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Vertebral metastatic fractures

Fractures of thoracic vertebrae in patients with locally advanced non-small cell lung carcinoma treated with intensity modulated radiotherapy

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ABSTRACT

Purpose: To report on the incidence of vertebral fractures in patients treated with Intensity Modulated Radiotherapy (IMRT) for locally advanced non-small cell lung carcinoma (NSCLC) and to analyse the association with clinical and dosimetric parameters.

Patients and methods: Between 2007 and 2012, 524 patients treated with $\geqslant$51 Gy were retrospectively analysed for the incidence of vertebral fractures (VF). Clinical parameters were assessed. In addition, a case control study in 50 patients was performed to study the association between the radiotherapy dose and fractured vertebrae.

Results: Three hundred and thirty-six patients were eligible for analyses. Twenty-eight patients (8%) were observed with VF at a median follow up of 12 months. Age was significantly higher in the group with VF ($p < 0.01$). After balancing age, the mean vertebrae dose was most significantly associated with fractures of the vertebrae ($p < 0.01$).

Conclusion: VF was observed in 8% of the patients with locally advanced NSCLC. RT dose was associated with the occurrence of thoracic vertebral fractures.

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Concurrent chemoradiation (CCRT) is the treatment of choice for locally advanced non-small cell lung cancer (NSCLC). The increase in survival, compared to sequential chemoradiation (SCRT) is 6% at 3 years and is mainly due to the improved local tumour control [1–3]. This is, however, at the cost of increased toxicity such as oesophageal and pulmonary toxicity [4–6]. Radiation-induced bone damage has not yet been thoroughly studied. This toxicity has mainly been described for stereotactic body radiotherapy (SBRT) [7,8] rather than conventional RT [9,10]. Case reports showed osteoradionecrosis (ORN) in patients treated with radiotherapy for NSCLC [9]. In head and neck cancer, ORN of the upper cervical spine has been observed [10]. A biopsy of the cervical vertebrae was performed in 3 patients with suspicion of local recurrence of disease but revealed only chronic inflammation and necrosis and no recurrent disease. In addition to RT studies, most demographic studies on the incidence and prevalence of VF take age and gender into account because of the relation with osteoporosis. Increased age and a decreased oestrogen level in post-menopausal women lead to a loss of bone mineral density (BMD) [11]. The prevalence of vertebral fractures in men and women aged >50 is 10% and 24% respectively, with an increased prevalence with growing age [12,13]. Beside age and gender, prevalent fractures, biomechanics, smoking, low body weight, chronic obstructive pulmonary disease (COPD), walking aid use, long-term use of systemic corticoid steroids and long-term oxygen therapy are prognosticators for VF [14–16]. A common obstacle of the VF studies was the lack of clinical recognition of VF, due to the difficulties in determining the cause of the symptoms. In most studies lateral X-rays of the thorax, or spinal radiographs were used for diagnoses [17,18], sometimes followed by morphometric analysis. Symptoms and quality of life in patients suffering from VF were summarized by Ryan et al. [19]: Sixty-three percent suffered from persistent back pain; 47% had difficulty with functional activities and 42% had difficulty finding suitable clothing.

With the introduction of Intensity Modulated Radiotherapy (IMRT), our institute has intensified the research on late-onset toxicities and started collecting data on VF. Because of the clinical implications and the limited knowledge on RT induced VF, we studied the incidence of thoracic VF and its relation with the radiotherapy dose, taking into account the clinical and demographic risk factors.

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Methods and materials

Patient selection

A total of 524 locally advanced NSCLC patients were treated with $\geqslant$51 Gy with or without chemotherapy between 2007 and 2012 in the Netherlands Cancer Institute (NKI). Medical records, clinical symptoms like pain and treatment schedules of these patients were retrospectively reviewed. Vertebral fractures were also retrospectively screened from the baseline/planning Computer Tomography Scan (CT) and follow-up CT (1 or 5 mm slices) or Magnetic Resonance Imaging (MRI). Patients were excluded from the study if no follow-up CT imaging was present, had prior irradiation to thoracic or head and neck, had VF prior to radiotherapy (identified from the planning CT scan), or had VF due to a trauma.

Treatment

The treatments consisted of concurrent chemo radiotherapy: daily cisplatin (6 mg/m^2) and 66 Gy (24 fractions of 2.75 Gy) on sequential working days [1,2]; sequential chemo radiotherapy: 2–4 cycles of chemotherapy doublets followed by 66 Gy in 24 fractions, or RT only: 66y in 24 fractions; 60 Gy in 30 fractions; 51 Gy in 17 fractions.

