time consuming steps in Multiplan. These three steps include: 1) the selection of beams and beam weights by designing a treatment plan using EPL dose calculation 2) re-calculation of the dose distribution for this beam-set using the MC algorithm and 3) optimization of these beam-weights using MC dose calculation. The MC prescription dose was prescribed to the isodose surface that enclosed exactly 95% of the PTV (rather than prescribing dose to a predetermined isodose surface that enclosed at least 95% of the PTV). This means that the PTV coverage with the prescribed dose is per definition 95% in each treatment plan, while the isodose surface varies between treatment plans. Our method of dose prescription will impact the dose heterogeneity of the PTV. Therefore, for the third aim of our study, the HI was used to assess the feasibility of prescribing dose to a variable isodose surface in MC re-calculated (but not re-optimized) plans. We compared the HI in plans recalculated with MC and EPL for peripheral and central tumors. As the current EPL prescription dose for central tumors has not yet been validated, we assessed the feasibility of MC dose prescription for peripheral tumors only. Dose prescription to MC re-calculated plans was considered feasible if the HI in MC re-calculated plans was $\geq 70\%$.

The consequence of prescribing the MC dose to plans recalculated with MC (but not re-optimized with MC) was also assessed for peripheral tumors only. We determined the difference in dose parameters between 1) the plans prescribed with MC and 2) the plans prescribed with EPL and re-calculated with MC (figure 1).

Statistics

The Kruskal-Wallis test was used to determine whether changes in EPL and MC calculated dose parameters were significantly different for the tumor size groups (<3 cm, 3-5 cm and >5 cm). The Spearman rank correlation test and linear regression analysis were used to evaluate the influence of multiple factors on the change in D95 between EPL and MC calculated plans.

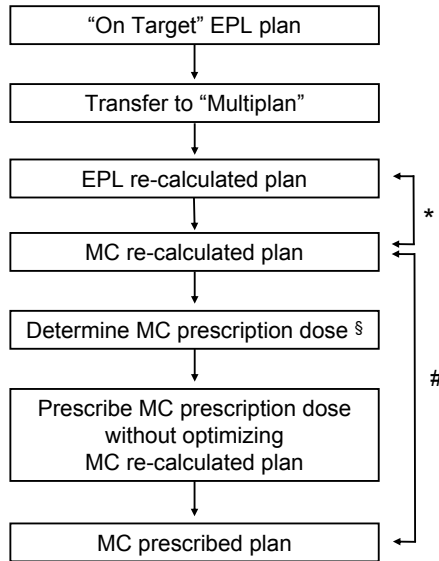


Figure 1. All treatment plans were transferred from “On Target” to the “Multiplan” treatment planning system. In Multiplan, treatment plans were first recalculated with EPL, and then with MC in order to eliminate subtle differences between the treatment planning systems. First aim: we compared EPL and MC re-calculated plans (*). Second aim: the MC prescription dose was determined (§), based on the comparison of D95 in plans recalculated with EPL and MC. Third aim: we determined the impact of MC dose prescription by comparing 1) the MC prescribed plan with 2) the EPL prescribed plan re-calculated with MC (= MC recalculated plan) (#).

The factors included: 1) GTV, 2) tumor diameter, 3) peripheral or central tumor location, 4) the minimal distance between the tumor and soft tissue and 5) the cone size used during treatment. A paired t-test was used to test the null-hypothesis that the average dose parameters were the same in plans prescribed with MC and plans prescribed with EPL and re-calculated with MC. All p-values are two-sided, and a significance level $\alpha = 0.05$ was used.

Results

Peripheral Tumors

The D95, D99 and mean dose to the PTV and GTV were reduced when EPL plans were recalculated with MC (table 2). The reduction in PTV D95, D99 and mean dose was significantly different for the three tumor size groups (Kruskal-Wallis test, $p < 0.01$). The median reduction in MC dose was greatest for small tumors but the inter-patient variation was also greatest for patients with small tumors (figure 2).

Table 2. Reduction in D95, D99 and mean dose when EPL plans are recalculated with MC. The median dose reduction, standard deviation and range are provided.

	% Reduction in D95 (peripheral)	% Reduction in D95 (central)
PTV		
< 3 cm	21 ± 8 (6-33)	-
3-5 cm	17 ± 6 (6-30)	12 ± 5 (7-22)
> 5 cm	10 ± 4 (7-18)	8 ± 4 (3-18)
GTV		
< 3 cm	14 ± 6 (2-25)	--
3-5 cm	12 ± 6 (4-25)	8 ± 3 (6-16)
> 5 cm	8 ± 2 (4-10)	7 ± 3 (3-14)
	% Reduction in D99 (peripheral)	% Reduction in D99 (central)
PTV		
< 3 cm	21 ± 8 (7-35)	-
3-5 cm	18 ± 7 (5-33)	10 ± 7 (3-25)
> 5 cm	11 ± 4 (6-18)	8 ± 5 (1-19)
GTV		
< 3 cm	15 ± 7 (1-27)	-
3-5 cm	13 ± 7 (4-25)	9 ± 3 (6-15)
> 5 cm	8 ± 2 (6-10)	6 ± 4 (0-13)
	% Reduction in Dmean (peripheral)	% Reduction in Dmean (central)
PTV		
< 3 cm	17 ± 7 (3-28)	-
3-5 cm	13 ± 5 (6-23)	12 ± 3 (7-16)
> 5 cm	8 ± 3 (5-13)	8 ± 4 (3-15)
GTV		
< 3 cm	14 ± 5 (2-22)	-
3-5 cm	11 ± 4 (5-19)	10 ± 3 (6-14)
> 5 cm	7 ± 2 (4-11)	7 ± 3 (3-14)

PTV= planning target volume, GTV= gross tumor volume.

D_{mean} = mean dose

D95= dose to 95% of the target volume

D99= dose to 99% of the target volume

The percentage of PTV receiving 60 Gy significantly decreased from on average 97% (range: 90-100%) to 42% (3-81%) when EPL plans were recalculated with MC ($p < 0.01$). Although our EPL dose prescription protocol requires at least 95% of the PTV to receive the prescribed dose, PTV coverage was merely 90% in one EPL plan. In this plan, a concession was made to the PTV coverage in order to spare a rib. The heterogeneity index decreased by on average 9% in tumors <3 cm, 8% in tumors of 3-5 cm, and 4% in tumors > 5 cm when EPL plans were recalculated with MC.

