

A study to investigate the influence of cardiac motion on the robustness of pencil beam scanning proton plans in oesophageal cancer

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ABSTRACT

While proton therapy offers an excellent dose conformity and sparing of organs at risk, this can be compromised by uncertainties, e.g. organ motion. This study aimed to investigate the influence of cardiac motion on the contoured oesophagus using electrocardiogram-triggered imaging and to assess the impact of this motion on the robustness of proton therapy plans in oesophageal cancer patients. Limited cardiac-induced motion of the oesophagus was observed with a negligible impact on the robustness of proton therapy plans. Therefore, our data suggest that cardiac motion may be safely ignored in the robust optimisation strategy for proton planning in oesophageal cancer.

1. Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is considered standard of care in the treatment of locally advanced oesophageal cancer [1,2]. However, this treatment strategy yields overall disappointing outcomes with low survival and high morbidity rates [3–6]. Because of radiotherapy-related toxicity, improving the dose distribution by more advanced radiotherapy techniques, e.g. proton therapy, is a key requirement to further ameliorate treatment outcome for these patients. There is recent evidence that supports a clinical benefit of proton therapy in oesophageal cancer, both with passive scattering and pencil beam scanning [7–10].

Because of the central location of the oesophagus within the thorax, radiotherapy for oesophageal cancer is challenging. In photon therapy, geometrical and anatomical variations can be generally handled with safety margins (planning target volume (PTV)) using well-known margin recipes [11]. The picture is completely different for proton therapy. Uncertainties related to organ motion (e.g. due to breathing), setup (e.g. positioning of patients) and anatomical (e.g. shrinkage of the tumour) variations greatly affect the position of the Bragg peak and thus the dose distributions [12,13]. A robust optimisation is necessary for

treatment planning to ensure that the delivered dose corresponds to the planned dose considering the aforementioned treatment uncertainties [14].

In literature, few studies investigated the cardiac-induced motion in radiotherapy using time-dependent trajectory analysis. The motion amplitude and motion range (2nd–98th percentile) of markers in/near lung tumours and in lymph nodes caused by the heart beat was 1.0 to 4.0 mm and 1.0 to 6.0 mm respectively [15,16]. A recent study of Hoffman et al. in 21 patients with oesophageal cancer, showed a mean motion magnitude over 63 tumour markers of 1.0 to 1.5 mm for cardiac motion using cone beam computed tomography (CT) projections [17]. One study used contrast-enhanced CT-based coronary angiography with electrocardiogram-gating of randomly selected patients to calculate more directly the oesophageal displacement caused by the heart [18]. Based on a deformable registration analysis, the mean motion of all voxels varied between 1.0 and 3.0 mm and the largest motion was seen in the distal oesophagus. To our knowledge, no study investigated the impact of the cardiac-induced oesophageal motion on the target volume coverage with proton therapy in oesophageal cancer.

The aim of this pilot study was to assess cardiac-induced motion of the contoured oesophagus using electrocardiogram-triggered imaging

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and to evaluate its influence on the robustness of proton plans in oesophageal cancer patients.

2. Material and methods

2.1. Cardiac-induced motion of oesophagus on electrocardiogram-gated CT

Cardiac-induced motion of the oesophagus was assessed using electrocardiogram-gated intravenous contrast (Ultravist 370 mg/ml) enhanced CT scans (Lightspeed VCT Scanner, General Electric Healthcare, Waukesha, WI, USA) from eight non-cancer patients from the University of Turin. The hospital authorised the retrospective use of the anonymised image sets for the study purposes. To minimise breathing motion a CT scan in breath-hold was performed. Simultaneously, the patient's electrocardiogram was recorded and images acquired across different heartbeats created a heart phase-consistent sequence. Reconstructions were performed in time steps of 11% of the heart cycle, defined as the interval between the R waves (R–R interval) of the QRS complex, leading to nine different datasets for each patient (phase 0% to 88%).

The electrocardiogram-gated CT scans were imported in our treatment planning system (Eclipse, Varian Medical Systems, Palo Alto CA). For every phase, four slices of the oesophagus were delineated at fixed transversal levels with the intervertebral disc as anatomic surrogate (Fig. 1). Level 1 is located in the distal part of the middle oesophagus according to the Union for International Cancer Control (UICC) TNM staging system (eighth edition) [19]; level 2, 3 and 4 in the distal oesophagus. All delineations were done by one radiation oncologist in training, specialised in oesophageal cancer.

