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Radiation induced rib fractures

Dose–effect analysis of radiation induced rib fractures after thoracic SBRT

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ABSTRACT

Background and purpose: To determine a dose–effect relation for radiation induced rib fractures after stereotactic body radiation therapy (SBRT) in early stage non-small cell lung cancer (NSCLC). Automatic rib delineation has enabled the analysis of a large patient group.
Material and methods: Four-hundred and sixty-six patients with stage I/II NSCLC received SBRT with a median of 54 Gy in 3 fractions. The optimal EQD2-corrected dose parameter to predict (a)symptomatic fractures was found using Cox regression. Three normal tissue complication probability (NTCP) models based on this optimal parameter were constructed: (1) at a median follow up (FU) of 26 months, (2) for all data, with time to toxicity taken into account and (3) at a FU of 26 months, excluding low dose ribs.
Results: The median time to fracture was 22 (range 5–51) months. Maximum rib dose best predicted fractures. The TD_{50} (dose with 50% complication) of the second NTCP model was 375 Gy. The TD_{50} was significantly higher for the other models indicating an under-estimation of the dose effect at the median follow-up time and/or when excluding low dose ribs.
Conclusions: The risk of symptomatic rib fractures after SBRT was significantly correlated to dose, and was <5% at 26 months when $D_{max} < 225$ Gy.
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For patients with inoperable peripheral early stage non-small cell lung cancer (NSCLC), stereotactic body radiation therapy (SBRT) has become the standard of care [1,2], with good local tumor control probabilities for both primary and secondary lung tumors [3]. Toxicity rates for lung, esophagus, airway, heart and spinal cord after SBRT for NSCLC were recently reported in a review [4]. Radiation induced rib fractures are a known side effect after SBRT. Rib fractures are diagnosed clinically when a fracture is found on a follow-up (FU) CT scan. This occurs in approximately 5% of patients (range 1.6–8.3%) [5–9]. A full evaluation of all available FU CTs with extra attention to fractures yields approximately 30% of fractures (range 21–41%) [10–15]. Significant dose–effect relations were reported by several groups that used manual contouring of ribs [10–12]. However, as manual contouring is cumbersome and time consuming, this was done on a limited number of patients, or only included ribs that received high doses. Analysis of a large group of patients is warranted, and automatic segmentation of the ribs allows for such an analysis. Recently, we showed that atlas based automatic segmentation of ribs is fast, accurate and significantly equivalent to manual segmentation [16]. In this paper we use automatic segmentation of ribs for a large group of patients to determine a dose–effect relation using the Lyman–Kutcher–Burman (LKB) model. As time to toxicity is relatively long for rib fractures, i.e., 15–22 months [10–12,14], a more accurate model could be obtained when time to toxicity is taken into account.

The aim of this paper is to determine a dose–effect relation for symptomatic, radiologically diagnosed radiation induced rib fractures after SBRT for a tumor in the lung, taking into account time to toxicity.

Material/Methods

Patient and treatment characteristics

From June 2006 to June 2013 494 consecutive patients with inoperable, mostly peripheral, lung tumors were treated with SBRT to a median of 54 Gy in 3 fractions. Four-hundred and thirty-two patients had stage T1a-T2b N0 NSCLC, two patients had T2b and T3a disease, and 60 patients were treated for oligometastatic disease from primary lung, colon, prostate, breast, rectum, bladder or melanoma tumors.

Four-hundred and sixty-six patients were included (table 1); 28 patients were excluded, due to non-radiation induced fractures (2), or technical issues (26). The median tumor diameter was 2.24 cm

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(0.7–6.9 cm), 4% of patients had a tumor >5 cm. Eight percent of patients previously received a lobectomy, pneumonectomy or wedge resection (35). Staging of tumors was done following the 6th TNM staging system.

All patients received a mid-ventilation (before Aug 2011) or mid-position (after Aug 2011) treatment planning CT scan, derived from a 4D scan [17]. The Gross Tumor Volume (GTV) was contoured on the mid-ventilation or the mid-position scan and typically expanded anisotropically by 8 or 10 mm (depending on the breathing peak-to-peak amplitude) to generate the Planning Target Volume (PTV). For treatment planning, the Pinnacle treatment planning system (Philips Radiation Oncology Systems, Milpitas, USA) was used, where dose calculations were performed using the collapsed-cone convolution/superposition algorithm. Treatment plans consisted of 16 to 20 coplanar and noncoplanar beams for intensity modulated radiotherapy (IMRT) plans, or dual arc volumetric arc therapy (VMAT). Dose prescription allowed for inhomogeneous dose to the PTV, with a maximum dose of 165% of the prescribed dose. There were no constraints on the ribs. Three-hundred and thirty-nine patients received 54 Gy in 3 fractions (73%). Twenty-six patients received 45 Gy in 3 fractions (6%), 28 patients received multiple treatments separated by several months or years; 18 patients received two series of 54 Gy in 3 fractions (4%), 8 patients received 54 Gy in 3 fractions followed by 66 Gy in 24 fractions (2%), and two patients received two consecutive treatments of 54 Gy in 3 fractions and a series of 66 Gy in 24 fractions (0.4%). Twenty-seven percent of patients received an adapted schedule because of normal tissue constraints, overlap with a previous radiation treatment, or prior multiple RT schedules, e.g. for metachronous primary lung tumors. Other dose schedules ranged from 24 to 60 Gy in 2 to 8 fractions (14%). In one patient treated to two tumors in both lungs the third fraction was cancelled due to a pneumonia during treatment.

