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SBRT of lung cancer

Local dose–effect relations for lung perfusion post stereotactic body radiotherapy

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ABSTRACT

Purpose: To model the local dose–effect relation for lung perfusion reduction in lung cancer patients treated with stereotactic body radiotherapy (SBRT).

Materials and methods: Forty-two patients having upper-lobe peripheral tumours <5 cm treated with SBRT (3×18 Gy) underwent single-photon emission computed-tomography (SPECT) scans to measure the lung perfusion 2 weeks pre-SBRT, 4-months post-SBRT, and for 8 patients 15-months post-SBRT. The relation between the calculated relative local perfusion reduction and the normalised total dose ($\alpha/\beta = 3$ Gy) at 4-months post-SBRT was modeled by 3-parameter logistic model and 2-parameter linear-maximum model.

Results: The relation between local dose and perfusion reduction at 4-months post-SBRT showed a maximum effect of 42.6% at doses >100 Gy and was best described by the logistic model with parameters (95% CI): $M = 42.6\%$ (40.7–44.6), $D_{50} = 28.7$ Gy (26.3–31.1) and $k = 2.2$ (1.8–2.5). A significant increase of this maximum effect to 65.2% was found at 15-months post-SBRT.

Conclusions: The relation between local dose and perfusion reduction in patients treated with SBRT can be modeled by a 3-parameter logistic model. This demonstrated relationship 4-months post-SBRT approaches a plateau for doses >100 Gy, where 90% of the maximum lung-perfusion reduction is observed at NTD = 78 Gy. A further perfusion reduction compared to 4-months post-SBRT was observed fifteen months post-SBRT.

Stereotactic body radiotherapy (SBRT) exploits the high-precision tumour localization and steep dose-gradients of modern delivery techniques allowing hypofractionated treatment schemes. Typical schemes include small high-dose volumes and steep dose-gradients, minimizing the dose to critical structures [1,2]. Prospective studies of lung cancer patients treated with SBRT report 2 year local control rates between 88% and 98% and 2 year survival rates that vary from 43% until 83% [3–6]. Retrospective studies of the incidence of toxicity in SBRT show acceptable low rates with incidences of grade >3 toxicity in $\leqslant$10% of the patients [3,7,8].

Despite the low toxicity rates in SBRT, validated toxicity models for hypofractionated schedules are lacking and SBRT has mainly been applied to medically inoperable patients with peripheral tumours of <5 cm diameter [2,9,10]. Before larger tumours can be treated with SBRT, lung toxicity models need to be validated, as done for conventionally-fractionated radiotherapy (CFRT) resulting in reliable models for radiation pneumonitis as a function of the mean lung-dose (MLD) [11–13]. For SBRT, a relation between the delivered MLD and the incidence of radiation pneumonitis has been reported [8,14,15].

The examination of global effect parameters, such as the MLD, gives much insight into overall dose–effect relations. A more accurate normal-tissue complication-probability (NTCP) model could be constructed by examining the local response as a function of the dose. A global response parameter can be derived from the local response as a function of the local dose (for the MLD this local dose-response is assumed to be linear) and a summation of these local responses [11,12].

Single-photon emission computed tomography (SPECT) scans show the local perfusion in the lung (in combination with a CT-scan), which highly correlates with lung ventilation and can thus be considered a surrogate for lung function [16]. For CFRT, local dose–effect relations have been modeled for healthy lungs of breast and lymphoma patients [17], and for lung cancer patients [18,19].

The significantly higher dose per fraction for SBRT compared to CFRT imparts doubt that the biological effect of SBRT is comparable to CFRT. The purpose of this study was therefore firstly, to determine the local dose–effect relation for lung perfusion reduction 4-months post-SBRT in patients with inoperable early stage lung cancer. Secondly, we analysed the temporal effect of SBRT on reduction in lung perfusion.

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Materials and methods

From April 2008 until August 2009, 42 patients with upper-lobe peripheral lung tumours were treated with SBRT (3 × 18 Gy in 8–10 days) at the Antoni van Leeuwenhoek Hospital, Amsterdam (Table 1). As lower-lobe tumours exhibit more breathing motion, only patients with upper-lobe tumours (70% of the patient population) were selected for this study to minimize the influence of the breathing motion on the dose delivery and the SPECT-signal. Patients underwent a free breathing SPECT/CT scan 11 ± 2.4 days before treatment and another SPECT/CT scan 4 ± 1 month after the first fraction on medical indication. Here we report on a retrospective analysis of the SPECT perfusion changes.

Treatment planning

A 4D mid-ventilation planning CT-scan of the whole thorax (3 mm slice thickness) was acquired [20]. GTV and organs at risk were delineated, from which the PTV was derived [21]. An IMRT plan with around 16 beams and 1–2 segments per beam was optimised in Pinnacle version 8.0h, (Philips, Best, The Netherlands). The dose distributions of the lungs minus the GTV were converted to the normalised total dose (NTD) distributions defined as the biologically equivalent dose as given in 2 Gy fractions with $\alpha/\beta = 3$ Gy [22].

SPECT/CT scanning

To measure the lung perfusion, ~5 ml TechneScan LyoMAA (Mallinckrodt Medica, Petten, The Netherlands) labelled with 1500–2000 MBq ^{99m}Tc was administered intravenously directly before scanning on a Symbia T TruePoint SPECT/CT scanner (Siemens AG, Erlangen, Germany). SPECT scans were acquired in 15 min with an isotropic voxel size of 7.8 mm on a 64 × 64 × 52 matrix, preceded by a free-breathing CT-scan with a slice thickness of 8 mm and an in-plane voxel size of 0.98 mm × 0.98 mm.

