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An assessment of PTV margin based on actual accumulated dose for prostate cancer radiotherapy

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Abstract

The purpose of this work is to present the results of a margin reduction study involving dosimetric and radiobiologic assessment of cumulative dose distributions, computed using an image guided adaptive radiotherapy based framework. Eight prostate cancer patients, treated with 7–9, 6 MV, intensity modulated radiation therapy (IMRT) fields, were included in this study. The workflow consists of cone beam CT (CBCT) based localization, deformable image registration of the CBCT to simulation CT image datasets (SIMCT), dose reconstruction and dose accumulation on the SIM-CT, and plan evaluation using radiobiological models. For each patient, three IMRT plans were generated with different margins applied to the CTV. The PTV margin for the original plan was 10 mm and 6 mm at the prostate/anterior rectal wall interface (10/6 mm) and was reduced to: (a) 5/3 mm, and (b) 3 mm uniformly. The average percent reductions in predicted tumor control probability (TCP) in the accumulated (actual) plans in comparison to the original plans over eight patients were 0.4%, 0.7% and 11.0% with 10/6 mm, 5/3 mm and 3 mm uniform margin respectively. The mean increase in predicted normal tissue complication probability (NTCP) for grades 2/3 rectal bleeding for the actual plans in comparison to the static plans with margins of 10/6, 5/3 and 3 mm uniformly was 3.5%, 2.8% and 2.4% respectively. For the actual dose distributions, predicted NTCP for late rectal bleeding was reduced by 3.6% on average when the margin was reduced from 10/6 mm to 5/3 mm, and further reduced by 1.0% on average when the margin was reduced to 3 mm. The average reduction in complication free tumor control probability ($P+$) in the actual plans in comparison to the original plans with margins of 10/6, 5/3 and 3 mm was 3.7%, 2.4% and 13.6% correspondingly. The significant reduction of TCP and $P+$ in the actual plan with 3 mm margin came from one outlier, where individualizing patient treatment plans through margin adaptation based on biological models, might yield higher quality treatments.

Introduction

Previous studies have reported that intensity modulated radiation therapy (IMRT) has fewer gastrointestinal complications such as proctitis and rectal bleeding compared to 3D-CRT for men with prostate cancer (Sheets *et al* 2012). With the development of IGRT, the target localization accuracy and precision have been improved (Ghilezan *et al* 2004). However, IGRT cannot correct for daily deformation of the prostate gland and organs at risk (OAR) such as bladder and rectum. We have developed and previously validated an image guided adaptive radiotherapy (IGART) framework ‘in-house’, to track anatomical changes, such as displacement and deformation in the target and surrounding tissues (via daily cone beam CT (CBCT) images), and to perform daily dose accumulation (Wen *et al* 2012). The goal of this framework is to determine the actual daily dose delivered to the patient through the treatment course. We hypothesize that, using our framework, we will be better able to account for systematic and random setup errors, as well as daily physiological changes in the prostate and surrounding normal organ volumes, and, consequently, that we will be able to reduce planning margins. The purpose of this work is to describe the methods and results of a margin reduction study involving dosimetric and radiobiologic assessment of cumulative dose distributions, computed using this framework.

Material and methods

Treatment planning

Eight prostate cancer patients receiving IMRT were included in this retrospective study approved by our Institutional Review Board. A partially full bladder and empty rectum were required during simulation and daily treatment. Patients were simulated using 3 mm slice thicknesses with a Brilliance CT 16-slice (Philips Medical Systems, Andover, MA). The technical settings of the pelvis protocol were 120 kV, 500 mAs. The prescription dose was 75.6 Gy (1.8 Gy $\times$ 42 fractions) except for patients 2 and 4, who had prescribed doses of 80 Gy (2 Gy $\times$ 40 fractions) for the requirement of a gene therapy study. The CTV included the entire prostate gland and the inferior 10 mm of the proximal seminal vesicles. The PTV was created by adding a 10 mm margin to the CTV except posteriorly, where the margin was 6 mm to limit dose to the anterior rectal wall. The rectum was drawn on CT slices starting at the anal verge and continuing superiorly for a maximal length of 15 cm or until the rectosigmoid junction. The standard margin scheme in our clinic will be referred to as ‘10/6 mm’. All patients were treated with 7–9, 6 MV, IMRT fields.