All patients were treated with IMRT (before Oct 2009) or VMAT (after Oct 2009) using online cone-beam guided position verification.

FU consultation consisted of a medical history, a physical examination and a CT scan at 4 months after treatment, every 6 months for two years, and yearly up to 5 years. Pain was graded using the Common Toxicity Criteria for Adverse Events (CTCAE) v3.0 [18].

Rib fractures were diagnosed on FU CT scans by the treating radiation oncologist and/or radiologist. Systematic (retrospective) evaluation of all available FU CTs was not performed, but patients that were suspected of fracture based on the CT in combination with reported pain were evaluated in detail by screening all FU CTs of these patients for fractures. Rib fractures were diagnosed radiologically and were either asymptomatic (Grade 1), or symptomatic: reported thoracic pain with intervention needed according to CTCAE criteria Grade 2 or 3. If the incidence of rib fractures was higher in patients that received multiple treatments was assessed via a student t-test.

Rib segmentation

We used atlas based segmentation in ADMIRE (2013, Elekta AB, Stockholm, Sweden) with a Random Forest implementation for rib segmentation. The method has been described previously [16,19,20]. In short, for 15 patients, the planning CTs with delineated ribcages were used as atlases. A non-rigid registration of each atlas to the planning CT of a new patient was performed, followed by a Random Forest supervised learning classification of voxels. The classification was combined with a multi-level label fusion, which merged the multiple atlas segmentations into a single new ribcage. All ribcage segmentations were manually checked for protrusions that caused connections between ribs and if necessary edited. Individual ribs were obtained from the ribcage segmentation after a triangulation of the surface mesh and separation of all unconnected surfaces, yielding 24 ribs per patient [16].

For some patients, parts of ribs 8–12 were not in the field of view of the CT. As the dose to these parts of the ribs was negligible, its influence on the NTCP model (in a smaller cohort) was negligible [16], and for these ribs only the dose on the part of the rib within the field of view was used in the calculations.

Dose–effect modeling

Physical dose distributions from the clinical plans were corrected to biologically equivalent doses, to account for the dose per fraction as given in fractions of 2 Gy (EQD2) using the linear-quadratic (LQ) model with an $\alpha/\beta = 3$ Gy [10,11,14]. For patients with synchronous tumors that were planned on a single CT scan and treated concurrently or sequentially (31 patients): either their 3D physical dose distributions were added and EQD2 corrected (concurrent), or their 3D EQD2 corrected dose distributions were

Table 1
Patient, tumor and treatment characteristics.

	Men	Women	All
No. Patients	246	220	466
Median age (range)	74 (47–91)	72 (37–89)	74 (37–91)
Median GTV volume (cc) (range)	6.3 (0.4–129)	4.55 (0.2–127)	5.46 (0.2–129)
Median PTV volume (cc) (range)	38.5 (7.1–347)	30.25 (2.3–274)	33.38 (2.3–347)
Median prescribed dose_Gy (range)	54 (24–60)	54 (24–60)	54 (24–60)
Median prescribed fractions	3 (2–8)	3 (3–8)	3 (2–8)
T stage: 1	155	147	302
T stage: 2	51	29	80
T stage: 3	1	0	1
T stage: unknown	39	44	83
Tumor location: LUL	74	80	154
Tumor location: LLL	27	34	61
Tumor location: RUL	92	63	155
Tumor location: RML	9	6	15
Tumor location: RLL	44	37	81
Median BMI (range)	25.4 (15.5–62.1)	23.4 (12.3–51.2)	24.4 (12.3–62.1)
Median FU (mo) (range)	23.3 (0.7–88.9)	28.3 (0.3–100.6)	26.1 (0.3–100.6)
No. patients with fracture ($\geqslant$G1)	32	32	64
No. patients with symptomatic fracture ($\geqslant$ G2)	26	16	42
Median time to fracture (mo) (range)	22.1 (4.5–51.2)	22.1 (9.1–41.1)	22.1 (4.5–51.2)

GTV = Gross tumor volume; PTV = Planning target volume; LUL = Left upper lobe; LLL = Left lower lobe; RUL = Right upper lobe; RML = Right middle lobe; RLL = Right lower lobe; BMI = Body mass index.