The x- (left-right) and y- (anterior-posterior) coordinates of the centre of mass (COM), the most anterior extension and the most posterior extension of the oesophagus were computed in each slice for every cardiac phase, resulting in 275 image slices to analyse. In one patient, we have no images of level 4 in phase 33% of the cardiac cycle due to technical issues by reconstructing the different phases of the electrocardiogram-gated CT scans. Similarly, no images were available of level 2, 3 and 4 in phase 88% in one patient, and of level 1 in all cardiac phases in one patient. Changes of the coordinates between the different cardiac phases provide us a measurement of the cardiac-related movement of the oesophagus. The motion amplitude, its mean value and standard deviation over all patients and transversal levels were calculated. It was not possible to compute the z-coordinates (cranio-caudal) due to the lack of an anatomical surrogate in the oesophagus.

2.2. Robustness of proton therapy plans towards cardiac-induced motion

Afterwards, we evaluated the robustness of proton therapy plans towards the worst-case scenario of the maximally observed cardiac-

induced displacement. For five patients with oesophageal cancer, six synthetic CT scans each simulating heart motion with the maximally observed displacement in one of six directions (six displacement vectors: anterior-posterior, posterior-anterior, superior-inferior, inferior-superior, left-right, right-left) were generated based on deformable image registration in our proton therapy planning system (RayStation, RaySearch Laboratories). Multi-field optimised proton therapy plans (two posterior beams with angles between 155° and 205°) prescribing 45.0 Gy in 25 fractions to the internal CTV (iCTV) were generated on the average image of the four-dimensional (4D) planning CT (robustness towards 7.0 mm setup and 3.0% range uncertainty) [20]. An IBA Proteus Plus beam model with spot sizes of $\sigma = 6.4$ mm at 70 MeV and $\sigma = 3.2$ mm at 225 MeV was used, together with hexagonal spot patterns, 5 mm spot spacing, no energy layer repainting, Monte Carlo dose calculation, 2.5 mm dose grid resolution and a relative biological effectiveness (RBE) scale factor of 1.1. Plans were evaluated by recalculating the dose in 28 scenarios simulating setup and range uncertainties (same as for optimisation), on the planning CT and on each of the six synthetic CTs. The minimum dose to 95% and 98% of the iCTV (D95% >95% and D98% >90% robustness constraints) and the mean heart dose (MHD) of each scenario were calculated.

3. Results

The motion amplitude of the COM, anterior and posterior part of the oesophagus was on the four levels in the left-right and anterior-posterior direction less than or equal to 2.0 mm throughout the cardiac cycle, except for level 3 in the anterior-posterior direction in one patient (2.2 mm). The amplitude mean (standard deviation) was left-right 1.5 (0.4) mm, 1.6 (0.4) mm, 1.5 (0.4) mm and 1.4 (0.4) mm for level 1, 2, 3 and 4 respectively; 1.5 (0.4) for all levels combined. Anterior-posterior, the amplitude mean (standard deviation) was 1.5 (0.3) mm, 1.2 (0.4) mm, 1.3 (0.5) mm, 1.5 (0.3) mm for level 1, 2, 3 and 4; 1.4 (0.4) for all levels combined.

As the maximally observed displacement (half of the amplitude) was >1.0 mm and <2.0 mm, synthetic CTs simulating 2.0 mm heart displacements were generated for every of the six directions. Robustness evaluation of five proton therapy plans recalculated on the synthetic CTs (168 scenarios) with respect to the planning CT (28 scenarios) resulted in a minimal reduction of worst-case scenario dose to the iCTV by on average 0.3% for D95 (range 0.1%–0.7%) and 0.9% for D98 (range 0.3%–1.9%). In four of the five patients, this worst case scenario was associated with the synthetic CT mimicking a motion of the heart contour in posterior direction (Fig. 2), while in one patient this was the inferior direction. The worst case hotspot dose (maximal point dose) increase due to cardiac motion was on average 1.4% (range 0.7–2.9%). For MHD limited increases were observed by on average 0.6 Gy (range 0.4 Gy–0.7 Gy).

