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Original Article

Adaptive Dose Escalation using Serial Four-dimensional Positron Emission Tomography/Computed Tomography Scans during Radiotherapy for Locally Advanced Non-small Cell Lung Cancer☆

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Abstract

Aims: Computed tomography (CT)-based radiotherapy dose escalation for locally advanced non-small cell lung cancer (LA-NSCLC) has had limited success. In this planning study, we investigated the potential for adaptive dose escalation using respiratory-gated 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography scans (4DPET/4DCT) acquired before and during a course of chemoradiotherapy (CRT).

Materials and methods: We prospectively enrolled patients with LA-NSCLC receiving curative intent CRT. Radiotherapy was delivered using intensity-modulated radiotherapy (IMRT) using the week 0 4DCT scan. Three alternative, dose-escalated IMRT plans were developed offline based on the week 0, 2 and 4 4DPET/4DCT scans. The FDG-avid primary (PET-T) and nodal disease (PET-N) volumes defined by the 50% of maximum standard uptake value threshold were dose escalated to as high as possible while respecting organ at risk constraints.

Results: Thirty-two patients were recruited, 27 completing all scans. Twenty-five patients (93%) were boosted successfully above the clinical plan doses at week 0, 23 (85%) at week 2 and 20 (74%) at week 4. The median dose received by 95% of the planning target volume (D95) at week 0, 2 and 4 to PET-T were 74.4 Gy, 75.3 Gy and 74.1 Gy and to PET-N were 74.3 Gy, 71.0 Gy and 69.5 Gy.

Conclusions: Using 18F-FDG-4DPET/4DCT, it is feasible to dose escalate both primary and nodal disease in most patients. Choosing week 0 images to plan a course with an integrated boost to PET-avid disease allows for more patients to be successfully dose escalated with the highest boost dose.

Key words: Adaptive radiotherapy; dose escalation; four-dimensional PET/CT; intensity-modulated radiotherapy; lung cancer; radiotherapy

Introduction

Lung cancer is the leading cause of cancer-related deaths in the world [1]. For stage III disease, overall survival remains low at about 15% at 5 years [2]. The addition of concurrent chemotherapy to radiotherapy has shown an improvement in local control and, in turn, an overall survival benefit.

The role of radiotherapy dose escalation has recently been explored in an attempt to improve outcomes for locally advanced non-small cell lung cancer (LA-NSCLC). Dose escalation of computed tomography (CT)-derived volumes at the outset of radiotherapy has been limited, due to doses to organs at risk (OARs). Recent phase III evidence showed that uniform dose escalation of the tumour volume was associated with worse local control and overall survival [3]. There is now increasing interest in dose escalation of positron emission tomography (PET)-derived target volumes, where subvolumes of high uptake are where recurrence is more likely to appear [4].

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We carried out a planning study based on serial respiratory-gated ^{18}F-fluorodeoxyglucose (FDG) PET/CT (4DPET/4DCT) scans during radiotherapy to investigate the dosimetric benefits of a PET-based adaptive dose-escalation technique at week 0, 2 or 4 during radiotherapy concurrent with chemotherapy (CRT).

The primary aim of this study was to assess the technical feasibility of dose-escalating FDG-avid disease above the clinical dose whilst respecting OAR thresholds. We also sought to evaluate the optimal time point in which to dose escalate.

Materials and Methods

Patient Recruitment

After institutional research ethics board approval was obtained, patients with stage II–III LA-NSCLC, who were planned for curative intent treatment, were prospectively recruited. Patients were eligible if they were >18 years, planned to be treated with CRT ≥ 60 Gy and had measurable tumour on both CT and PET/CT scans. Patients were excluded if they had previously received radiotherapy in the treatment field, were planned for surgery, or had other active malignancies.

Consenting patients received CRT with platinum-doublet chemotherapy as per clinical protocol. The radiotherapy dose was 2 Gy per fraction, treated 5 days per week, to a dose of 60–74 Gy. Patients were treated with intensity-modulated radiotherapy (IMRT) under daily cone-beam CT guidance. The follow-up schedule included a clinical review at 6 weeks and 3 months after radiotherapy, then 3 monthly for the first 12 months and 6 monthly thereafter.

