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Original article

Time and dose-related changes in lung perfusion after definitive radiotherapy for NSCLC

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ABSTRACT

Background and purpose: To examine radiation-induced changes in regional lung perfusion per dose level in 58 non-small-cell lung cancer (NSCLC) patients treated with intensity-modulated radiotherapy (IMRT).

Material and methods: NSCLC patients receiving chemo-radiotherapy (RT) of minimum 60 Gy were included prospectively in the study. Lung perfusion single-photon emission computed tomography (SPECT/CT) was performed before and serially after RT. Changes (relative to baseline, %) in regional lung perfusion were correlated with regional dose. Toxicity outcome was radiation pneumonitis (RP) CTC grades 2–5.

Results: Perfusion changes were associated with dose. Dose-dependent reduction in regional perfusion was observed at 3, 6 and 12 months of follow-up. Relative perfusion loss per dose bin was 4% at 1 month, 14% at 3 months, 13% at 6 months and 21% at 12 months after RT. In patients with RP, perfusion reduction was larger in high dose lung regions, compared to those without RP. Low dose regions, on the contrary, revealed perfusion gain in the patients with RP.

Conclusion: Progressive dose dependent perfusion loss is manifested on SPECT up to 12 months following IMRT. These findings suggest that the dynamic change in perfusion may have prognostic value in predicting radiation pneumonitis in NSCLC patients treated with IMRT.

Radiation pneumonitis (RP) is a common radiation-induced lung toxicity in patients treated with curative intent for localised or recurrent non-small-cell lung cancer (NSCLC) [1–3]. Despite technological advances and individualised treatment options, damage to normal lung tissue remains a major concern for patients' morbidity and survival [4]. Combined treatment modalities and older age of the patients contribute to the development of dose-limiting postradiation toxicity [5,6]. For most patients, the symptomatic RP may reduce their quality of life, while for others this condition may become invalidating and life-threatening [7–9].

Radiation-induced lung changes have been investigated previously by different imaging modalities [2,10–16]. It has been established that radiation injury in the lung after definitive chemo-radiotherapy (RT) for NSCLC is dose dependent. This is evident on spirometry tests, CT, as well as on imaging modalities capable of assessing pulmonary perfusion, such as single-photon emission computed tomography (SPECT/CT) [10–12,17–20]. Moreover, pulmonary perfusion changes progress over time up to 12 months after RT [21]. However, only few studies have related lung function changes to the clinical outcome of RP, and no association has been found in patients irradiated for different thoracic tumours [14,22,23]. In the recent prospective study, a 3-month-assessment of postradiation pulmonary tissue damage by perfusion SPECT showed a significant association with the severity of RP, and could predict the risk of later RP development [18]. Nevertheless, long time changes in lung perfusion and the significance of those for the RP development remains to be established.

The purpose of this study was to describe dose and time dependence of changes in regional lung perfusion in relation to symptomatic RP using a validated SPECT/CT method in NSCLC patients treated with definitive chemo-RT.

Materials and methods

Patients with histologically verified NSCLC receiving definitive chemo-RT of minimum 60 Gy were prospectively included after providing written informed consent. Institutional ethics board

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approval was obtained from The Central Denmark Region Ethics Committee (study number 1-10-72-11-12). The study was registered at ClinicalTrials.gov (ID NCT01745484).

Toxicity was assessed prospectively and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 for radiation pneumonitis [24]. Patients with minimum grade 2 toxicity were defined as having RP.

Radiotherapy planning and delivery

In each patient, a dose of 60–66 Gy was delivered in 2 Gy per fraction with external beam RT. Treatment simulation planning was performed in the supine position with intravenous contrast on a time-resolved four-dimensional (4D) CT scan. The mid-ventilation phase was selected for delineation of normal tissue, internal target volume and for treatment planning.

Margins accounting for microscopic disease, respiratory motion, and technical and setup uncertainties were applied in agreement with guidelines from the Danish Lung Cancer Group [25]. The organs at risk were lung parenchyma, oesophagus, spinal cord, and heart. The total lung volume was defined by subtracting the gross tumour volume (GTV) from the entire volume of both lungs. Intensity-modulated radiotherapy (IMRT) plans were created, using four to six coplanar 6 Megavolt photon beams. Inhomogeneity corrections were considered by the AAA algorithm (Varian, Eclipse) [26].

All patients irrespective of their registration in the trial received RT after the standard national guidelines [25]. RT plans were not altered using the functional data from SPECT/CT.