IGART

Previously, we developed and reported on an offline framework for performing IGART (Wen *et al* 2012). Validation of the various processes in the IGART workflow, including dose calculation on CBCT image data sets, and accuracy of the deformable image registration (DIR) algorithm, were also carried out. The accuracy of DIR on patient image sets was evaluated using three different approaches: landmark matching with fiducial markers, visual evaluation of CT images, and unbalanced energy (UE), a voxel based algorithm to quantify displacement vector field (DVF) errors (Zhong *et al* 2007). The dose calculated on each CBCT image set was warped back to simulation CT image datasets to

determine the ‘actual dose’ delivered to the patient. The dose delivered at each treatment fraction was accumulated to reflect the final dose given to the patient (Wen *et al* 2012).

Margin reduction

For each patient, two additional IMRT plans were generated using a smaller margin applied to the CTV. The PTV margin for the original plan was 10/6 mm. The margin was reduced to: (a) 5 mm uniformly except posteriorly, where it was 3 mm (5/3 mm), and (b) 3 mm uniformly (3 mm).

The new IMRT plans were recalculated on each CBCT image set. Using the same DVFs generated from offline DIR, dose was reconstructed and accumulated over all fractions to determine the actual dose. The actual dose was then compared to the dose calculated in the original plan (static plan), without deformation to evaluate the doses delivered to the PTV and OARs at each margin setting.

Plan evaluation

Tumor control probability (TCP) and normal tissue complication probability (NTCP) were evaluated to determine differences in dose distributions between the static and actual plans across the three margin settings. TCP was based on a Poisson statistics-based model that has been described previously (Liu *et al* 2009). We used the classic four parameter Lyman–Kutcher–Burman model to calculate NTCP. The parameter estimates of the gastrointestinal toxicity (GI,) i.e. late grade 2/3 and grade 3 rectal bleeding) for the model were defined by a large multi-center trial of 547 prostate cancer patients (Rancati *et al* 2004). Using grade 2/3 late bleeding as the endpoint, the parameters were as follows: TD_{50} 81.9 Gy, m (steepness) = 0.19, and n (seriality) = 0.23. TD_{50} is defined as dose received by the volume that could lead to a complication probability of 50 percent. m is the slope of the complication probability versus dose curve. n is the volume dependence of the complication probability. For grade 3 late bleeding as the endpoint, TD_{50} = 78.6 Gy, m = 0.06, and n = 0.06. The parameter estimates of the grade 1 or greater genitourinary toxicity (GU) were based on a previous study of 128 patients (Cheung *et al* 2007). The parameters were as follows: TD_{50} = 77.6 Gy, m 0.02, and n 0.01.

The complication free tumor control probability (P_+) was used to rank the static and actual dose at each margin setting by combining TCP and NTCP (Kallman *et al* 1992). P_+ is defined as:

$$P_+ = TCP - TCP \cap NTCP = TCP - NTCP + \delta \times (1 - TCP) \times NTCP, \quad (1)$$

where δ is fraction of patients having independent tumor and normal tissue response. A fixed value of 20% was used for δ in our study.

Results

Target coverage—dosimetric evaluation

The average values of CTV minimum, mean and maximum doses of all eight patients for both static and actual plans are shown in figure 1 at each margin setting. Error bars represent

the minimum and maximum values of all patients. With the 10/6 mm margin, differences in the CTV mean, minimum and maximum doses between the static and actual plans were all within 2%. When the margin was reduced to 5/3 mm, the difference in CTV minimum dose between static and actual plans was within 2% for three patients, 2–5% for four patients. The difference was 7% for patient 7. The CTV mean and maximum doses were within 2% agreement. When a 3 mm uniform margin was applied, there was a large variation in the percentage difference of the CTV minimum dose. The difference was within 1% for one patient, 4–7% in six patients, and 20% for patient 7. The differences in the CTV mean and maximum doses were within 2% for all patients.