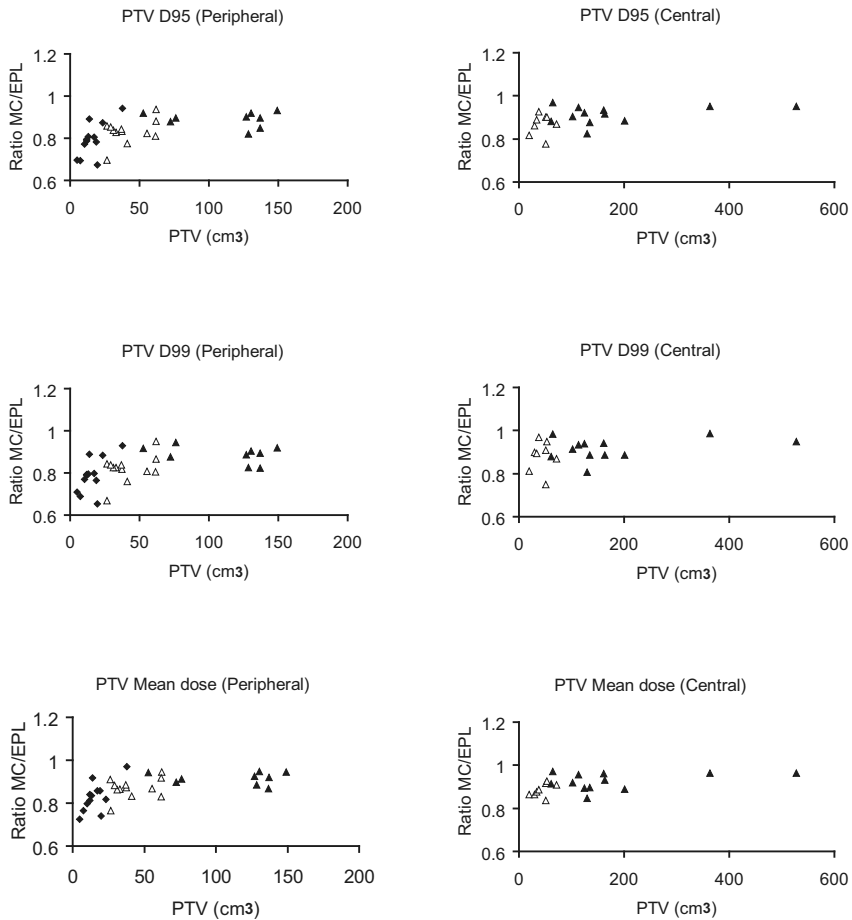


Figure 2. Ratio of MC and EPL calculated dose (PTV D95, D99 and mean dose) for peripheral and central tumors. Bold diamonds represent tumors <3 cm, open triangles represent tumors of 3-5 cm and bold triangles represent tumors >5 cm.

Central Tumors

The D95, D99 and mean dose to the PTV and GTV were reduced when EPL plans were recalculated with MC, but the reduction was less than for peripheral tumors (table 2). The percentage of PTV receiving the prescribed dose significantly decreased from on average 93% (range: 70-99%) to 52% (range: 32-88%) when EPL plans were recalculated with MC ($p < 0.01$). A concession was made to the PTV coverage in seven EPL plans in order to spare OARs. The heterogeneity index decreased on average by 3-5% when EPL plans were recalculated with MC.

Organs at Risk

The mean and maximum dose to OARs calculated with EPL and MC correlated strongly ($R^2 = 0.98-0.99$). When EPL plans were recalculated with MC, the mean doses to OARs decreased by 12% in the lung, 4% in the ribs and 11% in the spine, oesophagus, heart and bronchus (figure 3). The maximum doses to OARs decreased by 12% in the lung, 5% in the ribs, 7% in the spine, 6% in the oesophagus, 8% in the heart and 9% in the bronchus.

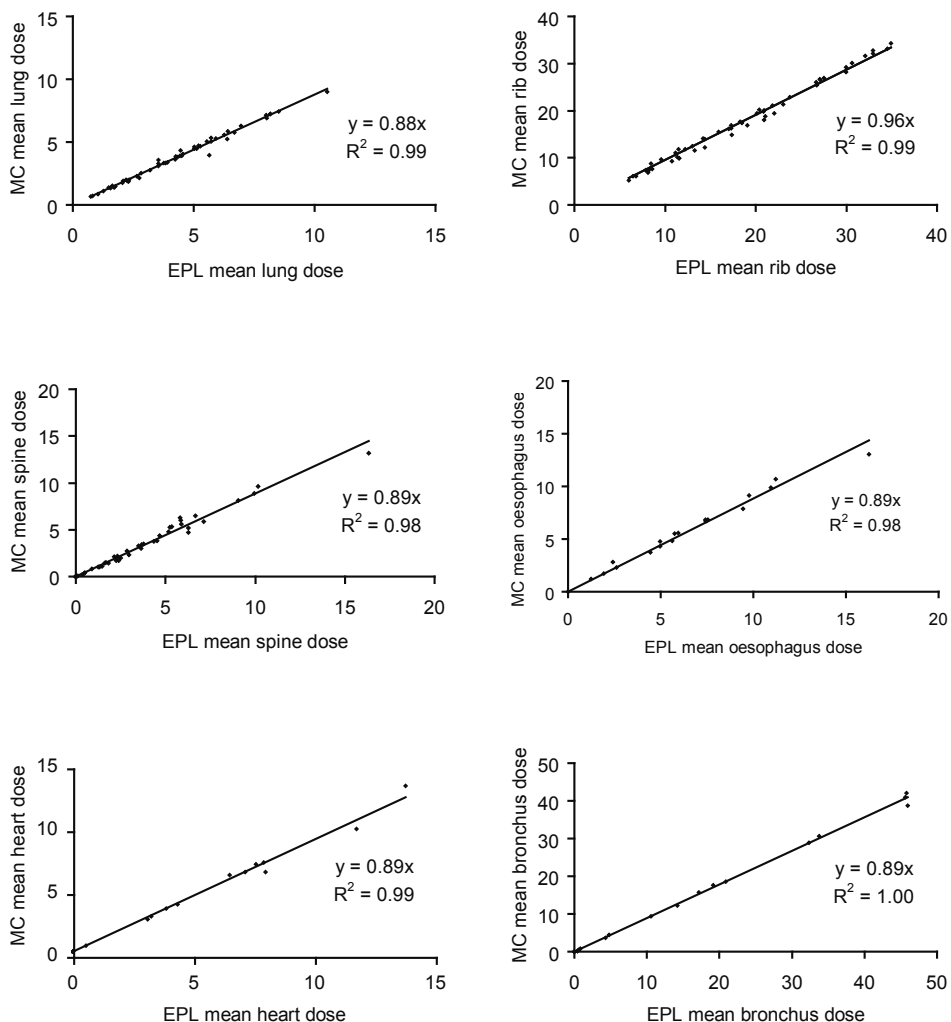


Figure 3. Comparison of EPL and MC mean dose (Gy) to the OARs (lung, rib, spine, oesophagus, heart and bronchus).

Correlation test and Multivariate analysis

The GTV, tumor diameter, peripheral or central tumor location, cone size and the minimal distance between the tumor to soft tissue (d_{\min}) were all associated with the magnitude of dose reduction when EPL plans were recalculated with MC. A multivariate regression analysis with GTV, peripheral or central tumor location and d_{\min} as prognostic variables indicated that only d_{\min} and GTV remained associated with the magnitude of dose reduction. As tumor diameter and cone size were highly correlated to the GTV, these variables were excluded from the multivariate analysis.

Monte Carlo Dose Prescription

Based on the median reduction in D95, the EPL dose to peripheral tumors (3 x 20 Gy) can be converted to the following MC prescription doses: 3 x 16 Gy for tumors <3 cm, 3 x 17 Gy for tumors of 3-5 cm and 3 x 18 Gy for tumors >5 cm. In central tumors located near the oesophagus the EPL dose (6 x 8 Gy) can be converted to the following MC dose: 6 x 7 Gy for tumors of 3-5 cm and 6 x 7.3 Gy for tumors >5 cm. The EPL fraction dose to all other central tumors (5 x 12 Gy) can be converted to 10.4 Gy per fraction for tumors of 3-5 cm and 11 Gy per fraction for tumors >5 cm.

