Physica Medica 31 (2015) 167–172

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Original paper

Assessment and clinical validation of margins for adaptive simultaneous integrated boost in neo-adjuvant radiochemotherapy for rectal cancer

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ARTICLE INFO

Article history:
Received 10 October 2014
Received in revised form
12 December 2014
Accepted 13 December 2014
Available online 10 January 2015

Keywords:
Rectal cancer
Margins
Adaptive radiotherapy
Tomotherapy

ABSTRACT

Purpose: An adaptive concomitant boost (ACB) for the neo-adjuvant treatment of rectal cancer was clinically implemented. In this study population margins M(90,90) considering rectal deformation were derived for 10 consecutive patients treated at 18 × 2.3 Gy with Helical Tomotherapy (HT) and prospectively validated on 20 additional patients treated with HT, delivering ACB in the last 6 fractions.

Methods: Sectorial margins M(90,90) of the whole and second treatment parts were assessed for 90% population through a method combining the 90% coverage probability maps of rectal positions (CPC90%) with 3D local distance measurements between the CPC90% and a reference rectal contour. M(90,90) were compared with the margins $M(90,90)^{95\%/99\%}$, ensuring CPC90% coverage with 95%/99% confidence level. M(90,90) of the treatment second part were chosen as ACB margins which were clinically validated for each patient by means of %volume missing of CPC5/6 excluded by the ACB margins.

Results: The whole treatment M(90,90) ranged between 1.9 mm and 9 mm in the lower-posterior and upper-anterior sectors, respectively. Regarding ACB, M(90,90) were 7 mm in the anterior direction and <5 mm elsewhere. $M(90,90)^{95\%/99\%}$ did not significantly differ from M(90,90). The %volume excluded by the ACB margin was<2% for all male and <5% for 9/10 female patients. The dosimetry impact on R_adapt for the patients with the largest residual error was negligible.

Conclusions: Local deformation measurements confirm an anisotropic motion of rectum once set-up error is rigidly corrected. Margins of 7 mm anterior and 5 mm elsewhere are adequate for ACB. Female patients show a slightly larger residual error.

Introduction

Among the strategies of treatment intensification for locally advanced rectal adenocarcinoma, the possibility of escalating the dose to the tumor has been considered with interest, both with sequential or simultaneous integrated boost approaches [1–4]. On the other hand, image-guided intensity-modulated radiotherapy currently permits the drastic reduction of the volume of bowel and bladder treated at the prescribed dose, adding further possibilities of dose escalation [5]. Very importantly, most rectal cancers are known to shrink during treatment, such that the possibility of escalating the dose to the residual GTV is attractive with regard to the objective of increasing the number of pathological complete responses (pCR) and/or reducing surgical side effects and/or improving sphincter preservation [1–5]. Although not the focus of the current study, such an approach could also find interesting applications in locally advanced, inoperable rectal cancers [6]. In addition, the perspective of avoiding surgery in a fraction of patients who presents a full imaging response after radio-

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http://dx.doi.org/10.1016/j.ejmp.2014.12.002
1120-1797/

chemotherapy is of paramount importance due to the expected better quality of life of patients that would skip surgery [7]: boosting the residual tumor may potentially increase the fraction of patients that could in future benefit from skipping surgery.

In this context, our group suggested and clinically activated an adaptive concomitant boost (ACB) approach where the dose to the residual tumor (imaged at half-therapy) is escalated in the last 6 (of 18) fractions in a moderately hypo-fractionated regimen delivered with daily image-guided Tomotherapy [8].

Rectal mobility is a critical issue for the definition of appropriate margins around the residual GTV: a previous study on rectal mobility in the 18 fractions scheme without ACB was previously carried out, focusing on rectal volume changes and leading to first estimates of margins by looking to the overlap between the isotropically expanded rectum and the envelope of all rectal positions [9]. The aim of this first study was to investigate the possibility of reducing the margins around the residual GTV in view of a dose escalation to the residual tumor.

In the current study, daily imaging data of 10 rectal cancer patients treated at 18 × 2.3 Gy (without ACB) were re-analyzed to assess local shape variations of the rectum. The main aims of current study were:

a) to quantify 3D margins including deformation, based on an original method combining probability coverage maps and local distance measurements.
b) to clinically validate these margins in an independent cohort of 20 patients (10 males, 10 females) treated with ACB, considering shape changes during the last 6 fractions.

