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CLINICAL INVESTIGATION **Physics**

SHOULD PATIENT SETUP IN LUNG CANCER BE BASED ON THE PRIMARY TUMOR? AN ANALYSIS OF TUMOR COVERAGE AND NORMAL TISSUE DOSE USING REPEATED POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY IMAGING

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Purpose: Evaluation of the dose distribution for lung cancer patients using a patient setup procedure based on the bony anatomy or the primary tumor.

Methods and materials: For 39 patients with non–small-cell lung cancer, the planning fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan was registered to a repeated FDG-PET/CT scan made in the second week of treatment. Two patient setup methods were analyzed based on the bony anatomy or the primary tumor. The original treatment plan was copied to the repeated scan, and target and normal tissue structures were delineated. Dose distributions were analyzed using dose–volume histograms for the primary tumor, lymph nodes, lungs, and spinal cord.

Results: One patient showed decreased dose coverage of the primary tumor caused by progressive disease and required replanning to achieve adequate coverage. For the other patients, the minimum dose to the primary tumor did not significantly deviate from the planned dose: $-0.2 \pm 1.7\%$ ($p = 0.71$) and $-0.1 \pm 1.7\%$ ($p = 0.85$) for the bony anatomy setup and the primary tumor setup, respectively. For patients ($n = 31$) with nodal involvement, 10% showed a decrease in minimum dose larger than 5% for the bony anatomy setup and 13% for the primary tumor setup. The mean lung dose exceeded the maximum allowed 20 Gy in 21% of the patients for the bony anatomy setup and in 13% for the primary tumor setup, whereas for the spinal cord this occurred in 10% and 13% of the patients, respectively.

Conclusions: In 10% and 13% of patients with nodal involvement, setup based on bony anatomy or primary tumor, respectively, led to important dose deviations in nodal target volumes. Overdosage of critical structures occurred in 10–20% of the patients. In cases of progressive disease, repeated imaging revealed underdosage of the primary tumor. Development of practical ways for setup procedures based on repeated high-quality imaging of all tumor sites during radiotherapy should therefore be an important research focus.

Patient setup, Lung cancer, Mediastinal lymph nodes, Adaptive radiotherapy, Dose distribution, Repeated imaging.

INTRODUCTION

In lung cancer treatment, the radiotherapy dose has been increased in many dose-escalation studies and has been shown to improve both local control and overall survival at reasonable normal tissue toxicity levels (1, 2). Both the primary tumor and the involved mediastinal lymph nodes are treated in the same treatment plan (3). Changes in volume of the primary tumor during treatment and also baseline shifts have been described in many studies (4–10). A complicating factor for accurate irradiation is that changes in lymph node position and their volume are not related to corresponding changes in the primary tumor, which hampers the use of the primary tumor as a surrogate for the lymph nodes (11–13).

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging combined with an intravenous contrast-enhanced CT scan has become the standard imaging technique in locally advanced lung cancer (14, 15).

In the past, volumetric imaging was restricted to a three-dimensional (3D) planning (PET-)/CT scan made during the treatment planning procedure, but recent advances in

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in-room imaging of predominantly kilovolt (kV) and megavolt (MV) cone-beam CT have increased the use of patient alignment based on 3D image information (16). These new techniques give quantitative information on the volume and position of the primary tumor during treatment, but for imaging of the mediastinal lymph nodes they remain suboptimal. Hence, localization and quantification of the mediastinal lymph nodes is difficult in such cone-beam CT images.

These multiple target volumes (primary tumor and lymph nodes) thus result in many regions of interest that can be registered for deriving the actual patient setup. Patient setup by registering the bony anatomy is the current state of practice, but also registration of the primary tumor might yield better primary tumor coverage and reduced margins. However, if an integrated elective or involved mediastinal lymph node irradiation in a single treatment plan is used, a match based on the location of the primary tumor might act to the detriment of the dose coverage of these nodes. By contrast, a match of the bony anatomy might cause underdosage of the primary tumor if a baseline shift of the primary tumor occurs during treatment.

PET/CT imaging with intravenous contrast medium as the most optimal image modality to detect nodal involvement was selected before and during treatment. The dose is recalculated inside the repeated CT imaging data set that has all target and normal structures delineated, and an analysis is performed in terms of dose parameters and dose coverage of the primary tumor, involved mediastinal lymph nodes, and normal tissue. Such an analysis combines the dose distribution based on different patient setup strategies with possible changes in patient anatomy and tumor volume. The aim of this study was to investigate the accuracy of the treatment plan for a setup procedure based on the bony anatomy or the primary tumor for a large group of unselected patients.

