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Late effects in lung cancer

Predictive parameters of symptomatic radiation pneumonitis following stereotactic or hypofractionated radiotherapy delivered using volumetric modulated arcs

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ABSTRACT

Purpose: To identify dosimetric factors that predict development of radiation pneumonitis (RP) following stereotactic or hypofractionated radiotherapy for lung tumors.
Methods: Seventy-nine consecutive patients with either a planning target volume (PTV) > 100 cm^3 ($n = 69$) or prior pneumonectomy or bi-lobectomy ($n = 13$) were identified. Radiation doses (range: 5–50 Gy, with 5 Gy increments) were converted to equivalent doses ($EQD_{2\ Gy}$) ($\alpha/\beta = 3$). Total lung (TL), ipsilateral (IL) and contralateral lung (CL) volumes minus PTV, receiving 5 Gy (V5) up to 50 Gy (V50) and mean lung dose (MLD) were analyzed. Predictors of grade $\geqslant 3$ RP (CTCAEv4.03) were identified with concordance-statistics (C-statistic) and *p*-values used to quantify the performance of the model. Factors found to be significant were entered into a recursive partitioning analysis (RPA).
Results: Median PTV was 150 cm^3. Grade $\geqslant 3$ RP was observed in 8 patients (10%). In univariable analysis, CL-MLD, CL-V5-15, TL-MLD, TL-V5-V10 and ITV size were predictive of RP ($p < 0.05$). In multivariable analysis, contralateral MLD ($p = .007$) and ITV ($p = .063$) were the strongest predictors of grade $\geqslant 3$ RP, with excellent discrimination (*C*-statistic: 0.868).
Conclusion: Contralateral MLD and ITV size are both strong predictors of grade $\geqslant 3$ RP post treatment. Planning constraints should aim to keep contralateral MLD below 3.6 Gy.
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The survival of patients with early-stage non-small cell lung cancer (NSCLC) has improved significantly since the introduction of stereotactic ablative radiotherapy (SABR), and SABR is now considered the standard of care for patients who are unfit to undergo surgery [1]. In patients who are considered at higher risk for surgical complications, growing data suggest that SABR could produce comparable results [2].

Although the overall incidence of SABR-related pulmonary toxicity is low, it has been reported to correlate with large tumor volumes [3,4] and higher mean lung doses [4–7]. However, such evidence has mainly been limited to outcomes following SABR for peripheral lung tumors presenting with a maximum diameter not exceeding 5 cm. A systematic review of outcomes following treatment of large and central tumors with SABR has reported encouraging results provided that less-toxic 'risk-adapted' dose-fractionation schemes are used [8].

Dosimetric predictors of radiation pneumonitis (RP) are not well characterized, largely due to the low incidence of high-grade RP following SABR. A previous report on the use of volumetric arc therapy (VMAT) (RapidArc) for SABR delivery to tumors over 80 cm^3, showed that the relative volume of the contralateral lung receiving more than 5 Gy was the best predictor for RP [9]. The goal of the present study was to assess predictors of RP in a larger clinical population considered at high risk for RP and to study how well such a predictive model performs in order to identify optimal planning constraints to minimize the risk of RP.

Methods and materials

Patient selection

Details of all patients treated using hypofractionated radiotherapy and SABR at the VU University Medical Center with volumetric arc therapy (RapidArc, Varian Medical Systems) for lung tumors are entered into a prospective database. A group of patients considered at high risk for radiation pneumonitis were arbitrarily defined as those with either having a planning target volume

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(PTV) > 100 cm^3, or those having undergone a previous pneumonectomy or bi-lobectomy. All patients were included in an analysis to explore risk factors, in the following analysis patients who underwent a pneumonectomy were excluded as they were ineligible for the study of contralateral lung doses. Patients with synchronous lung tumors, or receiving previous thoracic irradiation were excluded. Only patients receiving RapidArc were included, as this technique was introduced in 2008 together with the more accurate AAA planning algorithm (Eclipse version 8.2.23 and later, Varian Medical Systems).

In total, 79 eligible patients treated between October 2008 and December 2011 were identified. Diagnostic work-up included CT scan of the chest with intravenous contrast and ^{18}FDG-PET-CT scan to evaluate disease extent. Prior to referral, all patients were discussed in a multidisciplinary tumor board, and were considered ineligible for surgery or concurrent chemoradiotherapy, when appropriate, due to co-morbidity (84%) or patient refusal (16%). Seventy patients had non-metastatic primary NSCLC, 4 had oligometastic lung cancer (1 small cell lung cancer, 3 NSCLC) in which the primary tumor as well as the metastases were treated radically, and four were treated for a lung metastasis from an extrapulmonary tumor.