The heterogeneity index for peripheral tumors ranged from 72-90% in EPL recalculated plans and from 64-80% in MC recalculated plans. The HI was lower than 70% in only four plans (figure 4). The HI for central tumors ranged from 64-83% in EPL recalculated plans and from 61-79% in MC recalculated plans.

For peripheral tumors, the average dose parameters (D95, D99 and mean dose) did not differ significantly in 1) plans prescribed with MC and 2) plans prescribed with EPL and re-calculated with MC (table 3).

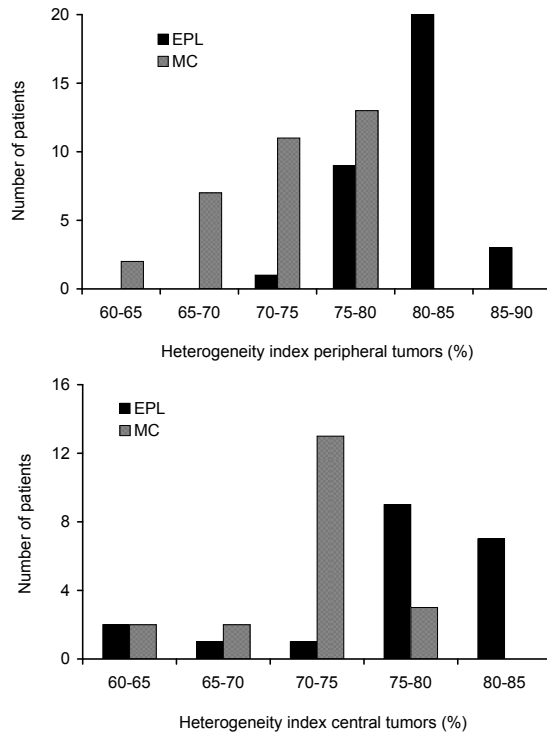


Figure 4. Distribution of the heterogeneity index calculated with EPL and MC for treatment plans of peripheral and central tumors.

Table 3. Average difference in dose parameters for plans prescribed with MC and plans prescribed with EPL (3 x 20 Gy) and recalculated with MC.

	Average dose difference (Gy)	Range in dose difference (Gy)	Paired T-test
D95			
< 3 cm	-0.4	-9.0 – 6.9	0.78
3-5 cm	0.1	-4.6 – 8.4	0.92
> 5 cm	0	-2.3 – 3.4	0.99
D99			
< 3 cm	-0.4	-8.6 – 6.3	0.75
3-5 cm	0	-4.4 – 7.8	0.93
> 5 cm	0	-2.2 – 3.2	1.0
Mean dose			
< 3 cm	-0.3	-10.0 – 8.0	0.83
3-5 cm	0.2	-5.1 – 10.0	0.87
> 5 cm	0.1	-2.5 – 3.8	0.95

D95: dose to 95% of the planning target volume, D99: dose to 99% of the planning target volume

Discussion

The validity of this study is based on a previous in-house validation of the MC algorithm used by Multiplan. The MC algorithm in Multiplan includes a number of simplifications intended to improve calculation speed. These include a measurement based virtual source model and variance reduction techniques (16-19). Despite these simplifications, the MC algorithm predicted dose within 3% of the measured dose in an anthropomorphic chest phantom (15). As the MC-calculated dose closely reflects the actual delivered dose, our results show that for peripheral tumors, EPL overestimates the dose delivered to 95% of the PTV by on average 21% in tumors <3 cm, 17% in tumors of 3-5 cm and 10% in tumors > 5 cm. The overestimation of dose delivered to central tumors is slightly lower: 12% in tumors of 3-5 cm and 8% in tumors >5 cm. Our results also imply that we are currently treating tumors with a wide range of doses as the dose calculated with MC deviated from the EPL dose by 6-33% for peripheral tumors and 3-22% for central tumors. Doses to OARs were also overestimated by the EPL algorithm. As EPL and MC doses to OARs correlate strongly, a simple conversion can be done from EPL to MC.

Other treatment planning studies also show that the EPL algorithm overestimates the dose delivered to pulmonary targets and that the discrepancy between planned and delivered dose varies widely. The EPL algorithm overestimated the mean dose to 72 pulmonary targets by on average 19% (range: 4-40%) compared with MC derived doses (4). A second study compared the dose to pulmonary targets calculated with EPL and the more accurate collapsed cone algorithm (5). EPL overestimated the dose to 95% of the PTV by on average 20% (7-43%). The dose to 95% of the PTV was overestimated most in small tumors. In a third study EPL overestimated the dose to 95% of the PTV by up to 40% of the prescribed dose compared with the more accurate anisotropic analytical algorithm (8). These studies all underline the inaccuracy of EPL dose calculation, but none suggest a prescription dose based on the more accurate algorithms. As the size of EPL dose calculation errors depend on multiple factors, a simply rescaling of the prescription dose is not possible. Despite this, it is generally agreed that dose adjustments are necessary to avoid an increase in dose levels, as this may increase morbidity (22, 23).

Our aim was to adjust the MC prescription dose for peripheral tumors so that it approached the current EPL dose of 3 x 20 Gy. This was the aim because local tumor control was high (96%) and toxicity was low (10%) at this EPL dose (2). Depending on tumor size, we pro-

pose a MC prescription dose of 16-18 Gy for peripheral tumors. For central tumors, the prescription dose can be converted from EPL to MC by reducing the EPL dose by 13% in tumors of 3-5 cm and by 9% in tumors > 5 cm. We cannot provide a MC prescription dose for central tumors at this point as the EPL dose recommendation for central tumors at our institute needs to be assessed after longer follow-up.

A separate dose recommendation was given for tumors < 3 cm, tumors of 3-5 cm and tumors > 5 cm as tumor size was shown to influence dose calculations (5, 8). Tumors smaller than 2.5-3 cm were more susceptible to 20% or higher differences in mean and minimum target dose (4). Distinguishing tumors according to tumor size also seems reasonable from a clinical point of view as large tumors may require a higher dose to achieve local tumor control (1, 2, 24, 25).

For peripheral tumors, we showed that the average dose parameters (D95, D99 and mean dose) did not differ significantly in 1) plans prescribed with MC and 2) plans prescribed with EPL and re-calculated with MC (table 3). Monte Carlo optimization was not required in the majority of cases as the HI was above 70% in all but four MC recalculated plans. Therefore it was feasible to prescribe dose to plans re-calculated but not re-optimized with MC as long as a HI $\geq 70\%$ is accepted. The lack of optimization was pointed out in a comment concerning the publication by Xiao et al. In contrast to Xiao's study, we optimized our treatment plans using EPL rather than no correction at all. Optimization using MC provides the possibility to further improve already acceptable treatment plans.