Target coverage—radiobiological evaluation

The CTV TCP was computed for all three planning margin scenarios. The average percent differences of TCP between the actual and static plans over eight patients were 0.4% (range, –3.7%–6.3%) with 10/6 mm margin, 0.7% (range, 2.8%–9.7%) with 5/3 mm margin, and –11.0% (range, –71.3%–2.1%) with 3 mm uniform margin respectively. There was significant percent difference (–71.3%) in patient 7 with 3 mm margin. The average percent difference in TCP between the actual and static plans was within 2.3% for the other seven patients.

Normal tissue evaluation

The average values of minimum, mean and maximum doses for rectum and bladder of all eight patients are summarized in figures 2 and 3 respectively at each margin setting. Error bars represent the minimum and maximum values of all patients.

The mean, minimum and maximum doses to rectum and bladder for each patient are summarized in figures 2 and 3 respectively. The actual treatment plans resulted in higher mean doses to the rectum and bladder in comparison to the corresponding static treatment plans. For the rectum this increase in dose in the actual plans was as follows: (a) 15.6% (range, 0.6%–42.4%) for the 10/6 mm margin; (b) 21.6% (range, 0.2%–51.8%) for the 5/3 mm–margin, and (c) 23.6% (range, –2.9%–55.6%) for the 3 mm –uniform margin. The difference in the maximum rectal dose was insignificant, within 2.4% for all three margin scenarios.

Similarly, for the bladder the actual plans showed higher mean dose than the corresponding static plans, as follows: (a) 4.1% (range, –18.1%–30.7%) for the 10/6 mm margin; (b) 5.4% (range, –24.8%–36.9%) for the 5/3 mm margin, and (c) 5.7% (range, 26.6%–37.8%) for the 3 mm uniform margin. The maximum bladder dose was within 2.8%–between the actual and static plans.

In general, the rectum and bladder doses were reduced as the planning margin was reduced. As the margin was reduced from 10/6 to 5/3 mm in the actual plans, the mean dose to rectum was reduced by 20.1% (range, 9.4%–40.3%) among eight patients. As the margin was reduced from 5/3 to 3 mm uniformly, the dose reduction was 8.5% (range, 3.3%–21.8%). For the bladder, the mean dose was reduced by 26.9% (range 14.1%–42.0%) as the margin was reduced from 10/6 to 5/3 mm and 14.3% (range, 6.6%–30.3%) as the margin

was reduced from 5/3 to 3 mm uniformly. Plans with different margin settings also had similar maximum dose, located at the rectal wall.

Grade 2/3 and grade 3 late rectal bleeding were also evaluated using parameters defined through a multi-center trial of 547 prostate cancer patients. The corresponding NTCPs for grades 2/3 and grade 3 rectal bleeding are shown in figure 4, for static and actual plans for the three different planning margins. The mean difference in NTCP for grades 2/3 bleeding between the static and actual plans with margin of 10/6, 5/3 and 3 mm was 3.5%, 2.8% and 2.4% respectively. For grade 3 late rectal bleeding, the mean difference was 4.1%, 3.5% and 2.6% respectively. In the actual plans, NTCP for late rectal bleeding was reduced by 3.6% on average when the margin was reduced from 10/6 mm to 5/3 mm, and further reduced by 1.0% on average when the margin was reduced to 3 mm uniformly.