Image mapping

The CT of the SPECT/CT was automatically registered rigidly to the planning CT based on the bony anatomy. This registration brought the SPECT scans in the same coordinate system as the planned dose distribution, allowing the assessment of the local effect of the given dose on the lung perfusion.

Pre-processing

Voxels were excluded from the analysis if they (i) had a dose gradient exceeding 10/0.78 = 12.8 Gy/cm (10 Gy dose difference over one voxel) or (ii) lay on the border of the lungs (⩽7.8 mm) or (iii) lay close to the diaphragm (⩽1 cm above the most cranial point of the diaphragm). These exclusion criteria were recommended by Seppenwoolde et al. [18], with the exception of the dose-gradient for which we used 12.8 Gy/cm instead of 10 Gy/cm. The planned dose distribution was binned into dose intervals of 4 Gy NTD. For each dose bin, the reduction in local perfusion was averaged over all voxels per patient.

Table 1
Clinical and pathological characteristics of the patients in this study.

Gender	Male/female	24/18
Age (years)	Median (range)	77 (50–90)
Prescription dose	3 × 18 Gy	42
Tumour pathology	Adenocarcinoma	6
	Squamous cell carcinoma	2
	Large cell carcinoma	7
	Metastatic disease (colorectal)	1
	Unknown	26
Tumour staging	T1N0	35
	T2N0	6
	Metastatic disease	1
Tumour location	Left upper lobe	19
	Right upper lobe	23
Tumour movement (cm)	Median (range)	0.5 (0.0–1.7)
GTV (cm^3)	Median (range)	7 (0.8–53.7)
Mean lung dose (Gy)	Median (range)	7.9 (3.4–16.6)
FEV1 score (% of predicted value)	Median (range)	61 (27–98)

Perfusion reduction was calculated based on normalised SPECT scans to allow for quantitative comparison of the pre-SBRT and post-SBRT SPECT scans [18]. As the effect of radiation dose is distorted in already ill-perfused regions of the lung, only initially well-perfused (WP) voxels x were considered for analysis, i.e., voxels for which the number of counts was ⩾60% of the medium of the 10% highest voxels in the pre-SBRT SPECT to be robust against noise/outliers. To calculate the normalised perfusion P_x before (pre) and after (post) SBRT, normalisation was performed to the average number of counts in the well-perfused voxels in the low-dose (⩽8 Gy) regions N_{wpld}, as described in Eqs. (1) and (2)

$$P_x^{\mathrm{pre}} = \frac{c_x^{\mathrm{pre}}}{\bar{C}_{wpld}^{\mathrm{pre}}} \text{ with } \bar{C}_{wpld}^{\mathrm{pre}} = \frac{1}{N_{wpld}^{\mathrm{pre}}} \sum_{n=1}^{N_{wpld}^{\mathrm{pre}}} c_n^{\mathrm{pre}} \tag{1}$$

$$P_x^{\mathrm{post}} = \frac{c_x^{\mathrm{post}}}{\bar{C}_{wpld}^{\mathrm{post}}} \text{ with } \bar{C}_{wpld}^{\mathrm{post}} = \frac{1}{N_{wpld}^{\mathrm{post}}} \sum_{n=1}^{N_{wpld}^{\mathrm{post}}} c_n^{\mathrm{post}} \tag{2}$$

where c_x is the number of perfusion counts in voxel x and N_{wpld} the number of well-perfused low-dose voxels. For each patient j the average local perfusion for all x in each dose-bin i was calculated pre-SBRT ($\bar{P}_i^{\mathrm{pre}}$) and post-SBRT ($\bar{P}_i^{\mathrm{post}}$), which was used to calculate the relative reduction in perfusion $E_{i,j}$ at a dose level i, formally given by Eq. (3).

$$E_{i,j} = \frac{\bar{P}_{i,j}^{\mathrm{pre}} - \bar{P}_{i,j}^{\mathrm{post}}}{\bar{P}_{i,j}^{\mathrm{pre}}} \tag{3}$$

Modelling the dose–effect relation

To find a dose–effect relation between the local dose d_i and the relative perfusion reduction E_i, two models were fitted to the data; a 3-parameter logistic model (Eq. (4)) as proposed by Boersma [16] and a linear-maximum model (Eq. (5)), as proposed by the Duke University and our group [23].

$$\text{logistic} : E_i = \frac{M}{1 + \left(\frac{D_{50}}{d_i}\right)^k} \tag{4}$$

$$\text{linear} : E_i = \begin{cases} d_i \leqslant d_{\max}\ b * d_i \\ d_i > d_{\max}\ b * d_{\max} \end{cases} \tag{5}$$

where M describes the maximal effect for doses approaching infinity ($d_i \to \infty$), D_{50} is the dose for which 50% of the maximal effect is obtained, k is the steepness parameter, b is slope of the linear part of the linear-maximum model and $d_{\max}$ is the lowest dose for a maximum effect.

The model was fitted by minimizing the residual sum-of-squares weighted over the standard error (SE) of the calculated $E_{i,j}$ per dose-bin i per patient j. The SE was corrected for oversampling [24]. To determine which model best describes the dose–effect relation, we compared the models using the Akaike Information Criterion (AIC) [25].

Temporal changes in the dose–effect relation

Eight patients underwent a second post-SBRT SPECT/CT scan with a median of 15-months post-SBRT (range 10–20 months).