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Original article

Consequences of anorectal cancer atlas implementation in the cooperative group setting: Radiobiologic analysis of a prospective randomized *in silico* target delineation study

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ABSTRACT

Purpose: The aim of this study is to ascertain the subsequent radiobiological impact of using a consensus guideline target volume delineation atlas.
Materials and methods: Using a representative case and target volume delineation instructions derived from a proposed IMRT rectal cancer clinical trial, gross tumor volume (GTV) and clinical/planning target volumes (CTV/PTV) were contoured by 13 physician observers (Phase 1). The observers were then randomly assigned to follow (atlas) or not-follow (control) a consensus guideline/atlas for anorectal cancers, and instructed to re-contour the same case (Phase 2).
Results: The atlas group was found to have increased tumor control probability (TCP) after the atlas intervention for both the CTV ($p < 0.0001$) and PTV1 ($p = 0.0011$) with decreasing normal tissue complication probability (NTCP) for small intestine, while the control group did not. Additionally, the atlas group had reduced variance in TCP for all target volumes and reduced variance in NTCP for the bowel. In Phase 2, the atlas group had increased TCP relative to the control for CTV ($p = 0.03$).
Conclusions: Visual atlas and consensus treatment guideline usage in the development of rectal cancer IMRT treatment plans reduced the inter-observer radiobiological variation, with clinically relevant TCP alteration for CTV and PTV volumes.
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In the pre-conformal radiotherapy era, standardized fields based on bony anatomy were utilized to ensure uniformity of treated regions. However, in the era of volume-based delineation, considerable operator dependent variation exists in target volume delineation. This factor affects the planned dose distributions complicating the clinical trial quality assurance and preventing the compatible comparison of treatment protocols.

The location of organs-at-risk (OAR) and their tolerance doses constitute a major factor that determines the prescribed dose in radiation treatment planning. OARs are usually located in the immediate vicinity of the CTV limiting dose deliverable to target volumes [1]. Intensity Modulated Radiotherapy (IMRT) generates more conformal distributions as compared to older techniques resulting in reduction of radiation dose and toxicity to OARs and thus potentially improving clinical outcomes.

Comparatively low tolerance doses, which characterize involved OARs relative to tumoricidal dose thresholds, are usually the major constraints in pelvic radiotherapy, especially when gross tumor volume (GTV) and clinical target volume (CTV) arise from potentially dose limiting normal tissue (as in cancer of the rectal

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mucosa). Isodose charts, dose volume histograms (DVH), dose–volume parameters and conformity-based indices are currently used for treatment plan evaluation. However, these evaluation measures do not account for radiobiological characteristics of tumors nor normal tissues [2], and thus are, at best, indirect correlates of clinically relevant parameters. Consequently, radiobiological measures should ideally be considered in order to estimate the expected treatment outcome. The applied radiobiological measures provide the expected treatment outcome within a clinical range of uncertainty, whereas the DVHs and other dosimetric quantities do not provide any association to the treatment outcome. This analysis uses tumor control probability (TCP), normal tissue complication probability (NTCP) and complication-free tumor control probability (P_+) as direct treatment plan evaluation parameters [3–5] to assess the utility of atlas-based educational intervention on plan quality.

In a previous prospective randomized effort [6], implementation of a consensus guideline-based atlas [7] demonstrably improved CTV but not GTV volumetric concordance with an expert reference for a standardized rectal cancer case. Additionally, consensus atlas use reduced inter-observer CTV delineation variance to a statistically significant degree.

The primary aim of this secondary analysis was determining whether the aforementioned alteration in volumetric coverage resulted in clinically meaningful differences in tumor control probabilities. Secondly, this analysis sought to estimate radiobiological parameter (e.g. TCP, NTCP, P_+) variability demonstrable in a standardized contouring protocol to serve as a benchmark for future cooperative group trials. Thus, an evaluation of radiobiological differentials attributable to consensus guideline atlas implementation could be achieved.

