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Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non-small cell lung cancer: A dose– and volume–response analysis

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ABSTRACT

Background and purpose: The aim of this study is to analyse the dose–response and the volume–response of radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy (SBRT).
Materials and methods: During the period 1998–2005, 68 patients with medically inoperable stage I non-small cell lung cancer (NSCLC) were treated with hypofractionated SBRT to 45 Gy in 3 fractions. Among the 33 patients with complete treatment records and radiographic follow-up exceeding 15 months (median: 29 months), 13 fractures were found in seven patients. Identifying all ribs receiving at least 21 Gy, 81 ribs (13 with and 68 without fracture) in 26 patients were separately contoured and their dose–volume histograms (DVHs) were obtained. The DVHs were assessed with the mean dose and cut-off models. Maximum likelihood estimation was used to fit dose–response and volume–response curves to each model.
Results: It was possible to quantify the risk of radiation-induced rib fracture using response curves and information contained in the DVHs. Absolute volumes provided better fits than relative volumes and dose–response curves were more suitable than volume–response curves. For the dose given by the 2 cm^3 cut-off volume, D_{2cm3}, the logistic dose–response curve for three fractions was parameterised by $D_{50} = 49.8$ Gy and $\gamma_{50} = 2.05$. Consequently, for a median follow-up of 29 months, if $D_{2cm3} < 3 \times 7.0$ Gy the risk is close to 0, and the 5% and 50% risks are given by $D_{2cm3} = 3 \times 9.1$ Gy and 3×16.6 Gy, respectively.
Conclusions: In this group of patients, the risk for radiation-induced rib fracture following hypofractionated SBRT was related to the dose to 2 cm^3 of the rib.
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Hypofractionated stereotactic body radiation therapy (SBRT) has been available for more than 10 years and is gaining clinical interest. The main aim of SBRT is to reduce the set-up margin and the internal margin in order to keep the planning target volume (PTV) and the irradiated volume as small as possible. This has mainly been utilized for the treatment of lung and liver tumours since these organs have large functional reserves and benefit from reducing the irradiated volume [1,2]. Several studies have reported good local tumour control for non-small cell lung cancer (NSCLC) patients treated with the SBRT technique [3], but so far no randomised study has been published which compares it to conventional radiotherapy or surgery.

The dose distributions in the organs at risk (OARs) arising from the combination of SBRT and hypofractionation have some distinct features. OARs close to or inside the PTV will be subject not only to a high dose, but also to a high dose per fraction; a situation sometimes referred to as 'double trouble' [4]. In addition, the dose (and the dose per fraction) gradient over OARs partly in the PTV will be very steep with some parts irradiated to low doses. On the other hand, the applied gross tumour volume (GTV) to PTV margin is small and more OARs will be completely outside the high-dose region. Late effects in normal tissue after SBRT have been reported [5–10], but few studies have been performed to establish clinical dose– and volume–response relationships when using large doses per fraction [11–13]. Radiation-induced rib fracture has been recognised as a normal tissue complication after conventional radiotherapy [14–19], and some studies have reported it after hypofractionated radiotherapy [6,16,20,21]. It is difficult to find parameters for normal tissue complication probability (NTCP) models for hypofractionated therapy in the literature, this is most likely due to scarcity of clinical data.

Patients with NSCLC treated with hypofractionated SBRT at Sahlgrenska University Hospital were prospectively evaluated with CT examinations. A dose– and volume–response analysis of

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radiation-induced rib fracture was performed on this cohort of consecutively treated patients.

Materials

Between September 1998 and December 2005, 68 patients with medically inoperable stage I NSCLC were treated with SBRT at the Sahlgrenska University Hospital, Sweden. The first 45 patients and the treatment technique have been described in detail elsewhere [6] and the following 23 patients were treated according to the same protocol. The end point in the current study was radiation-induced rib fracture, verified by CT scan at any time after treatment. The inclusion criteria for the dose–response analysis were at least 15 months of radiographic follow-up and availability of complete treatment data. Among the 68 patients there were 28 patients excluded due to follow-up shorter than 15 months and one due to that the SBRT treatment volume overlapped an area subject to previously administered radiotherapy. Furthermore, for six patients the 3D dose-distribution data could not be retrieved.

