Radiotherapy and Oncology 117 (2015) 442–447

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Adaptive radiotherapy

The influence of gastric filling instructions on dose delivery in patients with oesophageal cancer: A prospective study

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ARTICLE INFO

Article history:
Received 18 June 2015
Received in revised form 28 August 2015
Accepted 6 September 2015
Available online 10 September 2015

Keywords:
Oesophageal cancer
Adaptive radiotherapy
Dose-guided radiotherapy

ABSTRACT

Purpose: To evaluate whether adaptive radiotherapy for unaccounted stomach changes in patients with adenocarcinoma of the gastroesophageal junction (GEJ) is necessary and whether dose differences could be prevented by giving patients food and fluid instructions before treatment simulation and radiotherapy.
Material and methods: Twenty patients were randomly assigned into two groups: patients with and without instructions about restricting food and fluid intake prior to radiotherapy simulation and treatment. Redelineation and offline recalculation of dose distributions based on cone-beam computed tomography ($n = 100$) were performed. Dose–volume parameters were analysed for the clinical target volume extending into the stomach.
Results: Four patients who did not receive instructions had a geometric miss (0.7–12 cm^3) in only one fraction. With instructions, 3 out of 10 patients had a geometric miss (0.1–1.9 cm^3) in one ($n = 2$) or two ($n = 1$) fractions. The $V_{95\%}$ was reduced by more than 5% for one patient, but this underdosage was in an in-air region without further clinical importance.
Conclusions: Giving patients food and fluid instructions for the treatment of GEJ cancer offers no clinical benefit. Using a planning target volume margin of 1 cm implies that there is no need for adaptive radiotherapy for GEJ tumours.

A high level of evidence currently suggests that neoadjuvant chemoradiation (CRT) followed by surgery is the most efficient combination for improving survival in patients with oesophageal cancer [1]. In the Western world, a rise in the incidence of adenocarcinoma is observed, mostly located in the distal oesophagus or at the gastroesophageal junction (GEJ). The oesophagus is drained by a dense plexus of lymphatics, and disease readily spreads microscopically along this plexus, both superiorly and inferiorly from the primary tumour. Because of this behaviour, it is standard treatment planning practice to apply generous margins (30–50 mm) in the direction of mucosal tumour spread when defining the clinical target volume (CTV) [2]. The importance of this margin was recently shown in a study by Muijs et al. [3] that found that any microscopic remnant outside the radiotherapy field has a high impact on overall survival and disease free survival. For GEJ tumours, the CTV will inevitably extend into the stomach.

Over the course of radiotherapy, the dose delivery will be influenced by a number of factors: e.g. patient setup, anatomical changes and respiratory motion. The latter can be better controlled by implementing four-dimensional computed tomography (4D CT) for treatment simulation. Furthermore, several studies [4–6] have reported that dosimetric errors introduced by respiratory motion tend to average out with fractionation. Unfortunately, even the best gated treatment or breath holding or tracking technique does not take into account interfractional anatomical changes over the course of a treatment. It is recognised that heterogeneous variations in stomach shape and volume occur which may complicate target localisation and reproducibility during simulation and treatment [7–9]. Intake of food or carbonated drinks can cause gastric distension with a consequent shift of the CTV extending along the mucosal wall of the stomach. This shift could potentially influence dose coverage. In the ideal setting stomach shape and volume are conserved during radiotherapy, which could be assured by restricting food and carbonated drinks three hours before treat-

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http://dx.doi.org/10.1016/j.radonc.2015.09.006

ment. On the other hand, patients with oesophageal cancer often have problems maintaining their calorie intake and it is not preferable to change their dietary habits. With the implementation of image-guided radiotherapy (IGRT) and dose recalculation based on the kilovoltage cone-beam computed tomography (kV CBCT), we can calculate the delivered dose to the target volume during treatment and eventually adjust treatment if necessary [10,11].

This study has two main objectives: (1) to investigate the necessity of adaptive radiotherapy for patients with GEJ tumours in case of unaccounted stomach changes e.g. gas pockets in the stomach; (2) to evaluate the impact of food and fluid instructions to assess verification of geographic miss due to variation in gastric volume. A quantitative analysis is performed by comparing the dose distributions recalculated on cone-beam CT images (dose-of-the-day) of the patients' anatomy during the radiotherapy sessions compared to the planned dose.

Materials and methods

Patients

This prospectively designed study had the approval of our Internal Review Board; our clinical protocol was registered at https://clinicaltrials.gov/ct2/show/NCT02130011. Twenty patients with pathologically confirmed GEJ tumours were included. They were treated with (neoadjuvant) CRT between May 2013 and July 2014. All patients had tumour stage cT2–3N1–3. No patient needed gastrostomy or nasal tube feeding before starting treatment.