Although conversions of prescription dose from EPL to MC have not yet been published, conversions from other simple to more complex algorithms have been published for non-CyberKnife treatments. The Dutch ROSEL study recommended 3 fractions of 20 Gy when calculations were based on "type a" algorithms (such as the EPL algorithm) and 3 fractions of 18 Gy when treatment planning was based on more accurate "type b" algorithms (22). A study based on the RTOG 0236 trial suggested 3 fractions of 18-19 Gy when converting from dose calculation based on unit density to "type b" dose calculation (23). These studies did not provide a recommendation based on tumor size and the recommended dose was higher than our recommendation. The RTOG recommendation is probably higher than our recommendation because the current actual delivered dose is higher in the RTOG trial (3 x 20 Gy based on unit density without heterogeneity correction is a higher dose than 3 x 20 Gy based on EPL). Further research is recommended to define a new dose-effect relationship for MC

prescribed plans; either in prospective clinical trials or through retrospective analysis aimed at determining the true tumor control probability and normal tissue complication probability using MC recalculated plans.

Conclusion

The EPL algorithm overestimates the actual delivered dose and we are currently treating tumors with a wide range of doses. For a conversion from EPL to MC, we recommend a separate prescription dose according to tumor size. For peripheral tumors we recommend the following dose schedules: 3 x 16 Gy for tumors <3 cm, 3 x 17 Gy for tumors of 3-5 cm and 3 x 18 Gy for tumors >5 cm. If the dose is prescribed to the D95 and a HI of 70% is accepted, then for most patients it is not necessary to optimize treatment plans with MC. As the dose to organs at risk calculated with EPL and MC correlate strongly, a simple conversion can be done to obtain MC dose constraints. For central tumors, a dose recommendation cannot be given at this moment as our EPL dose schedules for central tumors need to be assessed after longer follow-up.

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CHAPTER 7

DISCUSSION

Discussion

The treatment of choice for patients with stage I non-small cell lung cancer is surgery. Despite this, many patients with operable tumors cannot tolerate surgery due to smoking-related comorbidity. The problem of inoperability due to severe comorbidity and patient frailty is expected to increase as the life expectancy of the general population increases. For inoperable patients with stage I non-small cell lung cancer (NSCLC) the results of conventional 3D-conformal radiotherapy have been disappointing. Long-term survival rates ranged from 5-30% and are far inferior to surgical results of 50-70% (1-3). It is known from conventional radiotherapy studies that higher radiation doses improve not only local tumor control but also improve the overall survival of NSCLC patients (3, 4). Dose escalation is however limited by the typically large radiation fields that are required to account for geometrical uncertainties related to patient set-up and tumor motion. The introduction of stereotactic radiotherapy has enabled dose escalation without increasing toxicity, as the radiation dose is precisely targeted and delivered to the tumor, while respiratory tumor motion is accounted for. Although there are several stereotactic radiotherapy systems, characteristic to all stereotactic radiotherapy (SRT) treatments is the precise delivery of large fraction sizes in a short overall treatment time.

At the Erasmus MC Daniel den Hoed Oncology Center, stage I NSCLC patients are treated with the CyberKnife stereotactic radiotherapy system using real-time respiratory tumor tracking. Real-time tumor tracking corrects for tumor motion during respiration by repositioning the radiation beam to the position of the moving tumor. As the tumor is not directly visible during treatment, this technique requires the insertion of radio-opaque markers in or near the tumor. In order to accurately target the tumor, it is essential that the position of the markers remain stable relative to the position of the tumor. The stability of these surrogate markers has been reported in **chapter 2**. The markers were placed via the percutaneous intrapulmonary approach. Similar to other studies (5, 6), our results show that markers placed via the percutaneous intrapulmonary approach are generally stable, with a median displacement of 1.3 mm. However, large displacements in marker position may occur; 12% of markers were displaced by more than 5 mm and 5% of the markers were displaced by more than 10 mm. As marker displacements may be large, we recommend the placement of multiple markers. Multiple markers enable a reliable check for marker displacement as changes in the marker configuration are easily detected. This is not possible if a single marker is used. Displacement of a single marker may therefore remain undetected and cause systematic,

potentially dangerous localization errors. An argument against the use of multiple markers is the higher risk of a pneumothorax when multiple markers are implanted. This risk has however been reduced by the development of transbronchial, trans-oesophageal and vascular marker placement techniques (7-9).

Stereotactic radiotherapy has emerged as an important treatment modality for inoperable patients with stage I NSCLC. In **chapter 3** the results of stereotactic radiotherapy using real-time tumor tracking are reported for 70 patients with stage I NSCLC. The local tumor control rate and treatment-related toxicity after real-time tumor tracking are comparable to the outcomes reported after treatment using other stereotactic radiotherapy approaches. Although not statistically significant, the actuarial local tumor control rate was higher in patients treated with a higher radiation dose (96% using 60 Gy versus 78% using 45 Gy) and for patients with smaller tumors (100% for T1 tumors versus 89% for T2 tumors). As merely four local recurrences were observed in our study, it is not possible to make conclusions about the influence of radiation dose and tumor size on local tumor control. Nevertheless it is interesting to note that other studies have also observed lower tumor control rates for lower radiation doses and larger tumors (10). The two-year overall survival rate in our study was 62% compared with 64-83% reported in the literature (11, 12). Presumably patient selection plays a role in the variation of overall survival. A drawback of our study is the absence of pathologic confirmation of malignancy in 49% of patients. In these patients, the risk of obtaining pathology via trans-thoracic biopsies was too high due to poor pulmonary function. This is a common problem in radiotherapy studies. Nevertheless, the risk of malignancy is very high in older patients with a growing lesion on the CT-scan, a corresponding avid lesion on the PET-scan, and a history of smoking (13). Taking this into account, the local tumor control rates achieved after stereotactic radiotherapy are high and stereotactic radiotherapy should be considered as a good alternative for inoperable patients with stage I NSCLC.

As the incidence of octogenarians with stage I NSCLC increases, and only selected patients are surgical candidates, it is important to investigate the role of stereotactic radiotherapy in this particular patient population. **Chapter 4** reports the outcome of stereotactic radiotherapy in 38 octogenarians with stage I NSCLC. In this population the rate of comorbidity was high (Charlson comorbidity score >5 in 16% of patients). Despite this, the local tumor control rate was excellent while toxicity related to marker placement and treatment was low. Five percent of patients had toxicity related to marker placement, 5% of patients had acute grade 3 toxicity and 16% of patients had late grade 3 toxicity after treatment. The overall survival

in octogenarians treated in our study is however low compared with surgical series (44% versus 34-79% at two years) (14-16). This difference in overall survival is not surprising as surgical series carefully select physically fit octogenarians. Despite careful patient selection, the current rates of mortality still vary enormously after surgery in octogenarians (0-15%) (14, 16-19). Favorable outcomes are reported after limited resections performed in high volume hospitals. Although not all octogenarians will be suitable candidates for surgery, best supportive care cannot always be justified. The two-year overall survival of untreated stage I NSCLC was merely 8% (20). The treatment of octogenarians with stage I NSCLC remains a challenge due to patient frailty and comorbidity. Unfortunately randomized trials are lacking and cannot guide treatment decisions. Despite the size of our study, our results show that stereotactic radiotherapy should be considered in octogenarians in whom the surgical risk is high, even when they have severe comorbidity.