METHODS AND MATERIALS

Patient characteristics, image acquisition, and treatment

Between June 2008 and December 2008, we prospectively imaged 39 lung cancer patients who received radical treatment in the second week during treatment. The protocol was approved by the Institutional Review Board, and all patients gave informed consent. Both small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC) patients were included. Patients scheduled for stereotactic body radiotherapy were excluded.

Four-dimensional (4D) respiration-correlated CT imaging was performed for all patients using our standard 4D respiration-correlated CT imaging protocol together with a 3D FDG-PET image and a 3D CT scan using an intravenous iodine-based contrast medium (XENETIX 300, Guerbet, Aulnay-sous-Bois, France) (4). Imaging was performed on a dedicated PET/CT scanner (Siemens TruePoint Biograph 40, Siemens Molecular Imaging, Knoxville, TN). Patients were positioned in the radiotherapy position using a dedicated arm support. The patient's breathing was monitored using a pressure sensor in a belt strapped around the patient's chest (AZ-733 V, Anzai Medical Corporation, Tokyo, Japan). The following 4D CT scan parameters were used: 120 kV tube voltage, 800 mAs, and 3 mm reconstructed slice thickness. The 4D CT was reconstructed in eight CT phases using an amplitude-based binning method. Injected activity (MBq) of FDG depended on the weight (kg) of the patient and was equal to 4 times the body weight plus 20 MBq.

The gross tumor volume of the primary tumor (GTVprim) and involved mediastinal lymph nodes (GTVlymph) were delineated by the radiation oncologist. Expanding the GTVs with a margin of 5 mm resulted in the clinical target volumes (CTVprim and CTVlymph, respectively); the radiation oncologist was allowed to edit the CTV to exclude possible invasion into bony anatomy or blood vessels. The planning target volume of the primary tumor (PTVprim) was defined as the CTVprim with an additional margin of 10 mm. For the PTV of the lymph nodes (PTVlymph) a CTV-to-PTV margin of 5 mm was used.

The patients were treated according to our clinical protocol. On the 50% exhale phase of the 4D CT scan, the target volumes and normal tissues were delineated and used for 3D conformal treatment planning using homogeneity constraints around the target volume of 90–115% of the prescribed dose.

For the SCLC, patients a dose of 45 Gy was delivered in 30 fractions (17). For the NSCLC patients, a dose-escalation protocol based on normal tissue constraints was used. Patients received no chemotherapy, induction, or concurrent chemotherapy with radiotherapy. For the NSCLC patients without chemotherapy or receiving sequential chemoradiotherapy, a maximum escalated dose up to 79.2 Gy in twice-daily fractions of 1.8 Gy was used, depending on normal tissue constraints (2, 18, 19). For the patients receiving concurrent chemoradiotherapy, a dose escalation based on normal tissue toxicity up to 69 Gy was performed; first a fractionation scheme of 30 fractions of 1.5 Gy twice daily, and afterwards a dose escalation with fraction sizes of 2.0 Gy once daily was used.

Repeated imaging during treatment and delineation

Repeated imaging was performed in the second week of radiotherapy treatment. For this imaging session, the FDG-PET/CT scan was acquired using the same protocol as the planning CT scan, including the contrast-enhanced CT scan, with the patient positioned in radiotherapy position. On this repeated scan, the GTVs and CTVs were copied from the planning CT scan and afterwards manually adjusted by a radiation oncologist using the same target volume definition guidelines as used for the planning scan. The lungs and spinal cord were also delineated on these scans.

Image registration procedure

The CT scans of both time points were manually registered. This rigid registration allowed only translations to mimic the current widely used patient setup procedure during external beam radiotherapy treatment. Two independent persons performed these registrations based on either the bony anatomy or the primary tumor. For the bony anatomy registration, all the visible bony anatomy in the axial slices surrounding the primary tumor and involved mediastinal lymph nodes was used for the registration. For the tumor match, the GTV of the primary tumor was registered between the planning and the repeated CT scan. The average of the values for the translation vectors in the three orthogonal directions of the two observers was used to calculate the applied setup vector.

Dose recalculation

The dose distribution was recalculated using the CT scan of the repeated imaging session and applying the original treatment plan, including all monitor unit settings and beam parameters but with the isocenter derived from the patient setup procedure. The two dose distributions were calculated with the isocenter derived from