For radiotherapy planning, a four-dimensional CT scan (4DCT) was acquired in all patients in order to minimize the respiratory induced systematic errors and assess the breathing amplitude of the primary tumour. A mid-ventilation scan (MidV scan) with the tumour closest to its time-averaged mean position was reconstructed from the 4DCT. This MidV-scan was used to delineate the gross tumour volume (GTV), involved lymph nodes and organs at risk (OARs). All patients had a Fluorodeoxyglucose/Positron emission tomography (FDG–PET) scan before the start of treatment.

The GTV was expanded to a planning target volume (PTV) using margins of 12 mm plus 1/4 of the primary tumour peak-to-peak amplitude in orthogonal directions as observed on the 4DCT. For the lymph nodes an isotropic PTV margin of 12 mm was used. Heart, spinal cord, lung and oesophagus were delineated according to departmental guidelines. Dose distributions were calculated using inhomogeneity correction (Pinnacle version 9.2). Dose constraints and objectives were defined in biologically equivalent dose in 2 Gy per fraction (EQD_2). For the oesophagus a $V_{35} < 65\%$ ($\alpha/\beta = 10$ Gy) was encouraged when optimizing the IMRT plan. Dose objectives for other OARs were: mean lung dose $\leqslant$ 20 Gy ($\alpha/\beta = 3$ Gy), spinal cord $\leqslant$ 52 Gy ($\alpha/\beta = 2$ Gy), total mean heart dose $\leqslant$ 40 Gy, 2/3 heart $\leqslant$ 50 Gy, and 1/3 heart $\leqslant$ 66 Gy ($\alpha/\beta = 4$ Gy). Patients received repetitive cone-beam CT scans for an off-line setup correction protocol.

Assessment of vertebral fractures

All patients with follow up CT images were first screened on VF by a pulmonologist and then forwarded to the radiologist. Patients in whom the vertebral cortex was taken over by soft tissue, VF was attributed to metastatic disease [10,18]. In case of a VF on the follow up imaging, the planning CT was reviewed for pre-existent fractures. If a fracture was identified on the planning CT, the patient was excluded from the study. Otherwise, the location and number of VF were recorded, and the date of the first identified follow-up imaging was recorded as the onset date. If no VF was identified on any of the follow-up imaging, the date of the last imaging was recorded as the date of the last follow-up for VF.

Preparation of explanatory variables

The following clinical parameters were taken into account: age, gender, chemotherapy, performance status (PS) and Chronic Obstructive Pulmonary Disease (COPD). For COPD, the Global initiative for chronic obstructive lung disease (GOLD) classification [20] was used based on the forced expiratory volume (FEV1) before treatment. To determine the loss of bone mineral density (BMD), the baseline RT planning CT was used to assess the Hounsfield units (HU). Information on thoracic back pain was also retrieved from medical records.

A one-to-one matched case control study was conducted to assess the relationship between RT dose and VF. The case control study allowed the analysis to be conducted on a subset of patients with balanced demographic risk factors. The process of matching case control patients was as follows: (1) for each patient with a VF, a subset of non-VF patients with longer follow-up was selected; (2) a smaller subset who had the same matching variables as the VF patient was further selected. The matching criteria included age (±5 years), PS and gender; (3) a patient from the qualified subset was randomly selected as the corresponding control patient.

After selection of the matched control cases, the vertebral corpora of Th1–Th12 were manually delineated on the planning CT (Fig. 1). The cylindrical shape vertebral corpora was delineated as the main portion of a vertebra anterior to the vertebral canal, as

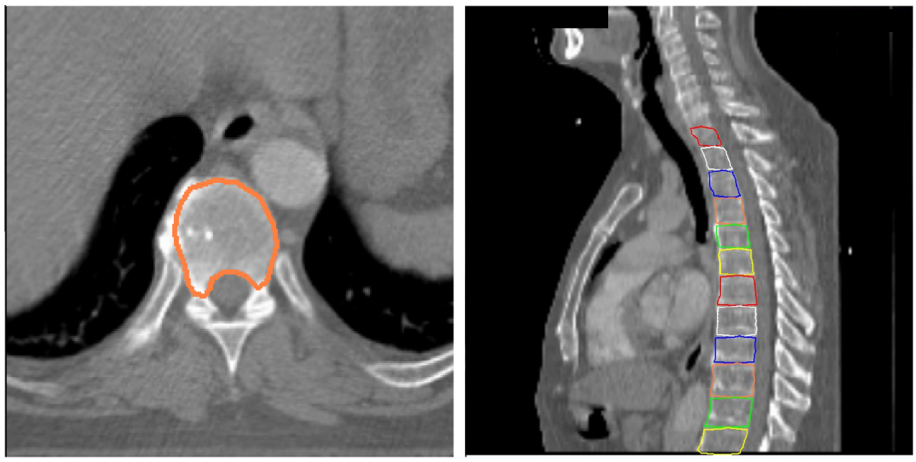

Fig. 1. Example of a delineated corpus vertebra in axial view and the delineated vertebra Th01–Th12 in sagittal view.