Although improvement of local tumor control and overall survival are the main goal of any cancer treatment, an equally important aim is to maintain or improve the patients' quality of life (QoL). The impact of treatment on the QoL is especially relevant in patients with NSCLC, given the limited overall survival and the high level of comorbidity in the majority of these patients. **Chapter 5** reports the impact of stereotactic radiotherapy on the quality of life of 39 patients with inoperable, pathology-proven, stage I NSCLC. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the lung cancer-specific questionnaire (EORTC QLQ-LC13) were used to investigate changes in quality of life. Assessments were done before treatment and at regular intervals after treatment. Global health status and respiratory symptoms did not deteriorate after stereotactic radiotherapy. The only significant change observed for QoL scores at every time interval was an improved emotional functioning score. Despite the limited size of our study, the lack of large changes in the QoL scores shows that patients with stage I NSCLC can be treated with stereotactic radiotherapy without causing significant deterioration in the patients' quality of life.

Despite the promising treatment outcomes after stereotactic radiotherapy, large deviations in planned and delivered dose are found when treatment planning is based on dose calculation using simple heterogeneity correction algorithms (21-24). In **chapter 6** fifty-three treatment plans calculated with the equivalent path-length algorithm (EPL) were compared to the same treatment plans recalculated with the more accurate Monte Carlo algorithm (MC). Our results showed that the EPL algorithm overestimated the delivered dose by 6-33%. This implies that

we are currently treating tumors with a wide range of doses. An aim of our study was to propose a Monte Carlo prescription dose that approached the EPL prescription dose (3 x 20 Gy). As the EPL dose is overestimated most in small tumors, we recommend a different MC prescription dose according to tumor size. Based on the reduction in dose to 95% of the planning target volume, the EPL dose to peripheral tumors can be converted to a MC prescription dose of 3 x 16-18 Gy depending on the tumor size. Distinguishing tumors according to tumor size also seems reasonable from a clinical point of view as large tumors may require a higher dose to achieve local tumor control (10, 11, 25, 26). The dose constraints to organs at risk can be easily converted due to the high EPL-MC correlation. Other treatment planning studies also underline the inaccuracy of the EPL dose calculation algorithm. A study based on the RTOG 0236 trial suggested 3 fractions of 18-19 Gy when converting to a more accurate dose calculation algorithm (27). This recommendation is higher than ours, but the initial delivered dose was also higher (as 3 x 20 Gy unit density without heterogeneity correction is a higher dose than 3 x 20 Gy based on EPL).

Future Directions

The use of more accurate dose calculation algorithms will give more insight into the actual dose-effect relationship and will also facilitate the comparison of treatment outcomes in clinical trials. The Monte Carlo calculation algorithm is the most accurate dose calculation algorithm currently available. It can now be used in clinical practice as the calculation times have been drastically reduced by high performance computers and variance reduction techniques. In chapter 6 we provided a recommendation for MC dose prescription. Further research is recommended to verify these prescription doses and to define a new dose-effect relationship for MC prescribed plans. This can be done either in prospective clinical trials or through retrospective analysis aimed at determining the true tumor control probability and normal tissue complication probability using MC re-calculated plans.

The majority of patients treated with stereotactic radiotherapy are inoperable patients and have peripherally located tumors. The experience with stereotactic radiotherapy in centrally located tumors is still limited. Risk-adaptive treatment schedules are currently used, as severe toxicity was reported after treatment with 60-66 Gy in three fractions (28). To determine the role of stereotactic radiotherapy in centrally located tumors, more research is needed to assess the long-term outcome after using the risk-adaptive treatment schedule. It is also

of great interest to examine the role of stereotactic radiotherapy in operable patients with stage I NSCLC. Although surgery is the treatment of choice for operable patients with stage I NSCLC, stereotactic radiotherapy may be a less-invasive and good alternative. A multi-institutional Japanese study reported promising outcome in a subgroup of operable patients treated with stereotactic radiotherapy. The local tumor control rate was >90% when operable patients were treated with a biological effective dose ≥ 100 Gy (11). These outcomes are comparable to those reported after surgery. Results from prospective randomized trials comparing surgery to stereotactic radiotherapy are on their way. One of these trials is the STARS trial, an international randomized study to compare CyberKnife stereotactic radiotherapy with surgical resection in stage I NSCLC. The other is the Dutch ROSEL trial.

In addition to the treatment of non-small cell lung cancer, the experience with stereotactic radiotherapy has been carefully extended to patients with oligometastases to the lung. Okunieff reported an excellent local tumor control rate of 91% at three years with the delivery of 50-55 Gy in 5 fractions (29). At our institute we are currently enrolling patients with a maximum of 5 oligometastases to the LUMERAS study. The aim of this single arm non-randomized trial is to determine whether stereotactic radiotherapy can achieve local tumor control rates of at least 90% in patients with lung metastases, an outcome considered comparable to surgery.

Conclusions

- Markers placed via the percutaneous intrapulmonary approach are generally stable but large displacements may occur.
- The placement of multiple markers is recommended for real-time tumor tracking as this allows marker displacements to be easily detected by changes in the marker configuration.
- The results after stereotactic radiotherapy using real-time tumor tracking are excellent and similar to those achieved using other stereotactic radiotherapy systems (two year local tumor control rate of 96% when treated with 60 Gy).
- Stereotactic radiotherapy should be considered in elderly patients even in the presence of multiple comorbidities.
- Patients with stage I NSCLC can be treated with stereotactic radiotherapy without causing significant deterioration in the quality of life.
- Emotional functioning improves in patients with stage I NSCLC after treatment with stereotactic radiotherapy using the CyberKnife.

- Simple dose calculation algorithms such as the Equivalent path-length algorithm overestimate the dose delivered to the planning target volume.
- For the conversion from equivalent pathlength (EPL) dose calculation to Monte Carlo (MC) dose calculation we recommend a different prescription dose according to tumor size (3 x 16 Gy for tumors <3 cm, 3 x 17 Gy for tumors of 3-5 cm, and 3 x 18 Gy for tumors >5 cm).

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CHAPTER 8

SAMENVATTING

Samenvatting

Chirurgie is de eerste keuze bij de behandeling van patiënten met een stadium I niet-kleincellig longcarcinoom (NKCLC). Veel van deze patiënten zijn echter inoperabel vanwege comorbiditeit. Inoperabiliteit op basis van comorbiditeit zal naar verwachting toenemen omdat de levensverwachting van de algemene bevolking stijgt. Voor inoperabele patiënten met een stadium I NKCLC zijn de resultaten van conventionele 3D-conformatie radiotherapie teleurstellend. Het overlevingspercentage is inferieur aan die van chirurgie (5-30% versus 50-70%) (1-3). Uit studies blijkt dat een hogere bestralingsdosis niet alleen de lokale tumorcontrole verbetert van patiënten met een NKCLC, maar ook de overlevingskans (3, 4). Een verhoging van de dosis wordt echter beperkt door de grote bestralingsvelden die doorgaans nodig zijn om te compenseren voor tumorbeweging en de onzekerheid in de exacte ligging van de patiënt. Met de introductie van stereotactische radiotherapie kan de bestralingsbundel nauwkeuriger op de tumor worden gericht. Hierdoor kan de grootte van de bestralingsvelden worden beperkt en de dosis worden verhoogd zonder dat de bijwerkingen van de behandeling toenemen. Er bestaan verschillende systemen waarmee stereotactische radiotherapie kan worden uitgevoerd, maar karakteristiek voor alle stereotactische radiotherapie behandelingen is dat in een kort tijdsbestek een hoge dosis wordt toegediend.