Treatment procedure

The patient was immobilized in a stereotactic body frame (SBF) (Elekta AB, Sweden) and a pre-treatment CT scan with a slice thickness of 3 mm was performed [6]. The GTV was contoured on each axial slice in the treatment planning system (Cadplan 6.4.7 or Eclipse 7.2.24, Varian Oncology Systems, USA), and the clinical target volume (CTV) was, in almost all cases, defined as the same volume as the GTV. To create a PTV, margins of 5 mm in the transversal plane and 10 mm in the cranio-caudal direction were added to the CTV. During the planning process, the movement of the tumour due to breathing was visualized fluoroscopically. If the motion exceeded the CTV to PTV margins, the SBF's breathing control device was applied. The prescribed dose was 45 Gy in three fractions. Using 4–6 coplanar or non-coplanar 6 MV photon beams and a multileaf collimator, a dose distribution with 45 Gy at the periphery of the PTV was created. This resulted in an inhomogeneous PTV dose distribution with a typical isocentre dose in the range of 63–65 Gy, and very steep dose gradients outside the PTV (Fig. 1). The dose distribution was calculated with the pencil beam convolution algorithm using the modified Batho method for inhomogeneity correction [22,23]. Immediately prior to the first treatment, the reproducibility of the tumour location relative to the SBF coordinate system was checked with a CT scan and accepted if inside the previously defined PTV. The 45 Gy was delivered in three fractions during 1 week.

End point and follow-up

The studied end point of radiation-induced rib fracture is binary with a score of 1 in case of fracture and otherwise. The end point is defined for each rib and each patient may therefore have multiple end points.

All patients were followed up with multiple CT scans: the first one after 3 months, followed by scans every 6 months. All available (regardless of whether dose–response analysis inclusion criteria were met) follow-up CT scans were checked for fractured ribs not only in proximity to the tumour but also in the whole rib cage. Among the 33 patients meeting the inclusion criteria for the dose–response analysis, 13 fractures were found close to the tumour site in seven patients. One patient had three fractures, four patients had two fractures and two patients had one fracture. The follow-up CT scans for the 13 fractured ribs were exported to the treatment planning system and co-registered with the pretreatment CT scans making it possible to assign the correct end point to each rib in the pretreatment scan (Fig. 1).

For one of the patients with non-retrievable dose distribution, two fractures were found in proximity to the tumour site. Among all available follow-up CT scans a total of three additional fractures were found on the contralateral side where the dose is practically zero; those fractures were not included in the analysis. Among the patients studied, no rib was fractured at more than one location.

Contouring and dose–volume histograms

For the 33 patients meeting the inclusion criteria, all ribs with a total dose of at least 21 Gy were contoured without margin for set-up movements. Due to a medially or centrally located tumour, there were seven patients in whom all ribs received significantly less than 21 Gy. This resulted in a total of 81 contoured ribs in 26 patients: 13 with and 68 without fracture (Table 1). Each cumulative dose–volume histogram (cDVH) was exported to a file using a dose bin size of 0.5 Gy. The mean volume of the 81 con-

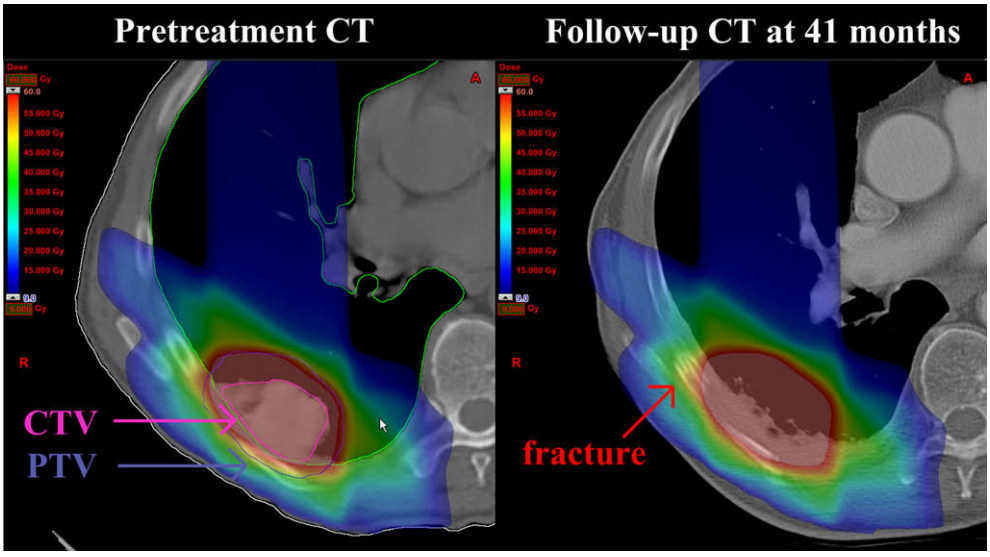

Fig. 1. Left: typical dose distribution in the transversal plane (patient number 16 from Table 1). Right: dose distribution in the corresponding plane on the follow-up CT after image registration.