Material and methods

The clinical protocol

Ten consecutive patients treated with hypofractionated radiotherapy (18 × 2.3 Gy/day) delivered with helical Tomotherapy and concomitant chemotherapy were selected. The eligibility criteria included: histologically proven adenocarcinoma, clinical stage T3-T4 or any T with N positive, age 18–75 years, ECOG PS ≤ 2, adequate bone marrow, renal and hepatic function [8,9].

Each patient underwent a planning contrast-enhanced CT (pCT) of the pelvis in the supine position. All patients were asked to have their bladder comfortably full; no other instructions were given concerning rectum and bowel filling. CTV included mesorectum, lymph-nodes of obturator, internal iliac, common iliac chains and the whole anterior surface of sacrum, coccyx and piriformis muscle. Planning target volume (PTV) was defined as CTV expanded by 0.5 cm in all directions.

For the whole population, 169 pre-treatment MVCTs were available and registered with pCT taking pelvic bones as reference, through the mutual information algorithm implemented in our planning system (Eclipse Varian v.8.6): if needed, manual adjustments were applied.

Procedure to derive margins

The suggested method for correctly taking into account the residual error after rigid registration combines the probability maps of the possible rectal positions with the measurement of local distances between high probability contours (i.e.:90–100%) and the reference rectal contour (Figures S1 and S3, Supplementary Material).

Five different steps can be recognized:

1. Contouring rectum after rigid correction.
2. Deriving probability distribution maps of rectal positions.
3. Calculating maps of local distances between high probability coverage contours and reference contours.
4. Splitting the rectum into clinically significant sectors and taking average values of local distances in each sector (average margin approximation) or directly evaluating the local distances encompassing the % of voxels belonging to the high probability contour (full statistic method)
5. Assessing population margins, considering a high confidence level. (i.e.: considering the patients with the largest residual error).

The method was applied to both the whole treatment and the second half, in order to determine possible different margins for the second part of the therapy where we planned to implement ACB.

For this study, we assumed the GTV to be coincident with the rectum: in fact, as the tumor mass, unseen on MVCTs, is adherent to the rectal wall, it is expected to have the same (or lower) mobility of the rectum.

Rectum was delineated from the sigmoidal curve to the middle of the pubic symphysis on all daily MVCTs by a single observer. Hence the cranial two-thirds were taken into account, while the caudal part of the rectum was excluded; this is because the caudal rectum/anal canal are stable [10,] and their delineation on MVCTs is not reliable [11]. For each patient, coverage probability contours (CPCs) [12], representing maps for the possible rectal positions assessed with X% probability, were created from all daily contours (VODCA, v.5.2.6). If N is the number of fractions, the CPCX% contour is simply the one encompassing all the voxels belonging to K fractions such as: X% = 100 × K/N. For our purposes, CPC90% was derived: the value of K corresponding to 90% probability was approximated by (N-2)/N and (N-1)/N for the whole treatment and the second part respectively (Fig. 1). Rectum was split into 8 octants (up-ant, up-post, up-left, up-right, low-ant, low-post, low-left, low-right) according to its cylindrical-like geometry: first, contours were divided into two main portions (lower and upper, using the median slice to separate them), each of which was partitioned into 4 sectors (anterior, posterior, left and right) [13]. Division into quadrants was performed on each image slice by finding the center of volume of the binary structure and by overlapping a labeled mask dividing the image into the same corresponding four sectors. Maps of 3D signed Euclidean distances were measured between the CPC90% and 2 reference contours chosen as: the rectum at first fraction (MVCT_1) and the contour at mid-therapy (MVCT_9). Distances were calculated in each sector using a 3D Euclidean distance map to find the closest point on the test contour from each reference contour point [14]; contour points inside/outside the reference volume had negative/positive distance values. The use of distance maps has already proven its effectiveness in estimating the closest point distance in situations like ours since volumes show a high shape similarity and weakly winding contours [15].

For each sector and patient, the mean values of local average distances between the CPC90% and the two references were regarded as the "average" sector margin M. The second largest value of M among the ten patients was taken as the average 90% population coverage margin M(90,90) for both the whole and the second part of treatment. Differences between margins for the whole treatment and the second half were considered and tested through the Wilcoxon signed rank test.

Margins: full statistical method

The impact of the "averaging" procedure based on sectors is intrinsically affected by uncertainties related to the regularity of the