In het Erasmus MC Daniel den Hoed Oncologisch Centrum worden patiënten met een stadium I NKSLC behandeld met het CyberKnife stereotactisch radiotherapie systeem, dat is uitgevoerd met “real-time respiratory tumor tracking”. “Real-time tumor tracking” corrigeert voor tumorbeweging als gevolg van de ademhaling door de bestralingsbundel de bewegende tumor te laten volgen. Omdat de tumor niet direct zichtbaar is tijdens de behandeling worden er radiopake markers geplaatst in of nabij de tumor. Om de bestralingsbundel nauwkeurig op de tumor te kunnen richten, is het essentieel dat de markers ten opzichte van de tumor niet verplaatsen (**hoofdstuk 2**). De markers worden via de percutane intrapulmonale techniek geplaatst. Onze resultaten tonen dat de markers zich over het algemeen niet verplaatsen ten opzichte van de tumor (mediane verplaatsing van 1.3 mm). Dit komt overeen met de resultaten van andere studies (5, 6). Grote verplaatsingen kunnen echter voorkomen; 12% van de markers waren meer dan 5 mm verplaatst en 5% van de markers waren meer dan 10 mm verplaatst. Omdat de verplaatsing van een marker groot kan zijn, raden wij aan om meer dan één marker te plaatsen. Het plaatsen van meer dan één marker maakt het mogelijk om marker verplaatsingen op eenvoudige wijze op te sporen door de onderlinge afstand van de markers te controleren. Dit is niet mogelijk als een enkele marker wordt geplaatst. De verplaatsing

van een enkele marker kan onopgemerkt blijven en leiden tot een grote systematische fout in het richten van de bestralingsbundel op de tumor. Een argument tegen het plaatsen van meer dan één marker is het grotere risico op een klaplong. Dit risico is echter gereduceerd door de ontwikkeling van alternatieve markerplaatsingstechnieken zoals transbronchiale, transoesofageale en vasculaire technieken (7-9).

Stereotactische radiotherapie is een belangrijke behandelmodaliteit voor patiënten met een stadium I NKCLC. In **hoofdstuk 3** rapporteren wij de resultaten van stereotactische radiotherapie met behulp van “real-time tumor tracking” in 70 patiënten met een stadium I NKCLC. De lokale tumorcontrole en de toxiciteit na “real-time tumor tracking” zijn vergelijkbaar met de resultaten na stereotactische radiotherapie met andere systemen. De lokale tumorcontrole was 96% na behandeling met 60 Gy en 78% na behandeling met 45 Gy. De lokale tumorcontrole was 100% voor T1 tumoren en 89% voor T2-tumoren. Het is op basis van onze studie niet mogelijk om conclusies te trekken over de invloed van bestralingsdosis en tumorgrootte op de lokale tumorcontrole aangezien er maar vier lokale tumorrecidieven waren. Desondanks is het opvallend dat ook andere studies een lagere lokale tumorcontrole hebben geobserveerd bij een lagere bestralingsdosis en bij grotere tumoren (10). De tweejaars-overleving was 62% in onze studie, vergeleken met 64-83% in andere studies (11, 12). Waarschijnlijk speelt patiëntselectie een belangrijke rol in de variatie van de overleving. Een nadeel van onze studie is dat er geen pathologische bevestiging van maligniteit was in 49% van de patiënten. In deze patiënten was de longfunctie vaak te slecht, en het risico van een klaplong te groot, zodat een transthoracale biopsie niet werd verricht. Dit is een veelvoorkomend probleem in radiotherapie studies, aangezien patiënten met een acceptabele longfunctie meestal geopereerd worden. Desondanks is het risico op maligniteit groot bij patiënten in deze oudere rokende bevolkingsgroep die een groeiende lesie hebben op de CT-scan, en een corresponderende aankeurende afwijking op de PET-scan (13). Hiervan uitgaande, is de lokale tumorcontrole na stereotactische radiotherapie hoog. Stereotactische radiotherapie kan als een goed alternatief voor chirurgie worden beschouwd in inoperabele patiënten met een stadium I NKCLC.

Het is van belang om de rol van stereotactische radiotherapie bij ouderen te onderzoeken aangezien het aantal ouderen met een stadium I NKCLC toeneemt en veel van deze patiënten geen geschikte kandidaten zijn voor een chirurgische behandeling. **Hoofdstuk 4** beschrijft de resultaten van stereotactische radiotherapie in 38 patiënten van 80 jaar en ouder met een stadium I NKCLC en met veel comorbiditeit (Charlson comorbiditeit score >5 in 16% van de

patiënten). Desondanks is de lokale tumorcontrole uitstekend en zijn er weinig bijwerkingen van de markerplaatsing en de bestraling. Vijf procent van de patiënten had bijwerkingen na markerplaatsing. Na de bestraling had 5% van de patiënten acute graad 3 bijwerkingen en 16% van de patiënten had late graad 3 bijwerkingen. De overleving van tachtigjarigen na stereotactische radiotherapie is echter kort vergeleken met chirurgische studies (44% versus 34-79% na 2 jaar) (14-16). Het verschil in overleving is echter niet verassend aangezien chirurgische studies zeer zorgvuldig patiënten selecteren met een goede conditie. Ondanks de zorgvuldige patiëntselectie, varieert de mortaliteit aanzienlijk na een chirurgische behandeling van tachtigjarigen (0-15%) (14, 16-19). Er worden betere uitkomsten gerapporteerd na beperkte resecties in gespecialiseerde centra. Helaas komen lang niet alle tachtigjarigen in aanmerking voor een chirurgische behandeling. “Best supportive care” in deze patiënten is echter niet altijd gerechtvaardigd. De twee-jaars-overleving van patiënten met een onbehandeld stadium I NKCLC was slechts 8% (20). De behandeling van tachtigjarigen met een stadium I NKCLC blijft uitdagend door de kwetsbaarheid van deze patiënten, en de hoge incidentie van comorbiditeit. Helaas ontbreken gerandomiseerde studies om keuzes in de behandeling te vergemakkelijken. De grootte van onze studie is beperkt. Desondanks toont onze studie aan dat stereotactische radiotherapie een goede behandeloptie is bij tachtigjarigen die niet in aanmerking komen voor een chirurgische behandeling, zelfs wanneer er sprake is van veel comorbiditeit.