Study Imaging

The imaging schedule during radiotherapy is depicted in Figure 1. A respiratory-gated CT planning scan (4DCT) was carried out in all patients. This was carried out free breathing, although in patients with tumour respiratory excursion of >1 cm, an in-house abdominal compression device was used. This scan was used for clinical purposes and for the purposes of the planning study. A 4DPET/4DCT scan of the thorax was carried out before treatment, for use in the planning study only. Patients had repeat 4DCT and 4DPET scans of the thorax at weeks 2 and 4 for the purposes of this study. In addition, a 4DCT and 4DPET were acquired at week 7 and 3 months after radiotherapy, for a further study beyond the scope of this paper.

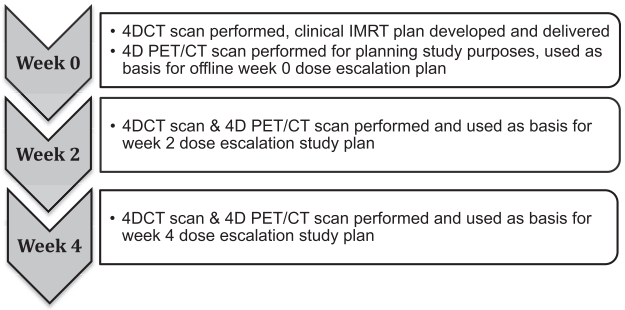

Fig 1. Schema of clinical and study imaging carried out during the radiotherapy course.

All patients underwent planning 4DPET/4DCT scans (Discovery ST, GE Healthcare, Waukesha, WI, USA) in the treatment position, supine on a standard chest-board with both arms above head. Free breathing scans were carried out and maximum-exhale and maximum-inhale datasets were then transferred to the planning system (Versions 8 and 9 Pinnacle^3, Philips Radiation Oncology Systems, Milpitas, CA, USA) for subsequent contouring and plan generation.

4DPET/4DCT scans were acquired on the same scanner described above. All patients were required to fast before receiving the 18F-FDG injection. The PET image acquisition was taken about 60 min after injection. All scans followed protocol and were carried out by a single technician dedicated to this study. The maximum-exhale and maximum-inhale datasets, as well as their associated attenuation correction CT scans, were transferred to the Pinnacle^3 system for study purposes.

4DCT datasets acquired in weeks 2 and 4 were registered to the week 0 4DCT data and week 0 clinical planning volumes were copied over to each of the datasets. Planning 4DPET/4DCT datasets were fused to the planning 4DCT images using the Pinnacle^3 rigid registration tool. The fusion was then manually checked by the contouring physician and, if necessary, adjusted according to spine, carina and visible disease.

Clinical Plan

OARs were contoured on the exhale phase of all 4DCTs, per institutional protocol. CT-based primary tumour gross tumour volumes (GTVs) were contoured on exhale and inhale CT datasets (GTV-T-EX, GTV-T-IN) using lung and mediastinal windows. CT-based nodal GTVs were also contoured based on exhale and inhale CT datasets (GTV-N-EX, GTV-N-IN) using mediastinal windows. A diagnostic 3D-FDG-PET/CT scan was used to aid delineation of the GTVs. A 5 mm margin was added to the GTVs to form clinical target volumes (CTV-EX and CTV-IN, respectively). The union of the CTV-EX and CTV-IN formed the internal target volume (ITV) and a 5 mm set-up margin [5] was added to form the planning target volume (PTV). An IMRT plan was derived from clinical volumes using, typically, five to seven beam angles. The prescribed dose was 60–74 Gy. Planning target parameters included D99 of the PTV to be >93% of the prescribed dose and the maximum dose outside of the PTV to be <115%. The tolerance doses included lung V5 < 50% (acceptable up to 70%), V20 < 30% (acceptable up to 37%), mean lung dose < 18 Gy (acceptable up to 20 Gy), spinal cord maximum dose (d_{max}) < 50 Gy, spinal cord 3 mm PRV < 53 Gy, oesophagus d_{max} 0.5 cm^3 < 74 Gy, oesophagus V35 < 60%, heart V60 < 1/3, V45 < 2/3, V40 < 100%, trachea and proximal bronchial tree < 90 Gy, great vessels < 90 Gy and brachial plexus d_{max} < 66 Gy.

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