Original Research Article

Pre-clinical experience of an adaptive plan library strategy in radiotherapy of rectal cancer: An inter-observer study

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A B S T R A C T

Background and purpose: The clinical target volume (CTV) in radiotherapy of rectal cancer is subject to large deformations. With a plan library strategy, the treatment may be adapted to these deformations. The purpose of this study was to determine feasibility and consistency in plan selection for a plan library strategy in radiotherapy of rectal cancer.

Material and methods: Thirty rectal cancer patients were included in this retrospective study with in total 150 CBCT scans. A library of CTVs was constructed with in-house built software using population statistics on daily rectal deformations. The library consisted of five plans based on: the original CTV, two larger, and two smaller CTVs. An inter-observer study (study-I) was performed to test the consistency in plan choices between four observers (all RTTs). After five months the observers were asked to re-evaluate (study-II) the same set of scans based on refined guidelines.

Results: In study-I the observers reached accordance with the majority choice in 69% of cases. This improved to 87% in study-II. The consensus meeting revealed that inconsistency in choices mainly arose from inadequate instructions, which were later clarified and formulated more accurately.

Conclusion: Plan selection based on daily CBCT scans for rectal cancer patients is feasible, and can be performed consistently by well-trained RTTs.

1. Introduction

Clinical target volume (CTV) shape variation is a major geometric uncertainty [1] in radiotherapy of rectal cancer. To account for this, large planning target volume (PTV) margins are needed. Despite intensity modulated radiation therapy (IMRT) and on-line position verification which can reduce the dose to the normal tissues and organs at risk, for example; small bowel [2,3], large PTV margins are still necessary. Several studies have shown a clear relationship between dose to the small bowel and acute radiation enteritis, as well as late toxicity, such as chronic diarrhea, bowel stricture, perforation and hemorrhage [4–6]. By implementing an adaptive strategy with a plan library for radiotherapy in rectal cancer patients, CTV shape variations can be partly accounted for. This allows a reduction in PTV margins, which could lead to a reduction of dose to the small bowel and to other healthy tissue.

The concept of a plan library involves the a priori creation of a number of plans based on changing patient anatomy and then selecting one of these plans on a daily basis [7]. For example: a planning CT (pCT) is a snap shot of the pelvic region at a certain point in time. Within the pelvic region organs like bladder, rectum and small bowel can show organ filling which is not representative for the filling on treatment days [8]. Despite strict protocols for bladder and rectum filling, radiation side effects, non-compliance and dysfunction due to the presence of tumor tissue, will lead to day-to-day variations [9]. With a library of treatment plans it is possible to choose the best fitting plan based on the patient’s anatomy for that particular day.

The plan library approach has been successfully applied in several institutes for bladder and cervical cancer [10,11]. For these sites, libraries were created by interpolation of structures of interest defined on CT scans in full and empty bladder state. However, for rectal cancer patients this approach was not feasible, as a major source of uncertainty was not bladder, but rectal filling [9]. For our study, the library was therefore based on patient population data studied by Nijkamp et al. [1]. They concluded that the systematic CTV shape variation was heterogeneous and ranged from 0.2 cm SD close to bony anatomy to 1.0 cm SD at the upper-anterior edge of the mesorectum. This heterogeneous error distribution is reflected in the libraries that were created for this
current study [12]. In this novel method the libraries were generated using ± 1 and 2 SDs of the patient population data from the original CTV. Thus broadly speaking, this plan library strategy was used to correct for a major part of the systematic error, while the margins compensated for random variations in filling, plus organ deformations.

In 2016 de Jong et al. [13] reported an inter-observer study on plan selection for rectal cancer patients. Our study is comparable to the study of de Jong et al. since we both performed an inter-observer study for a plan library strategy in rectal cancer. However, there is an important difference in the methods that were used to create the plan library. De Jong et al. used plans with different PTV margins at the ventral side of the upper mesorectum position. Their PTV margins were varied based on rectal and bladder filling on the planning CT. In our study the library was generated by in-house developed software containing: population statistics, different rectal regions and different rectal movement [12]. So the aim of this study was to investigate the feasibility of plan selection in rectum cancer patients and to determine inter-observer consistency in plan selection, given the sometimes challenging image quality of CBCT data.

