Radiotherapy and Oncology 109 (2013) 200–203

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Esophageal cancer

Reduction in cardiac volume during chemoradiotherapy for patients with esophageal cancer

Lotte J. Lutkenhaus *,[1], Martijn Kamphuis [1], Niek van Wieringen, Maarten C.C.M. Hulshof, Arjan Bel

Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 12 July 2013
Received in revised form 29 August 2013
Accepted 1 September 2013
Available online 3 October 2013

Keywords:
Chemoradiotherapy
Esophageal cancer
Cardiac volume
Cone beam CT

ABSTRACT

We investigated the change in cardiac volume over the course of chemoradiotherapy in 26 patients treated for esophageal cancer, using cone beam CT imaging. The cardiac volume reduced significantly, with a median reduction of 8%. A significant relationship with planned cardiac dose was not found.
 Radiotherapy and Oncology 109 (2013) 200–203

With the introduction of chemoradiotherapy (CRT) as part of the standard treatment regimen for esophageal cancer, the overall survival increased, but toxicity increased as well [1]. Radiotherapy for esophageal cancer gives rise to late locoregional complications, such as esophageal, cardiac and pulmonary toxicity [2]. Reducing radiation dose to the organs at risk (OARs) can reduce these late complications.

Inaccurate delivery of the planned dose is one of the causes of unnecessary dose to the OARs. In radiotherapy for esophageal cancer, various uncertainties limit the accuracy of the dose delivery. Such uncertainties include morphological changes over the course of treatment, for example tumor response or differences in stomach filling. These morphological changes have become apparent due to the increased implementation of image guided radiotherapy [3].

To compensate for morphological changes, the treatment plan can be adapted during the course of treatment. Adaptive radiotherapy (ART) has the ability to correct for underdosage of the target and to reduce the dose to the OARs [4,5]. For esophageal cancer, ART strategies have been designed to account for patient-specific respiration-induced motion [6,7]. An ART strategy to account for morphological changes in esophageal cancer patients has not been described yet.

In identifying morphological changes over the course of CRT for esophageal cancer, we have recently observed a decrease in heart contour on weekly acquired cone beam CT (CBCT) scans, which reflects a reduction in volume (Fig. 1) [8]. A volume change can result in inaccurate dose delivery, for which implementation of ART could be beneficial. Therefore this volume change should be quantified.

The aim of this retrospective study was to quantify the reduction in cardiac volume over the course of CRT for esophageal cancer. Additionally, we assessed the possible relationship between cardiac volume reduction and possibly relevant determinants such as planned cardiac dose.

Materials and methods

Patients

Between March 2012 and August 2012, 44 consecutive patients with potentially curable primary esophageal or esophagogastric junction carcinoma received preoperative or definitive CRT in our institute. Patients with a cervically located esophageal tumor were excluded from this retrospective study, since for these tumors the heart is not imaged during treatment. A total of 26 patients met criteria for inclusion. Histology was adenocarcinoma in all patients. Of the 26 patients, 12 received cardiac medication for either hypertension or a previous episode of unstable angina or myocardial infarction. Medication regimen remained unchanged for the duration of CRT. In total 110 CBCT scans were available for analysis.

Chemoradiotherapy

Three-dimensional conformal irradiation plans were created using a four-field beam arrangement (6 and 10 MV photon beams),

* Corresponding author. Address: Academic Medical Center, Department of Radiation Oncology, Office Z1-217, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
E-mail address: l.j.lutkenhaus@amc.uva.nl (L.J. Lutkenhaus).
[1] These authors contributed equally to this work.

0167-8140/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2013.09.003

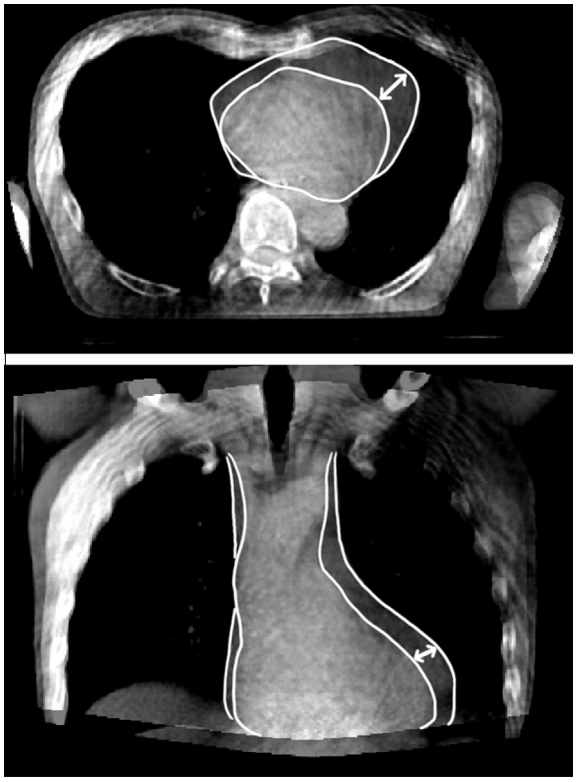

Fig. 1. Overlay of planning CT (outer contour) and final CBCT (inner contour). Images are matched on bony anatomy. The heart contour is clearly larger on the planning CT scan in both views.

using Oncentra treatment planning system (Oncentra 4.1, Elekta, Uppsala, Sweden). For preoperative and definitive treatment, 41.4 Gy and 50.4 Gy were prescribed, respectively, in 1.8 Gy dose per fraction. The gross tumor volume (GTV) was delineated on the free breathing planning CT scan. By extending the GTV up to 38 mm superiorly and inferiorly, the clinical target volume (CTV) was created. The planning target volume (PTV) was generated by expanding the CTV 10 mm in all directions. Delineations on the planning CT scan were used for treatment planning purposes only.