De verbetering van overleving en lokale tumorcontrole zijn de primaire doelen van elke kankerbehandeling. Even belangrijk is het behouden of verbeteren van de kwaliteit van leven (QoL) van de patiënt. De invloed van een behandeling op de QoL is vooral van belang bij patiënten met een NKCLC omdat de overlevingsduur beperkt is en de incidentie van comorbiditeit in deze patiëntengroep hoog is. **Hoofdstuk 5** rapporteert de invloed van stereotactische radiotherapie op de kwaliteit van leven bij 39 patiënten met een niet operabel, pathologisch bewezen stadium I NKCLC. De “European Organization for Research and Treatment of Cancer Quality of Life Questionnaire” (EORTC QLQ-C30) en de longkanker specifieke vragenlijst (EORTC QLQ-LC13) werden gebruikt om veranderingen in de kwaliteit van leven op te sporen. De vragenlijsten werden voor de behandeling ingevuld en op regelmatige intervallen na de behandeling. De globale gezondheid en respiratoire symptomen bleven onveranderd na stereotactische radiotherapie. De enige significante verandering in QoL scores was een verbetering in het emotioneel functioneren. Ondanks de beperkte grootte van onze studie laat de afwezigheid van grote veranderingen in QoL zien dat patiënten met een

stadium I NKCLC behandeld kunnen worden met stereotactische radiotherapie zonder dat dit een significante verslechtering van de kwaliteit van leven geeft.

De uitkomsten van stereotactische radiotherapie zijn veel belovend. Desondanks worden er grote verschillen gezien in de bestralingsdosis als deze wordt berekend met een eenvoudig of een geavanceerd algoritme (21-24). **Hoofdstuk 6** vergelijkt de dosis van 53 bestralingsplannen berekend met het “equivalent path-length algoritme” (EPL), en daarna herberekend met het nauwkeurigere “Monte Carlo algoritme” (MC). Onze resultaten laten zien dat de dosisberekening met het EPL algoritme de gegeven bestralingsdosis overschat met 6-33%. Dit impliceert dat tumoren op dit moment worden behandeld met een zeer uiteenlopende dosis. Een van de doelen van onze studie was om een aanbeveling te maken voor een MC dosisvoorschrift welke het huidige EPL dosis voorschrift benadert (3 x 20 Gy). Aangezien de EPL dosis het meest wordt overschat in kleine tumoren, raden wij aan om de MC dosis te laten afhangen van de grootte van de tumor. Op basis van de afname in D95 (dosis in 95% van het PTV), stellen wij voor om de EPL dosis om te zetten naar een MC voorschrift van 3 x 16 Gy, 3 x 17 Gy, of 3 x 18 Gy afhankelijk van de tumorgrootte. Het onderscheid in tumorgrootte lijkt ook klinisch relevant omdat grotere tumoren mogelijk een hogere dosis nodig hebben om lokale tumorcontrole te bereiken (10, 11, 25, 26). De dosis “constraints” voor gezonde weefsels kunnen gemakkelijk worden omgerekend doordat de EPL en MC dosis voor de gezonde weefsels sterk aan elkaar gecorreleerd zijn. Andere treatment planning studies benadrukken ook de onnauwkeurigheid van het EPL dosisberekeningsalgoritme. Een studie gebaseerd op de RTOG 0236 trial suggereert 3 fracties van 18-19 Gy indien nauwkeurigere algoritmes worden gebruikt (27). Deze aanbeveling is hoger dan die van ons (3 x 16-18 Gy) omdat het oorspronkelijke dosisvoorschrift in die studie was gebaseerd op 3 x 20 Gy “unit density” zonder heterogeniteitscorrectie (hetgeen een hogere dosis is dan 3 x 20 Gy EPL).

Toekomst Perspectieven

Het gebruik van een nauwkeuriger algoritme voor dosisberekening zal niet alleen een beter inzicht geven in de werkelijke dose-effect relatie, maar het zal ook de vergelijking van behandeluitkomsten vergemakkelijken. Het Monte Carlo algoritme is nu het meest nauwkeurige dosisberekeningsalgoritme. Het kan tegenwoordig in de praktijk worden toegepast omdat de berekentijden drastisch zijn verlaagd door “high performance” computers en “variance

reduction” technieken. In hoofdstuk 6 geven wij een aanbeveling voor MC gebaseerde dosisvoorschriften. Aanvullend onderzoek is nodig om de nieuwe MC dosisvoorschriften te verifiëren en een nieuwe dosis-effect relatie te definiëren voor dosisverdelingen berekend met MC. Dit kan via prospectieve klinische studies worden onderzocht of via retrospectieve analyse, waarbij bestaande bestralingsplannen worden herberekend met MC en de MC dosis wordt gerelateerd aan 1) de lokale tumorcontrole en 2) de incidentie van complicaties.

Het merendeel van de patiënten die met stereotactische radiotherapie worden behandeld zijn inoperabel en hebben perifeer gelegen tumoren. De ervaring met stereotactische radiotherapie bij patiënten met een centraal gelegen tumor is nog beperkt. Risicoaangepaste behandelingschema's worden op dit moment gebruikt aangezien ernstige toxiciteit is gemeld bij een dosis van 60-66 Gy in drie fracties (28). Om de rol van stereotactische radiotherapie bij patiënten met een centraal gelegen tumor te bepalen is aanvullend onderzoek nodig om de uitkomst na langere termijn van aangepaste schema's te bepalen. De rol van stereotactische radiotherapie bij operabele patiënten met een stadium I NKCLC staat in de belangstelling. Voor operabele patiënten met een stadium I NKCLC heeft chirurgische behandeling de voorkeur. Desondanks kan stereotactische radiotherapie een minder invasief en goed alternatief zijn. Een multi-institutionele Japanse studie rapporteerde een veel belovend resultaat na stereotactische radiotherapie in een subgroep van operabele patiënten. Bij operabele patiënten behandeld met een biologische effectieve dosis ≥ 100 Gy was de lokaal tumorcontrole $>90\%$ (11). Deze uitkomsten zijn vergelijkbaar met die na chirurgie. Prospectief gerandomiseerde studies die chirurgie vergelijken met stereotactische radiotherapie zijn gestart. Een hiervan is de STARS trial, een internationale studie die CyberKnife stereotactische radiotherapie vergelijkt met chirurgische resectie van een stadium I NKCLC. Een andere studie is de Nederlandse ROSEL trial.

Naast de behandeling van patiënten met een niet-kleincellig longcarcinoom, wordt de ervaring met stereotactische radiotherapie nu voorzichtig uitgebreid naar patiënten met oligometastasen in de long. Okunieff rapporteerde een uitstekend lokale tumorcontrole van 91% na drie jaar met 50-55 Gy in 5 fracties (29). In het Erasmus MC Daniel den Hoed Oncologisch Centrum worden op dit moment patiënten met maximaal 5 oligometastasen geïncludeerd in de LUMERAS studie. Het doel van deze “single-arm”, niet gerandomiseerde studie is om te bepalen of stereotactische radiotherapie een lokale tumorcontrole van tenminste 90% kan bereiken in patiënten met long metastasen; een uitkomst die vergelijkbaar wordt geacht aan chirurgische behandeling.