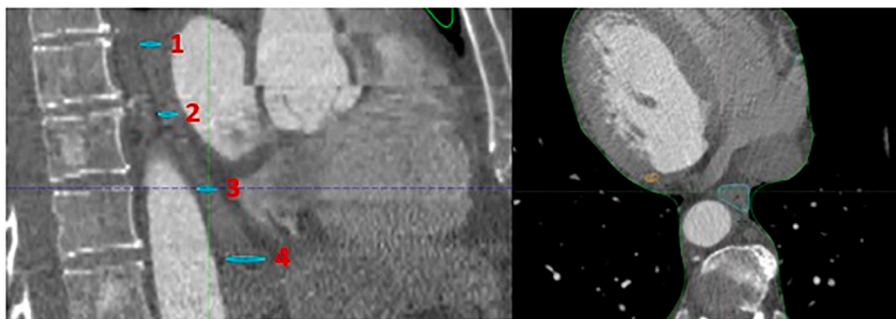


Fig. 1. Delineation of four slices of the oesophagus on fixed levels on the CT scans; from level 1 (most cranial part of the oesophagus) to level 4 (most caudal part of the oesophagus). Left: Four slices of the oesophagus are delineated on the fixed levels on the CT scan (sagittal plane). Right: The delineation of level 3 is shown in the transversal plane of the CT scan.

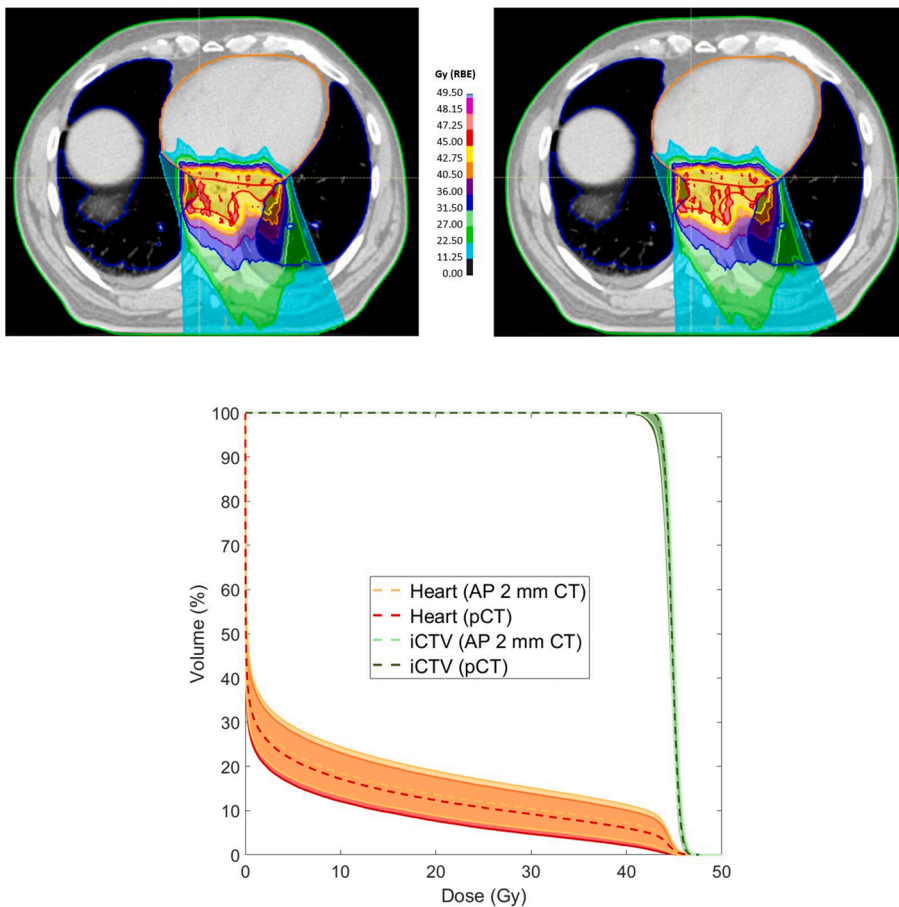


Fig. 2. One example patient. Top: A two posterior beam plan covering the internal clinical target volume (iCTV) contour on the average planning image (pCT) (left) and a dose recalculation on a synthetic image generated from a worst-case 2 mm posterior motion of the heart contour (AP 2 mm CT) (right). Bottom: Dose volume histogram (DVH) comparison of the example patient (pCT and AP 2 mm CT; dashed line = nominal scenario) including uncertainty bands reflecting robustness evaluation in 28 setup and range error scenarios indicates that this motion has minimal impact on iCTV coverage for a limited increase in heart dose. RBE = relative biological effectiveness; iCTV = internal clinical target volume; pCT = planning CT image; AP 2 mm CT = synthetic image generated from worst-case 2 mm posterior motion of heart contour; DVH = dose volume histogram.