2. Materials and methods

2.1. Patients and treatment

Thirty rectal cancer patients were included in this retrospective study. The patient group consisted of nineteen males and eleven females with an average age of 67 years. See supplementary material 1 for patient characteristics. Patients received short-course-radiotherapy (SCRT), 5xGy with on-line position verification using daily CBCT. All patients received full bladder instructions: i.e. to empty the bladder and drink a fixed amount (350 ml) of water 1 h before pCT and each treatment fraction. All pCT scans were acquired with a flat table top. The patient was scanned in supine position with a knee support. The scan length included the L4-L5 junction as the cranial border and the trochanter minor as the caudal border. Delineations on the pCT were performed according to the guidelines by Roels et al. [14]. The CTV contained the mesorectum-upper and -lower (separately [9]), presacral area, pelvic lymph node areas (internal iliac lymph node areas and obturator lymph node areas), GTV and if indicated the anal sphincter complex. Delineated organs at risk were femur, bowel area, bladder and vulva/testis. Treatment was delivered (Elekta Synergy, Elekta Oncology Systems Ltd., Crawley, West Sussex, UK) using dual VMAT arcs with 10 mm, in 660 frames, over 360 degrees) on bony anatomy of the pelvic complex. Delineated organs at risk were femur, bowel area, bladder and vulva/testis. Treatment was delivered (Elekta Synergy, Elekta Oncology Systems Ltd., Crawley, West Sussex, UK) using dual VMAT arcs with 10 MV within 5–7 min including online CBCT registration (120 kV, 32 mA, 40 ms, in 660 frames, over 360 degrees) on bony anatomy of the pelvic area. In total 150 CBCT scans were available for this study.

2.2. Creating a plan library

As explained by Hartgring et al. [12] the method to create plan library CTVs was based on 3D population statistics of the shape variation of the rectum CTV [1]. The population statistics were derived from shape variation data of thirty-three SCRT patients with daily repeat CT scans on which the rectum CTV was delineated. Rather than using patient specific data from several scans only one single pCT was used for structure generation.

The plan library CTVs were created by expanding or contracting the delineated CTV perpendicular to its surface, proportional to the local statistics of shape variation of the population and a global scaling factor, assuming 100% correlation between all regions of the surface. The scaling factor was tuned such that the largest distance between the CTVs was 1 cm. This was done to generate structures with a desired distance from each other.

Besides the original CTV four additional CTVs were created, see Fig. 1 and supplementary material 2; two smaller with a maximum of -1, -2 cm (belonging to treatment plan -1 and plan -2) and two larger with a maximum of +1, +2 cm (belonging to treatment plan 1 and plan 2) than the original CTV (belonging to treatment plan 0). In total five CTVs were available for plan selection.

By introducing plan library for rectal cancer patients we were able to reduce the PTV margin from 2.5 cm to 1.5 cm in the upper-mesorectum region. This meant that healthy tissues could be spared by selecting plans 0 to ~ 2. Selecting plan “1” gave comparable PTV margins to the original PTV margins without a plan library approach.

2.3. Observer studies

The purpose of the observer studies was to test feasibility of plan selection in rectal cancer patients and to determine the inter-observer consistency in plan selection. For this we performed a baseline measurement (study-I) with four observers (all RTTs). The observers had differing levels of experience in CBCT image registration, one with less experience (three years) and the other three with extensive experience (> 10 years). The aim of study-II was to identify the reproducibility of the plan library approach.

The observers selected plans individually for 150 CBCT scans based on a priori set of instructions. The guidelines consisted of four steps: first, choose the best plan based on the coverage of the whole mesorectum, using the CTV structures. Second, check if that CTV encompassed the tumor (GTV). Third, focus on the ventral part of the mesorectum (less movement is seen at the dorsal part) [9] and fourth, coverage of presacral region is less important due to fewer recurrences in this area, except when the GTV lies within the presacral region [15,16]. We investigated and evaluated the feasibility of plan selection in rectal cancer patients in study-I by scoring the amount of times observers were able to select the correct plan on the CBCT scan images. We defined “correct plan” as: A plan chosen by the majority was determined for each scan. Majority was reached if at least three of the four observers chose the same plan. If only two observers choose the same plan the majority choice was discussed in the consensus meeting and the radiation oncologist made the final decision.

Due to variation in rectal filling, and corresponding differences in movement, we divided the mesorectum in three rectal regions: presacral, upper-mesorectum and lower-mesorectum, see supplementary material 3. For these three regions the optimal plan was selected as well as a plan which covered the whole mesorectum (overall plan). Using this practical approach evaluation of influence by one rectal region in selecting an overall plan would become insightful. The plan number difference between the optimal plan selected for a rectal region and an overall selected plan could be explained as followed: If the observer

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This is a continuation of text from the previous page, focusing on the methodologies and results of the observer studies in the context of rectal cancer treatment planning using plan libraries. The text discusses the setup, execution, and analysis of inter-observer studies to evaluate the feasibility and consistency of plan selection for rectal cancer patients, emphasizing on the role of dual VMAT arcs and the importance of presacral and upper-mesorectum coverage. The approach involves creating a plan library with delineated structures based on 3D population statistics to account for shape variation and using these libraries to assess observer consistency, particularly in the context of rectal filling and organ movement. The study also considers the impact of experience levels among observers, aiming to identify the reproducibility of plan library approach and understand variations in planning accuracy across different rectal regions. The text highlights the technical and clinical considerations involved in such studies, including the use of CBCT scans for daily position verification and the role of radiation oncologists in decision-making process. The emphasis is on the practical implications of these methodologies in real-world clinical settings, particularly in improving treatment precision and reducing margins where possible.
chose the same plan for both the “overall” plan and a particular rectal region, then there was no difference (meaning zero plan number difference). If the difference between both plans was smaller than zero a smaller plan was selected for a rectal region than the overall plan and vice versa.

