Radiotherapy and Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

# Intra thoracic anatomical changes in lung cancer patients during the course of radiotherapy

Margriet Kwint [1], Sanne Conijn [1], Eva Schaake, Joost Knegjens, Maddalena Rossi, Peter Remeijer, Jan-Jakob Sonke, Jose Belderbos *

*Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*

ARTICLE INFO

*Article history:*
Received 13 May 2014
Received in revised form 14 October 2014
Accepted 18 October 2014
Available online xxxx

*Keywords:*
Lung cancer
Cone beam CT
Image guided radiotherapy
Adaptive delivery
Inter-fractional variations

ABSTRACT

*Background and purpose:* Conebeam-CT (CBCT) guidance is often used for setup verification of lung cancer patients treated with radiotherapy. The purpose of this study was to quantify intra-thoracic anatomical changes (ITACs) during the radiotherapy treatment and to hand over a decision support system to guide the radiation therapy technologist and radiation oncologist in prioritizing these changes.

*Materials and methods:* 1793 CBCT-scans of 177 lung cancer patients treated in 2010 in our institute with radical radiotherapy were evaluated. Our decision support system: "the Traffic Light Protocol", was retrospectively applied to these CBCT-scans. The protocol has four levels: red (immediate action before treatment), orange (action before next fraction), yellow (no action required) and green (no change).

*Results:* In 128 patients (72%), 210 ITACs were observed with a maximum level of red, orange and yellow in 12%, 36% and 24% respectively. Types of observed ITACs were, tumor regression (35%), tumor baseline shift (27%), changes in atelectasis (19%), tumor progression (10%), pleural effusion (6%) and infiltrative changes (3%).

*Conclusions:* ITACs have been observed in 72% of all lung cancer patients during the course of radical radiotherapy. The clinical relevance of the proposed ITAC classification in lung radiotherapy needs to be validated in a prospective analysis.



In the Netherlands, about 12,000 new lung cancer patients are diagnosed annually. 80% of these patients are medically or technically inoperable at diagnosis [1]. Patients with inoperable locally advanced lung cancer are often treated with radical radiotherapy and depending on physical condition and/or tumor stage with or without chemotherapy. The overall treatment time of the radiotherapy courses in our clinic is 5/6 weeks and it is generally assumed that the anatomy of the patient is stable during this treatment. However, during this course of radiotherapy several anatomical changes may occur, such as atelectasis, infiltrative changes, tumor progression or regression and pleural effusion [2–14].

With the introduction of advanced image-guided systems like kilovoltage (kV) cone-beam computed tomography (CBCT), megavoltage (MV) CBCT, and tomotherapy, we have the ability to visualize the tumor and organs at risk (OAR) in 3D [15,16]. These modalities primarily minimize target misalignment and setup-error [9]. Many studies investigate setup precision in lung radiotherapy [17,18]. However, only a few studies reported anatomical changes during the course of lung radiotherapy [9,11,19]. In clinical practice repetitive CBCTs make us aware of intra thoracic anatomical changes (ITACs) during the course of a radical treatment. In the Netherlands, CBCTs are typically analyzed by radiation therapy technologists (RTTs), the radiation oncologist is only informed when a change is observed. In our institute, we developed an action level protocol as a decision support system to guide the RTT in prioritizing these changes. In this study we quantified ITACs during radiotherapy and present a decision support system (Traffic Light Protocol).

## Methods and materials

### *Patient selection*

The Traffic Light Protocol was introduced clinically in our institute in 2011. All CBCTs of lung cancer patients radically treated with radiotherapy or chemo-radiotherapy (⩾44 Gy) in our institute in 2010, were retrospectively analyzed on the basis of this Traffic Light Protocol.

Patients treated with stereotactic radiotherapy were excluded as they had a different decision protocol. Inclusion criteria for this

* Corresponding author at: Department of Radiation Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
*E-mail address:* j.belderbos@nki.nl (J. Belderbos).
[1] Both authors have contributed equally.

http://dx.doi.org/10.1016/j.radonc.2014.10.009

study were radical treatment with radiotherapy (>44 Gy), histology or cytology proven lung cancer and image guided radiotherapy (IGRT) with the use of 3 or 4D-CBCT. All CBCT-scans were available for all patients. Several radiotherapy regimens, all planned with Intensity Modulated Radiotherapy (IMRT) and concurrent or sequential chemotherapy or radiotherapy alone were included.

*Radiotherapy preparation*

A 3D-midventilation-CT (MidV-CT) was selected for all patients from a respiration correlated 4DCT, in which the moving tumor was closest to its time-averaged mean position [20]. The gross tumor volume (GTV) and pathological lymph nodes were delineated on the MidV-CT. A recent flu-deoxyglucose-positron-emission-tomography-(FDG-PET)-scan was registered to the MidV-CT [21]. The GTV was expanded to a planning target volume (PTV) using margins of 12 mm +1/4 of the 4DCT peak-to-peak tumor amplitude in orthogonal directions. A uniform PTV margin of 12 mm was used for the lymph nodes [22] according to our institutional protocol. The planning-constraints used for the OAR were; esophagus V35 < 65% (physical dose), Mean Lung-Dose $\leqslant$20 Gy ($EQD_2$ $\alpha/\beta$ = 3 Gy), spinal cord $\leqslant$50 Gy ($EQD_2$ $\alpha/\beta$ = 2 Gy), total heart $\leqslant$40 Gy, 2/3 of the heart $\leqslant$50 Gy and 1/3 of the heart $\leqslant$66 Gy (physical dose). Equally spaced, 7-field IMRT-plans were designed using 6/10 MV photons and direct machine parameter optimization (Pinnacle version 9.0, Philips, Best, the Netherlands) on the homo-lateral lung [23]. The prescription-dose was specified at a representative point in the PTV. The dose distribution within 99% of the PTV was >90% and <115% of the prescribed dose.