Conclusies

- Markers die geplaatst worden via de percutane intrapulmonale techniek zijn over het algemeen stabiel; er kunnen echter grote verschuivingen optreden.
- Het is raadzaam om meer dan één marker te plaatsen voor “real-time tumor tracking” aangezien multiële markers het mogelijk maken om marker verplaatsingen op eenvoudige wijze op te sporen door de onderlinge afstand van de markers te controleren.
- De resultaten van stereotactische radiotherapie met “real-time tumor tracking” zijn uitstekend en vergelijkbaar met de resultaten na behandeling met andere stereotactische systemen (lokale tumorcontrole na twee jaar van 96% na behandeling met 60 Gy).
- Stereotactische radiotherapie moet overwogen worden bij de behandeling van ouderen, ook bij de aanwezigheid van comorbiditeit.
- Patiënten met een stadium I NKCLC kunnen behandeld worden met stereotactische radiotherapie zonder dat hun kwaliteit van leven significant afneemt.
- Het emotioneel functioneren verbetert significant in patiënten met een stadium I NKCLC die behandeld zijn met stereotactische radiotherapie door middel van het CyberKnife.
- Simpele dosis berekeningsalgoritmes zoals het “equivalent pathlength” algoritme overschatten de dosis in het “planning target volume”.
- Voor het omrekenen van de dosis met “equivalent pathlength” naar Monte Carlo (MC) raden wij aan om de MC dosis voor te schrijven op basis van tumor-grootte (3 x 16 Gy voor tumoren <3 cm, 3 x 17 Gy voor tumoren van 3-5 cm, en 3 x 18 Gy voor tumoren >5 cm).

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Lieve pap en mam, zonder jullie had ik dit nooit bereikt. Ik kan jullie niet genoeg bedanken!

Curriculum Vitae

Noëlle Caroline Marie-Germaine van der Voort van Zyp was born on the 23rd of August 1978 in Hilversum, the Netherlands. In 1996, she obtained the International Baccalaureate at the Jakarta International School in Indonesia, and then went on to study medicine at the Rijksuniversiteit in Groningen. After obtaining her medical degree in 2003, Noëlle worked briefly in the community medicine sector. Subsequently she went to the John D. Dingell VA Medical Center in Detroit where she did research on the cell signal cascades involved in wound healing. Upon returning to the Netherlands, Noëlle worked at the department of Internal Medicine, Diaconessenhuis in Utrecht. In 2006, she started her residency program at the Department of Radiation Oncology, Erasmus MC Daniel den Hoed Cancer Center in Rotterdam. From 2008-2010, she carried out research focused on a number of different aspects of the treatment of lung tumors with stereotactic radiotherapy. She is now continuing with the radiation oncology residency program.



List of publications

1. van der Voort van Zyp NC, Hoogeman MS, van de Water S, et al. Stability of markers used for real-time tumor tracking after percutaneous intra-pulmonary placement. *Int J Radiat Oncol Biol Phys* 2011 (Epub ahead of print).
2. van der Voort van Zyp NC, Hoogeman MS, van de Water S, et al. Clinical introduction of Monte Carlo treatment planning: a different prescription dose for non-small cell lung cancer according to tumor location and size. *Radiother Oncol* 2010;96:55-60.
3. van der Voort van Zyp NC, van der Holt B, van Klaveren RJ, et al. Stereotactic body radiotherapy using real-time tumor tracking in octogenarians with non-small cell lung cancer. *Lung Cancer* 2010;69:296-301.
4. van der Voort van Zyp NC, Prevost JB, van der Holt B, et al. Quality of life after stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2010;77:31-37.
5. van der Voort van Zyp NC, Prevost JB, Hoogeman MS, et al. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: clinical outcome. *Radiother Oncol* 2009;91:296-300.
6. Nuyttens JJ, Prevost JB, Van der Voort van Zyp NC, Hoogeman M, Levendag PC. Curative stereotactic robotic radiotherapy treatment for extracranial, extrapulmonary, extrahepatic, and extraspinal tumors: technique, early results, and toxicity. *Technol Cancer Res Treat* 2007;6:605-610.
7. van Zyp J, Conway WC, Craig DH, van Zyp N, Thamilselvan V, Basson MD. Extracellular pressure stimulates tumor cell adhesion in vitro by paxillin activation. *Cancer Biol Ther.* 2006 Sep;5(9):1169-78.
8. van der Voort van Zyp NC, Davin JC, Idu M, Aronson DC. Kidney transplant survival rates and surgical complications in kidney transplants in children; experiences in the Emma Children's Hospital AMC. *Ned Tijdschr Geneesk.* 2005 Mar 12; 149(11):584-8.

PhD Portfolio Summary

Name PhD student: NC van der Voort van Zyp
 Erasmus MC Department: Radiation Oncology
 Erasmus Postgraduate School Molecular Medicine

PhD period: January 2008 – January 2010
 Promotor(s): Prof. P.C. Levendag
 Supervisor: J.J. Nuyttens

1. PhD training	Year	Workload
General academic skills		
• Biomedical English Writing and Communication	2008	4 ECTS
• Research Integrity	2009	11 hours
Research skills		
• Basiscursus regelgeving en organisatie voor klinisch onderzoeker (BROK)	2010	25 hours
• 11 th ECCO-AACR-ASCO workshop “Methods in Clinical Cancer Research”	2009	8 ECTS
Presentations		
• “Stereotactic Radiotherapy for Lung Metastases”	2008	1 ECTS
• IKR regiobijeenkomst “Radiotherapie, wat zijn de nieuwe mogelijkheden?”	2008	1 ECTS
• 8 th CyberKnife users meeting “Feasibility of CyberKnife treatment in Octogenarians with Stage I NSCLC”	2009	1 ECTS
• 8 th CyberKnife users meeting “Quality of Life in patients with Stage I NSCLC treated with the CyberKnife”	2009	1 ECTS
• “Margins for subclinical disease in lung cancer”	2009	1 ECTS
• 10 th Biennial ESTRO physics conference “Consequence of Monte-Carlo dose calculation for CyberKnife treatment planning in patients with non-small cell lung cancer”	2009	1 ECTS
• RKF meeting “Stability of markers after percutaneous intrapulmonary placement for CyberKnife treatment	2009	1 ECTS
• Spanish radiotherapy and oncology meeting (SEOR) “CyberKnife image-guidance and real-time tumor tracking”	2009	1 ECTS
• 9 th CyberKnife users meeting; Best poster award “Stability of markers after percutaneous intrapulmonary placement for CyberKnife treatment”	2010	1 ECTS
• 3 rd European stereotactic radiotherapy workshop Brussels. “The role of stereotactic radiotherapy in patients with NSCLC	2010	1 ECTS
• CyberKnife symposium Liege “Treatment of stage I non-small cell lung cancer with stereotactic radiotherapy”	2010	1 ECTS
• 3 rd SBRT focus group meeting Guangzhou “Stereotactic radiotherapy in patients with stage I NSCLC”	2011	1 ECTS

International conferences

• 7 th Annual CyberKnife User's meeting	2008	1 ECTS
• ESTRO 27 Goteborg, Sweden	2008	1 ECTS
• 8 th Annual CyberKnife User's meeting	2009	1 ECTS
• 10th Biennial ESTRO physics conference	2009	1 ECTS
• 51 st Annual ASTRO Meeting	2009	1 ECTS

2. Teaching activities**Year****Workload**

Lecturing

• Onderwijs studenten geneeskunde "Klinisch onderzoek en nieuwe behandelingen"	2006-2009	25 hours
• Skillslab "Pharynx tumoren"	2010	6 hours
• Onderwijs radiotherapeutisch laboranten in opleiding "Stereotactische radiotherapie voor longtumoren"	2010	3 hours