Plans were designed with the 95% isodose surface covering the PTV. The main dose constraint was to limit the dose to both lungs to a V20 (i.e., the percentage of total lung volume receiving 20 Gy or more) of less than 30%. Other constraints included a V50 $\leqslant$10% for the spinal cord and V45 $\leqslant$50% for the whole heart. All treatments were delivered on Elekta linear accelerators (Elekta, Stockholm, Sweden) in five daily fractions per week. In the first week, daily kilovoltage CBCT scans were acquired to enable repositioning for systematic errors in an off-line protocol [9]. After the first week, weekly CBCT images were acquired.

Chemotherapy was administered intravenously on days 1, 8, 15, 22, and 29. Chemotherapy consisted of paclitaxel at a dose of 50 mg per square meter body surface, administered over one hour. This was followed by carboplatin, targeted to an area under the concentration–time curve of 2 mg per milliliter per minute, administered over 30 min. Patients were intravenously premedicated with dexamethasone, clemastine and ranitidine, and received antiemetic drugs. Chemotherapy was always administered after the radiotherapy fraction of that day.

Data acquisition

The CBCT scans used for evaluation were acquired at the start of every treatment week (Elekta Synergy, 360° scan, 120 kV, 1 mm^3 voxels). CBCT-scans are acquired over a 2-min period, thus averaging the scan over many cardiac contractions and breathing cycles. The treatment days on which the CBCTs were acquired could vary, but CBCTs were acquired at least one day after chemotherapy administration. Also, per patient, the time between CBCTs was kept constant. Subsequently, the images were imported in the treatment planning system with proper scaling of gray values such that they were in the range of CT Hounsfield Units (HU) [10]. On these image sets, heart contours were delineated according to guidelines developed by Feng et al. [11]. For optimal visualization of the heart, a level of −40 and a window of 1500 corresponding HU were chosen. Due to limited image quality of the CBCT scans, not all separate heart components were distinguishable. Delineation was therefore started superiorly at the bifurcation of the trachea, and the pericardium was used as a substitute for myocardium border.

Delineations were performed by a single observer per patient to avoid inter-observer variations. To determine intra-observer variation, for 3 patients the heart volume was delineated a second time by the same observer for all fractions, at least one month after the initial delineation. Per patient, the volumes were normalized, with the initial volume as measured on the first CBCT set to 100%. Using a Wilcoxon signed-rank test, a significant difference was not found between the delineated volumes acquired on both time points.

Data analysis

Volumes were normalized, with the initial cardiac volume as measured on the first CBCT set to 100%. Changes in cardiac volume were obtained by subtracting the weekly volumes from each other. The heart volume on the planning CT scan was not included in the evaluation, to prevent possible volume differences due to image modality. To enable comparability between patients, the measurement in week 5, available for only the minority of patients treated with the definitive protocol, was not taken into consideration.

To assess whether cardiac volume change can be predicted, planned heart dose, overall weight loss during CRT, and tumor location, according to the AJCC staging criteria [12], were recorded. Planned heart dose was quantified by assessing V20, V30 and V40, i.e., the heart volume receiving 20 Gy, 30 Gy or 40 Gy or more, respectively, as well as the average heart dose. For comparability reasons, heart dose was assessed at a delivered tumor dose of 41.4 Gy.

Statistical analysis

The calculated cardiac volume changes were quantified as medians with interquartile ranges (IQR), since not all data were normally distributed. A Friedman test was performed to determine the difference in cardiac volume between the treatment weeks. Post-hoc analysis was performed using Wilcoxon signed-ranks tests.

We examined the associations between the change in heart volume, i.e., the difference between the first and final week expressed as a percentage of the initial cardiac volume, and potential explanatory variables using Spearman's correlation coefficient, Mann–Whitney U or Kruskal–Wallis tests as appropriate. Statistical analysis was performed with SPSS software, version 19.0 (IBM Corp., Armonk, NY).

Results and discussion

The median volume reduction over all included patients was 8.0% (IQR 3.0–11.3%), between the initial measurement of cardiac volume in week 1 and the measurement in week 4. This is a statistically significant decrease ($p < 0.001$). Significant differences were observed between week 1 and 2 (reduction = 5.1%, $p = 0.001$), between week 2 and 3 (reduction = 1.9%, $p = 0.019$), and week 1