After the analysis of study-I, a consensus meeting with an expert radiation oncologist was scheduled to discuss alternative choices. Discussion between observers after study-I, regarding the guidelines and the individual overall plan selection choices, led to refinement of instructions and a second observer study (study-II). Additional guidelines were defined:

- Start with the evaluation of the original CTV and GTV delineations projected on the CBCT scan,
- consider the specific filling situations and switch to the best fitting plan.
- If the rectal wall is pushed outside the original CTV due to air pockets within a 1–2 cm range from the tumor in cranial-caudal direction a larger plan must be selected to cover microscopic spread. Otherwise a larger plan is not needed.

Study-II was performed after five months. The observers were asked to re-evaluate the same set of scans using the refined guidelines.

2.4. Statistical analysis

Inter-observer variability was evaluated by calculating the plan number difference from the majority choice among the observers. This was done by subtracting the majority choice from the chosen plans of the individual choices of the observers.

Beside the inter-observer variability we also looked into plan number differences between rectal regions and the overall selected plans, plan number difference from majority choice (inter and intra observer), amount of times a plan was selected in the majority choice and the number of times a plan was selected per fraction (time trend).

3. Results

Selecting a plan from the plan library in radiotherapy for rectal cancer was feasible, all observers were able to select a plan on all (150) CBCT scans.

Fig. 2 shows that in 78%, 87% and 73% of the cases, the overall selected plan matched the rectal region presacral, mesorectum-upper and mesorectum-lower. The selected overall plan was too small in 7% of the cases for the presacral region, in 4% for the mesorectum-upper and in 9% for the mesorectum-lower (Fig. 2; see plan number difference plan 1 and 2).

The inter-observer variability is shown in supplementary material 4. In study-I the consensus between the observers was 69%. In 30% of cases the observers differed by one plan from the majority choice (in 25% a smaller plan was chosen by the observers compared to the majority choice and in 5% a larger plan was chosen) and in 1% of cases they differed by two plans. The inter-observer variability improved in study-II to 87% and a plan number difference by one plan in 13% after using the refined guidelines. The spread in plan number difference from the majority choice became less in study-II, visualized in Fig. 3. Both inter- and intra-observer variations have decreased, see Fig. 3.

The original CTV plan (plan 0) was selected in 99 of the 150 CBCT scans, see Fig. 4. In 8 times plan −1 was selected, 0 times plan −2, 33 times plan 1 and 10 times plan 2 were selected from the 150 CBCT scans. In 107 cases healthy tissues were spared, in 33 cases there was no difference from the original treatment plan without a plan library and in 10 cases there was a better coverage of the tumor but no sparing of healthy tissues.

We did not find any trends in plan selection in our patient cohort, see supplementary material 5.

![Plan number difference between rectal regions and overall selected plan](image1)

**Fig. 2.** The difference between the rectal regions and the overall plan choice of the observers. In green the presacral rectal region, in pink the meso-upper rectal region and in red the meso-lower rectal region. No differences (zero difference in plans) means: the same plan is chosen for a rectal region and an overall region. Difference smaller than zero means: a smaller plan has been chosen for a rectal region compared to an overall selected plan. Difference larger than zero means: a larger plan has been chosen for a rectum region compared to an overall selected plan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

![Observer study I and II](image2)

**Fig. 3.** Plan deviation from the majority choice per observers in study-I and study-II. Each bar represents an observer and the different colors correspond to the observer studies. The dark red bars represent study-I and the blue bars study-II. The consistency between observers has increased in study-II. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In this study we showed that selecting a plan based on daily-CBCT scan images is feasible and that consistency was reached between observers for plan selection in rectal cancer patients. This is evidenced by
the inter-observer variability study in which the consensus between the observers increased from 69% in study-I to 87% in study-II. In a review written by Collins et al. about plan library in adaptive radiotherapy of bladder cancer the same rates of concordance among RTTs are seen [17]. The reported studies highlighted the importance of education ensuring competency and confidence in evaluating CBCT pelvic scans. We agree on this topic but also want to stress the need for adequate plan selection instructions.