We randomly assigned patients to two groups:

(1) Ten patients received food and fluid instructions before treatment simulation and radiotherapy treatment. They were asked to fast (ingest no food or carbonated drinks) for at least three hours before treatment simulation and radiotherapy planning.
(2) Ten patients received no instructions for gastric emptying or filling.

CT scanning

Patients were scanned in a supine position and immobilised using an adjustable cranial and upper arm support (Civco, Posirest-2, USA) and a kneefix cushion device (Civco, Posirest-2, USA). All patients underwent a respiratory-correlated 4D CT scan (Sensation Open, Siemens Erlangen, Germany) using 140 kV and 800 mAs with 3 mm reconstructed slice thickness to incorporate intrafractional mobility of the target volume. The CT number to electron density calibration of the 4D-CT scan was undertaken using a Gammex CT phantom with tissue-equivalent inserts (Gammex Inc., Wisconsin, USA).

Target volume delineation

The gross tumour volume (GTV) was delineated by experienced radiation oncologists on the mid-expiration phase of the 4D CT scan, using all available diagnostic information. An expansion of the GTV by 3 cm is used in the superior and inferior direction to define the thoracic (CTV_thor) and abdominal (CTV_abd) part of the CTV, respectively. We applied a 1 cm margin in the radial dimension, excluding normal tissue. In terms of radiotherapy fields, our institution irradiated prophylactic nodal areas according to the primary tumour site [12]. For this study, only the CTV_abd was of particular interest, compatible with extension of the target volume along the gastric wall. The abdominal planning target volume (PTV_abd) was generated by expanding the CTV_abd with a 1 cm margin to account for setup uncertainties. For the thoracic part of the tumour we applied a 5 mm PTV margin (PTV_thor). In this way we limit the volume of lung irradiation and consequently treatment-related complications.

Treatment planning and verification

Radiotherapy consisted of administering a radiation dose of 41.4 Gy or 50.4 Gy in 23 or 28 daily fractions of 1.8 Gy, five times per week. We used the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, USA) to generate a RapidArc plan that ensured PTV coverage by the 95% isodose in accordance with the International Commission on Radiation Units and Measurements report 83 and fulfilled the planning constraints for the critical organs [13,14]. One patient (Appendix A: patient n°3) had a seven-field intensity-modulated radiotherapy plan for which the Anisotropic Analytical Algorithm (AAA version 10.0.28) in Eclipse was used to calculate dose. For the other patients, dose was calculated by the Acuros XB algorithm in Eclipse version 10.0.28 (Varian Medical Systems, Palo Alto, USA).

All beam deliveries had pretreatment verification with an electronic portal imaging device which is an important part of our inhouse patient-specific quality assurance programme for these advanced treatment techniques [15].

Workflow of dose-guided radiotherapy

To determine the estimated delivered dose and investigate the influence of potential gastric and consequent CTV_abd variation during radiation treatment, we developed the following procedure (Fig. 1).

Step 1: After positioning the patient on the couch for treatment, we acquired a kV CBCT image (125 kV, 262 mAs, 13 s acquisition time) to align the patient as closely as possible to the planned position using a match of bony structures. After the automatic image rigid registration based on mutual information, the radiation therapists could perform an additional manual rigid image registration to ensure proper alignment of soft tissue in the CTV_abd region. We performed IGRT on a daily basis throughout the treatment course for on-line setup correction and for visual detection of anatomical changes.

Step 2: The GTV was copied to the kV CBCT of fractions 1, 6, 11, 16 and 21 for all patients and after visual inspection there was no need to adjust the GTV delineation. Furthermore, redelineation of the CTV_abd was performed on the kV CBCT and a second radiation oncologist reviewed delineation on these 100 kV CBCTs. The PTV_abd of the initial planning CT was copied without alteration to the respective kV CBCT. No other structures were redelineated because they were of no further relevance for this study. Geographic miss was defined as expansion of the redelineated CTV_abd outside the initial planned PTV_abd. This was checked by visual inspection and calculated as the volume of the CTV_abd subtracted from the existing planned PTV_abd.

Step 3: Due to the limited field of view (FOV) of the kV CBCT acquisition, total PTV length systematically oversised the kV CBCT. We developed a validated automated method for accurately stitching the three-dimensional CT data to the kV CBCT data, using an image registration scheme (Appendix B). Preliminary experimental results demonstrated that "3D data stitching" provides a good solution to the voxel mismatch caused by limited FOV length in the craniocaudal direction [16]. For the treatment of oesophageal cancer, radiotherapy fields are often large and stitching is a suitable solution for features like CTV_abd near a field boundary especially when part of the beam is out of the field geometry.

Step 4: We performed a registration of the stitched kV CBCT to the initial planning CT and recalculated the 3D dose distribution to the patient on the kV CBCT. To achieve higher accuracy in kV CBCT image-based dose calculation, we used a calibration method