4. Discussion

While proton therapy offers an excellent dose conformity and sparing of organs at risk, this can be substantially compromised by uncertainties such as motion. In this study we investigated the influence of cardiac motion on the contoured oesophagus using electrocardiogram-triggered imaging and assessed the impact of this observed motion on the accurate proton therapy dose deposition in oesophageal cancer patients. Limited cardiac-induced motion of the oesophagus was observed with a negligible impact on the robustness of proton therapy plans.

The displacement of the oesophagus during the cardiac cycle on the four studied levels was limited in the eight patients in our study. In literature, there are only a few studies reporting on the influence of cardiac motion on the oesophagus. One study investigated the cardiac-induced motion indirectly by analysing the displacement of oesophageal tumour markers [17]. The cardiac motion was small and the mean motion magnitude was in the same range as our study. We did not observe a larger motion in one of the four levels of the contoured oesophagus. However, all levels were located in the distal oesophagus, except level 1 which was located in the distal part of the middle oesophagus. One other study used retrospective electrocardiogram-gated contrast-enhanced CT and found that the mean cardiac-induced motion of the oesophagus was up to 3.0 mm [18]. The oesophageal motion amplitude was larger than in our study (up to 10.0 mm) and they stated that the magnitude of cardiac-induced oesophageal motion was similar to other sources of motion, such as respiratory motion. These higher numbers were likely due to their analysis of average voxel-wise displacements based on non-rigid registrations. Our data reported the COM and the cranial and caudal oesophagus extension displacements based on manual contours, which are relevant metrics for the simulation of dose deposition.

To our knowledge, the impact of the cardiac-induced oesophageal motion on the radiation target volume coverage with proton therapy in oesophageal cancer has not been investigated. Nevertheless, the impact of a minor movement on a proton plan quality could be detrimental as the CTV position and the tissue density along the beam path can change, thereby affecting the planned dose distribution (Bragg peak). The limited impact of cardiac deformation on the dose volume histograms of the heart and the target volumes observed in our study can partially be explained by the posterior beam setup which are frequently used in proton therapy for oesophageal cancer [7,21]. In all the studied cardiac deformation scenarios, even in the one with maximal impact on D98 of the iCTV (1.9% reduction), our D98 and D95 constraints on the iCTV were met. We did not investigate the interplay effects between pencil beam scanning delivery and the cardiac motion phase. The interaction between pencil beam scanning and breathing motion was studied previously in patients with oesophageal and lung cancer, resulting in a limited impact on the prescription dose [22–24]. Given the small displacement of the heart compared to breathing motion, the influence of interplay effects for cardiac motion is probably even more limited.

A first limitation of the study is that we do not have a planning CT in radiation position of the eight patients with an electrocardiogram-gated scan. The scans were taken in non-cancer patients with a field of view limited to the heart and the mediastinum. However, we did not expect a difference in cardiac-induced oesophageal motion in patients with and without oesophageal cancer. The robustness analyses incorporating cardiac deformation were therefore calculated on proton plans of five patients with oesophageal cancer, which were treated with photons in our institution. An advantage of this strategy is that these five patients had a 4D planning CT which accounts for respiratory motion, which is currently the state of the art for treatment planning in oesophageal cancer (in contrast to the electrocardiogram-gated CTs in breath hold)

[2,25–27]. We used the average image to optimise plans robustly covering the iCTV. Cardiac-induced motion was then simulated based on this reference average image. Secondly, we acknowledge that the motion of the heart is more complex than the vector-based simulations used in our robustness evaluation. However, the worst-case scenario of the maximum observed displacement of the heart in all directions was used, so probably the impact on the proton plan is overestimated and our conclusions on plan robustness are valid for potentially larger cardiac motion undetected in our patient sample. In this study, we could not investigate the cardiac-induced motion on the oesophagus in the cranio-caudal direction due to the lack of an anatomical surrogate in the oesophagus. However, we added these vectors (superior-inferior, inferior-superior) into the simulation of the proton therapy dose delivery. Thirdly, our conclusions are valid for the planning strategy that was used to optimise the proton plans (beam angles). The influence on the robustness of the proton plans is therefore not just applicable to other planning specifications (other spot size, etc.). Lastly, the influence of the cardiac motion on the robustness of a proton plan could be more relevant at the level of a cardiac substructure, such as the circumflex artery [28].

We conclude that, based on the results of this pilot study, the impact of the motion of the heart on the robustness of a proton therapy plan of oesophageal cancer patients is limited. Therefore, we believe cardiac motion could be safely disregarded in the robust optimisation strategy for proton planning in oesophageal cancer. Research and development efforts should of course continue to incorporate other sources of uncertainties, like respiratory motion and anatomical changes during the course of treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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