SPECT data acquisition

Lung perfusion SPECT/CT was performed within a week before RT started and 1, 3, 6, and 12 months after RT ended. Lung perfusion SPECT was performed on a dual-head SPECT/CT scanner (Siemens Symbia T 16, Siemens Healthcare GmbH, Erlangen, Germany) with a low-energy-high-resolution collimator after intravenous administration of 200 Megabecquerels of ^{99m}Tc-labelled macroaggregated albumin (MAASOL, GE Healthcare, Milan, Italy). The patient was positioned in the supine position on a flat board identical to the position used for RT treatment and was breathing freely during the entire scan. SPECT of the thorax was acquired with 64 projections, 5 s/view, matrix size 64, pixel size 4.8 mm, followed by a non-contrast-enhanced low-dose CT scan (110 kV, 40 Ref. mAs, slice thickness 6 mm). Data were transferred to a Hermes workstation (Hermes Medical Solutions Inc. Stockholm, Sweden) for processing using ordered subset expectation maximisation method with CT-based scatter and attenuation correction.

Image processing

The CT component of each of the pre-and posttreatment SPECT/CT images was co-registered to the planning CT scan, which contained structures and planned dose grid, using rigid and deformable registration. The same registration was then applied to each perfusion SPECT image resulting in identical frame of reference in all image data sets. Image registration and analysis were performed using MIM Software (MIM Software, version 6.4, Cleveland, OH), and perfusion counts in each dose bin calculated.

Radiation dose to the total lung volume minus GTV was then segmented into regions corresponding to 0–5, 6–20, 21–40, 41–60 and over 60 Gy. Regional perfusion on SPECT was calculated before and serially after completion of RT for each dose bin as previously described [18]. Percent changes in regional lung perfusion relative to baseline images were recorded in each regional isodose bin for each patient.

Data analysis and statistics

First, data analysis was performed on population level with composite perfusion changes calculated per planned dose level for the entire patient cohort at each time interval. The relationship between composite perfusion change and regional dose was described with a linear fit and coefficient of determination R^2. The same linear model with intercept was used to assess the rate of perfusion change per dose bin for each time interval by calculating the slope of the line. Perfusion changes with time in the whole lung (minus GTV) were related to the initial perfusion before treatment. Percent perfusion change relative to baseline was estimated for patients with and without RP, respectively.

Change in perfusion at each time point after RT relative to baseline was expressed as either perfusion gain (negative values) or perfusion loss (positive values).

Additionally, data were analysed on individual level, where the mean perfusion value in each isodose contour was determined. The changes (reduction or gain) in mean perfusion values relative to baseline were recorded in each isodose bin contour at the different time points. The calculations were adjusted for changes in the entire anatomic lung volume with time. Patients were divided into two groups, those with non-symptomatic RP (grade 0–1), and those who developed RP of grades 2–5. Student's t-test was used to compare mean regional perfusion changes between the two groups.

Results

A total of 58 patients were included in the study. Patients' tumour and treatment characteristics were reported previously [17]. 51 patients underwent 1 month follow-up (FU) scans, 45 3-month scans, 34 6-month scans, and 23 12-month scans. Drop out in the follow-up period was due to disease progression, general weakness without detectable progression of the disease, and one patient died of RP.

Composite perfusion changes were associated with dose and progressed over time. Statistically significant dose-dependent reduction in regional perfusion was observed at 3, 6 and 12 months of FU ($p < 0.05$).

An example of a perfusion defect appearing on SPECT/CT scan 3 months after RT is shown in Fig. 1.

Comparison of population dose–response curves showed a dose-dependent reduction in perfusion at 3, 6 and 12 months of intervals with strong correlation revealed for these time points ($R^2 = 0.8–0.9$). The weaker correlation with $R^2 = 0.4$ was found at a 1 month FU. Based on the slope of the line, relative perfusion loss per dose bin was 4% at 1 month, 14% at 3 months, 13% at 6 months and 21% at 12 months of FU (Fig. 2).

Relationship between perfusion loss at 3 months after RT and initial perfusion before RT was investigated for patients with and without RP. Fig. 3 shows the proportional loss of perfusion within the whole lung excluding the GTV relative to the absolute baseline perfusion. Perfusion loss was proportional to baseline perfusion for patients with RP, while this association was not observed for the patients without RP.

The course of SPECT-defined regional perfusion changes with time differed between patients with and without RP, as demonstrated in Fig. 4. Patients with radiation pneumonitis had a larger perfusion loss in the high dose regions, as well as relatively larger perfusion increase in regions receiving low dose, compared to those without the complication. Patients who developed RP, had a larger relative perfusion reduction in 21–40 Gy dose bin at 3 months of FU ($p = 0.02$), and in >60 Gy dose bin at 6 months ($p = 0.03$), compared to those without RP. Low dose regions, on the con-

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