Methods and materials

This prospective *in silico* study was deemed exempt and was conducted under the auspices of the University of Texas Health Science Center at San Antonio institutional review board. Pilot data from the study have been presented previously [6]. Briefly, thirteen radiation oncologist observers from eight SWOG-affiliated institutions were recruited and were asked to contour a standardized case (an anonymized patient with Stage T3N0M0 adenocarcinoma of the rectum) with instructions from an (at that time) in-development SWOG protocol (S0713: "*A Phase II Study of Oxaliplatin, Capecitabine, Cetuximab and Radiation in Pre-operative Therapy of Rectal Cancer*", ClinicalTrials.gov Identifier NCT00686166) (Supplementary Fig. 1). The observers were experienced in the treatment of carcinoma of the rectum and in the delineation of rectal carcinomas. Subsequently, the observers were randomly assigned to receive an electronic copy of an unpublished (at that time) rectal cancer atlas [7]. The observers re-contoured the same case with (atlas group – six observers) or without the atlas (control group – six observers). The use of the atlas for the re-contouring of the tissues will be notated as intervention. Data collection was performed using "Big Brother", a custom target volume delineation evaluation software platform developed at The Netherlands Cancer Institute [6]. The observers were asked to contour the GTV, CTV_A, and CTV_B targets (Supplementary Table A) [6,7]. The CTV encompassed the GTV as well as the peri-rectal, pre-sacral, internal and external iliac nodal regions. The PTV1 is defined as a GTV expansion of 2.0–3.0 cm, including the CTV, whereas the PTV2 (the boost volume) is defined as an expansion of the GTV by 2.0 cm including the whole of the sacral hollow. Contours from a "reference expert" involved in the development of the RTOG consensus atlas and guidelines [LAK] served as a comparator for the observer-derived contours. During the study period, none of the observers other than the reference expert had a previous knowledge of this atlas. A statistical comparison of the volume differentials and *post hoc* exploratory contour surface variability analysis [8,9] was previously reported [6]. In this analysis, the statistical significance of the presented results is investigated.

Treatment planning

Treatment planning was performed using a commercial treatment planning software (Pinnacle, Philips Medical Systems, Inc.). A volumetric modulated arc technique (VMAT), which employs 2 arcs of 6 MV photons, was applied. The organs-at-risk were delineated as ROIs by a single observer [CDF]. The individual treatment plans were produced by a single physicist [DG] using the dosimetric constraints for the target volumes and organs at risk that were specified in the SWOG S0713 protocol (Supplementary Table B). The individual treatment plans were produced using the first set of delineations of each observer. The same treatment plans were subsequently applied on the second sets of delineations of each observer (no re-planning took place, only renormalization), in order to determine the impact of delineation/segmentation alone upon plan quality.

Radiobiological measures for treatment plan evaluation

Secondary radiobiological evaluation was performed using previously defined literature-derived metrics [10]. Tumor response was calculated using the Poisson model, with parallel tumor structural organization assumed (i.e. 100% clonogenic kill required for tumor control). Thus, tumor control probability (TCP) for a tumor volume is given by the expression:

$$\mathrm{TCP} = \prod_{i=1}^{M} P(D_i)^{\Delta v_i} \tag{1}$$

where M is the total number of voxels or sub-volumes in the target. Response of a normal tissue to a non-uniform dose distribution was obtained using the relative seriality model, with normal tissue complication probability expressed as [3]:

$$\begin{aligned}\mathrm{NTCP} &= 1 - \prod_{j=1}^{N_{organs}} \left(1 - P_{\mathrm{I}}^{j}\right) \\ &= 1 - \prod_{j=1}^{N_{organs}} \left(1 - \left[1 - \prod_{i=1}^{M_j} \left(1 - P^{j}(D_i)^{s_j}\right)^{\Delta v_i}\right]^{1/s_j}\right)\end{aligned} \tag{2}$$

where P_{I}^{j} is the probability of injuring organ j and N_{organs} is the total number of OARs. $P^{j}(D_i)$ is the probability of response of the organ j having the reference volume and being irradiated to dose D_i. $\Delta v_i = \Delta V_i / V_{ref}$ is the fractional subvolume of the organ (ΔV_i) that is irradiated at the dose level D_i compared to the reference volume (V_{ref}) for which the values of the model parameters have been calculated. M_j is the total number of voxels or subvolumes in the organ j, and s_j is the relative seriality parameter that characterizes the internal organization of that organ.

Complication-free tumor control probability (P_+) was used to estimate the overall effectiveness of a treatment plan, expressed in terms of PTV tumor control probability (TCP) and normal tissue complication probability (NTCP) [3]:

$$P_+ = \mathrm{TCP}(1 - \mathrm{NTCP}) \tag{3}$$

Here, the TCP that was used for calculating the P_+ values was based on PTV2. Biologically effective uniform dose, $\bar{D}$, is defined as the dose that causes the same TCP or NTCP as the actual dose distribution delivered to the patient [4]. Generalized equivalent uniform dose (gEUD) was used as a mean dose to a given tissue

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