Treatment and follow-up

Stereotactic and hypofractionated fractionation schemes used were 'risk adapted', depending on the tumor size and location [10,11]. Three fractions of 18 Gy were delivered for T1 tumors, five fractions of 11 Gy for T1 tumors with broad chest wall contact or T2 tumors, eight fractions of 7.5 Gy for central tumors without overlap with mediastinal structures and twelve fractions of 5 Gy for very large tumors or tumors with major overlap with mediastinal structures. All fractionation schemes were prescribed to the encompassing 80% isodose.

Details of our protocols for target definition and optimization have been described previously [9,12]. Briefly, an internal target volume (ITV) is created by delineating the tumor on all phases of the 4-dimensional CT (4D-CT) dataset. A planning target volume (PTV) is generated by adding an isotropic margin of 5 mm to the ITV. Treatment planning was performed on the average intensity projection of the 4D-CT. Treatment plans were optimized to limit high-dose radiation to organs-at-risk such as chest wall, hilum and heart. In the esophagus, brachial plexus and spinal cord a maximum point dose (Dmax) was allowed, depending on fractionation schedule, and PTV underdosage was accepted to meet these constraints. For the 12 fraction-scheme Dmax in the esophagus was 48 Gy, in the brachial plexus 42 Gy and in the spinal cord 32 Gy. After early experience revealed that contralateral lung dose best predicted risk of RP [9], high priority optimization objectives were introduced for reducing contralateral lung receiving >5 Gy (V5) by using an avoidance sector for the contralateral lung. Each RapidArc plan consisted of at least one pair of clockwise and counter-clockwise coplanar arcs using 6 MV photons at a maximum dose rate of 600 monitor units (MU)/minute [9,12].

Routine follow-up consisted of visits after 3, 6, 12, 18, and 24 months and yearly thereafter. At each follow-up visit, new symptoms were recorded, and a diagnostic CT scan was performed.

Dosimetric factors and endpoints

Contours of both lungs were automatically generated, and the lung volume at risk was defined as the lungs minus the PTV. All dosimetric parameters were analyzed for the total lung (TL), the ipsilateral lung (IL) and the contralateral lung (CL) volume. In order to correct for differences in fractionation schedules, the local dose was converted to equivalent doses in fractions of 2 Gy ($EQD_{2\ Gy}$) using the linear quadratic (LQ) model, and an α/β ratio of 3 for lung tissue [4,5,7,13]. Dose levels from 5 to 50 Gy, with 5 Gy increments, were corrected with this method in order to evaluate relative volume of the lung receiving more than 5 Gy ($EQD_{2\ Gy}$) (V5), 10 Gy (V10) up to V50. No correction was applied for determining mean lung doses (MLD).

Primary endpoint was high-grade radiation-induced pneumonitis (RP), which was independently and retrospectively scored in all patients by two experienced clinicians, using the Common Terminology Criteria for Adverse Events, version 4.03 (CTCAEv4.03). RP was considered high-grade if it was grade $\geqslant$3; defined by CTCAE as pneumonitis for which either oxygen or hospitalization is needed or if it is limiting self care in daily activities. This endpoint was chosen as a clearly identifiable event in this retrospective analysis. Due to the retrospective study of data generated during routine patient treatment, medical ethics committee approval was not needed in accordance with the Dutch Law.

Statistical analysis

Univariable logistic regression analysis was performed on all patient and tumor characteristics shown in Table 1, and dosimetric parameters, in order to identify significant predictors of high-grade RP. *p*-Values and concordance-statistics (*C*-statistic) were used to quantify degree of association of each of the factors with high-grade RP.

A multivariable logistic regression model was generated using forward-stepwise selection procedures. Beginning with the factor shown to have the strongest association, additional factors shown to be significant ($p < 0.05$) on univariable analysis were entered into the base model sequentially according to order of ascending *p*-value. Factors were retained in model only if: (1) *p*-value of most recent factor remained significant or displayed some association (i.e., $p < 0.10$), and (2) there was an increase in the overall C-statistic for the model compared to the base model. The calibration of the model was tested using the Hosmer and Lemeshow goodness of fit test, where a non-significant *p*-value indicates good calibration. For multivariable models, patients are included in the model only if data are available on all variables being modeled for that

Table 1
Patient and tumor characteristics.

	No. of patients or median	% or range
Age (years)	75.5	49–91
Male	61	77
Performance status		
WHO 0–1	51	65
WHO 2–3	28	35
COPD[*]		
Gold 0	24	30
Gold 1–2	38	48
Gold 3–4	17	22
TNM stage (7th edition)		
I	26	33
II	38	48
IIIA	6	8
IV	9	11
Tumor diameter (mm)	53.0	12–107
ITV (cm^3)	73.1	3–274
PTV (cm^3)	149.4	13–411
Fractionation scheme		
3 fractions of 18 Gy	2	3
5 fractions of 11 Gy	25	32
8 fractions of 7.5 Gy	23	29
12 fractions of 5 Gy	29	37

[*] COPD, chronic obstructive pulmonary disease.