Since our consensus meeting revealed that inconsistency in plan selection mainly arose from inadequate instructions. For instance, should an air pocket, which is rather far from the tumor also be covered? During the consensus meeting the instructions were clarified, and formulated more accurately. Two new additional guidelines made it possible to increase the inter-observer consistency. These were: first, use as start position the original CTV and GTV delineations projected on the CBCT scan, consider specific filling situations and choose the best fitting plan. Second, if the rectal wall is pushed outside the original CTV due to air pockets within a 1–2 cm range from the tumor, a larger plan must be selected.

Fig. 2 also shows that in 7%, 4%, and 9% of cases, the selected overall plan was too small for the presacral, upper-mesorectum and lower-mesorectum, respectively. Different rectal filling stages between these regions caused this. Fortunately, this is a minor concern because we selected a plan based on CTV and the PTV was used to correct for geometrical uncertainties.

Our PTV margin is anisotropic with 1 cm in left–right, cranial-caudal and posterior direction and 1.5 cm in anterior direction. The study of Seppenwoolde et al. they investigated the dosimetric impact on OAR sparing and PTV coverage using fixed and adaptive margin concepts. They concluded that in two of their adaptive PTV scenario’s (one simple ITV strategy, based on one week of CBCT imaging versus a more complex library approach, based on full and empty bladder scan) both performed better in terms of target coverage [18]. If the PTV margins are not sufficient we could identify this problem using our traffic-light protocol [19] regarding anatomical changes during radiation treatment. In a clinical setting all plan selections will be checked after treatment by a team of specialized imaging RTTs. If necessary, feedback will be given to the RTTs involved with plan selection.

Fig. 4 shows the number of times a plan was selected as the majority choice. We expect to see the same spread in plan selection clinically. The graph shows that the majority of chosen plans were plan 0; with this plan, a 1 cm margin reduction is gained in contrast to our old margins. We found in literature for bladder [20] and cervical cancer [21,22] a larger spread in the selected plans from the library, mainly caused by the different bladder filling situations. For rectal cancer, de Jong et al. [13] found the same results (the most selected plans were comparable to the pCT situation) as we did.

A limitation of our study was the absence of a gold standard for comparison with the observer plan selections. We were not able to create a gold standard for the 150 CBCT scans due to lack of imaging information on which the “right” plan would have been chosen. This leaves room for online-adaptive approaches such as the MR-linac, in which daily high quality soft-tissue contrast images are available. As mentioned in the review of Collins et al. [17] weekly MR imaging in MR-IGART is done for gynecological [23] and bladder cancer [24] but up to now, no MR-IGART studies described daily imaging. Therefore, we introduced the majority choice. The radiation oncologist also had to make a final choice if the observers had a two-two result. This was done in a consensus meeting after study I, which was organized to discuss and adjust the plan selection guidelines. In total, 26 CBCT scans had the two-two result and were reviewed with the radiation oncologist. The main reasons for discussing the CBCT scan were: when the anatomy of the rectum was between two plans (11), air pockets close to GTV (6), poor CBCT image quality (5), intestinal loop of the small bowel (2) and uterus position (2). Another limitation of our study was the patient positioning. A remark must been made that the data Nijkamp et al. reported was based on patients lying prone, clinically our patients where lying supine. Nijkamp concluded in another study that there are differences between supine and prone orientation, but they are small [25].

Plan selection using a plan library is not new in radiotherapy for treatment in the pelvic area, for example; cervix/uterus [11], bladder [10,20] and rectum [26]. Thörnqvist et al. [27] wrote a systematic review of clinical implementations regarding this topic. Since then, there was only one other observer study describing a plan library strategy in rectum cancer patients. The results of our study were in line with the results of de Jong et al. [13], although they utilized a different plan library strategy. De Jong et al. used three PTV structures varying the anterior margin for the upper-mesorectum. We were not focused on one rectal region but used the known population averaged variation of all rectal regions [9]. Our CTV plan library structures therefore changed shape in all directions, see Fig. 1 and supplementary material 2. This was also explained by the difference in plan selection guidelines. De Jong et al. selected a plan based on “the smallest PTV that encompassed the complete target volume”. We created guidelines to encompass the tumor (GTV) with the CTV and selected the “best” fitting overall CTV. Since the outcome of our study was very promising we have implemented our plan library method into daily clinic practice, in treating patients with hypo fractionated SCRT (5x5 Gy) in which coverage of the GTV is important. Our clinical workflow consists of: Online position verification inclusive plan selection followed by a dual arc VMAT treatment and a post CBCT scan for monitoring the intra-fraction motion. The total treatment is delivered by two RTTs within approximately 20 min with an actual plan selection time of about 30–60 s. If intra-fraction motion will lead to differences in plan selection between pre- and post CBCT, a traffic light protocol will be followed.

In conclusion, the observer study showed consistency between observers in selecting the plan that would best fit the anatomy on the treatment day. Therefore, for rectal cancer patients, plan selection by RTTs based on daily CBCT scans was feasible and has been clinically implemented.
Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pjro.2018.06.003.

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