*Setup correction protocol*

An off-line shrinking action level setup correction protocol was used for all patients [24] with *N*max = 3 and $\alpha$ = 9 mm. For this off-line shrinking action level setup correction protocol, CBCTs were acquired the first three fractions using Elekta Synergy 4.2 (Elekta Oncology Systems Ltd., Crawley, UK). If no correction was necessary (average setup error over 3 fractions <5.2 mm in each direction) then weekly follow-up scans were acquired. If a correction was required, the protocol restarted with three fractions with CBCT verification. This resulted in a minimum of 7 CBCTs per patient. 4D-CBCTs were acquired if the motion of the tumor, measured on the 4DCT, was $\geqslant$8 mm. The CBCTs were registered, by two RTTs, to the MidV-CT based on the bony anatomy of the vertebrae [25].

*Decision support system*

A team of dedicated CBCT RTTs, radiation oncologists and physicists evaluated examples of collected ITACs. Four types of urgency levels were defined (Fig. 1): A protocol for communication and/or consultation was defined for each urgency level

1) Action level red: The GTV is outside the PTV due to ITACs. The radiation oncologist is called immediately and treatment is only given when approved by the radiation oncologist.
2) Action level orange: The GTV is just inside the PTV due to ITACs. The radiation oncologist is notified by email and has to respond before the next fraction. Further diagnostics are considered as a result of the ITAC.
3) Action level yellow: There is an ITAC visible but the GTV is well inside the PTV. The radiation oncologist is notified by email about the ITAC but no response is necessary and treatment may continue.
4) Action level green: No change visible. No action needed.

The Traffic Light Protocol is a practical guideline to the RTTs visual inspection of the patients CBCT in the absence of the possibility to quantify the dosimetric influence of ITACs immediately after a CBCT is made. Not that a CBCT is not of diagnostic quality. A visual assessment that the CBCT visualized GTV is (well) within the PTV gives confidence but do not guarantee that the tumor receives an adequate dose. The traffic light color therefore reflects a risk assessment of the occurrence of clinically relevant dosimetric changes. In case of an ITAC, the RTT informs the radiation oncologist. The radiation oncologist and clinical physicist make an estimation of the dosimetric influence of the ITAC on the tumor and/or OAR. When is estimated that the dosimetric influence is relevant for treatment outcome, a new planning-CT and possibly adaptive treatment plan will be made.

*Intra thoracic anatomical changes*

All CBCTs were added to a database. All CBCTs were scored retrospectively and compared to the planning-CT (bony anatomy, carina, trachea and mediastinal contour were used to compare the CBCT with the planning-CT). Two IGRT-specialists independent of each other visually evaluated every CBCT. For each CBCT, the observed ITACs were scored: changes in atelectasis, infiltrative changes, pleural effusion, considerable tumor baseline shift, tumor regression and tumor progression. If an ITAC was detected, the date of the first occurrence of the highest level (red, orange, yellow or green) of each ITAC was compiled. Furthermore, subsequent actions, e.g. a repeat radiotherapy planning-CT-scan or re-planning were scored.

*Statistical analysis*

To evaluate the ITACs during the course of radiotherapy SPSS for windows software, version 20, was used for statistical analysis. Firstly descriptive statistics were used to analyze the number of ITACs. Thereafter Spearman's rank correlation coefficients were used to analyze if there were any significant correlations between progression and an adaptive treatment plan with the following parameters: tumor regression, tumor baseline shift, changes in atelectasis, pleural effusion, infiltrative changes, traffic light level of changes, changes in the first week, patient characteristics, tumor stage, tumor location, type of treatment and time interval between planning-CT and first day of treatment.

## Results

*Patients*

Between January 2010 and December 2010, 226 patients were treated with a radical radiotherapy scheme for lung cancer. A group of 177 patients with complete data were selected (Table 1). Mean age was 66 years (range 32–87). A total of 1793 CBCT-scans from these 177 patients were evaluated. Ninety-seven (55%) patients were treated with concurrent chemoradiation (CCRT), 57 (32%) with radiotherapy only (RT), 23 (13%) received sequential chemoradiation (SeqCRT) and 17 patients were irradiated after surgery.

*Intra thoracic anatomical changes*

ITACs were observed in 128 patients (72%). In total 200 ITACs were scored (Table 2). Sixty patients (47%) had 1 ITAC, 46 patients (36%) 2 ITACs and in 22 patients (17%)>2 ITACs were observed. The highest ITAC scored per patient was level red, orange and yellow in 12%, 36% and 24% respectively. 28% of the patients had no observed ITACs (level green). Sixteen patients (9%) required an adapted treatment plan to account for the changed anatomy, for which 14 received a new planning-CT-scan (8%). It took 1–3 working-days