Complication free tumor control probability

P_+ was calculated using TCP and NTCP for the rectum since late rectal toxicity is relatively more important in the decision making. The P_+ values are shown in figure 5, for static and actual plans for the three different planning margins. The average percent differences of P_+ between the actual and static plans over eight patients were -3.7% (range, 8.3% – -5.4%) with 10/6 mm margin, -2.4% (range, -7.5% – -10.0%) with 5/3 mm margin, and -13.6% (range, -73.0% – -2.6%) with 3 mm uniform margin respectively. Similarly, there was a significant percent difference (-73.0%) in patient 7 with 3 mm margin. The average percent differences of P_+ were within 5.0% for the remaining patients.

Discussion

This study explored dosimetric and radiobiological endpoints arising from margin reduction in an IGART framework for prostate cancer. Validation of the accuracy of the steps involved in deformation and dose mapping is a crucial process. We have evaluated procedures in our framework by performing phantom experiments and patient studies (Wen *et al* 2012). Studies have shown that smaller PTV margins can reduce the computed rectal NTCPs by up to 10% (Huang *et al* 2008; Ghilezan *et al* 2004). Sandler *et al* showed that patient-reported quality of life outcomes were improved by decreasing PTV margin to 3 mm (Sandler *et al* 2010). We have completed a prospective study of 27 patients, in which the interfraction setup error and residual errors were investigated using multiple imaging modalities (Mayyas *et al* 2013). The PTV margin, derived following Van Herk's formalism (van Herk *et al* 2000) was on the order of 10 mm to compensate for inter-fraction setup errors using skin-tattoo alignment for localization. Using CBCT-based alignment, residual errors were less than 3 mm in all directions (Mayyas *et al* 2013). Using daily CBCT-based image guidance it was concluded that the setup margin can be reduced to 3 ~ 5 mm to properly account for setup uncertainties (Mayyas *et al* 2013). (Chung *et al* 2004) analyzed the position of fiducial markers in 17 patients using portal imaging. The center of mass displacement of the prostate was within 3 mm in all directions. The data from Beltran *et al* suggested that 3.0 mm was the minimum necessary margin to compensate for inter- and intra-fraction prostate motion (Beltran *et al* 2008). While this study only included eight patients, the results here are in agreement with other groups that the minimum population-

based margin is approximately 3–5 mm. However, if geometric uncertainties resulting from organ deformation are not considered, the implementation of a smaller PTV margin is likely to have a negative dosimetric and radiobiological impact. We noted that there were no differences in the mean and maximum doses in the CTV for the three margin scenarios. However, as the margin was reduced, the discrepancy in the CTV minimum dose increased. Patient 7 showed the largest deviation in the CTV minimum dose coverage with 3 mm margin due to the geometric shift caused by deformation. For this patient, the uniform 3 mm margin plan could lead to significant reduction in the predicted TCP value. Wu *et al* reported that a 5 mm PTV margin is required to keep the difference between accumulated and prescription doses within 2% (Wu *et al* 2006). Our results are generally consistent with the study of Wu *et al* but it is important to view any margin reduction study, different than standard-of-care, with extreme caution. Ultimately clinical outcomes need to be studied to unequivocally assess the benefit of margin reduction.

The rectal mean dose increased in the actual plans relative to the corresponding static plans for all patients likely due to the lack of adherence to the full bladder/empty rectum initial conditions in the simulation. This suggests that IGRT alone cannot correct the daily deformation of the rectum. The treatment plans tend to underestimate the rectal dose delivered in the actual treatment. Several studies have discussed the impact of dose schemes and techniques on the therapeutic ratio for prostate cancer treatments (Amer *et al* 2003; Huang *et al* 2008). In our study, predicted NTCP (for late rectal bleeding endpoint) was 2.4–4.1% higher in the actual plan than that in the static plan. Such variability should be considered in evaluating the radiobiological effects of treatments.

We also predict that reducing the margin is an effective means to reduce GI toxicity. When the margin was reduced from 10/6 to 5/3 mm, NTCP of late rectal bleeding was decreased by 3.6% on average. When the margin was reduced to 3 mm uniformly, NTCP was further reduced by another 1.0%. Considering that smaller margins do not result in a significant reduction in the predicted TCP value, IGRT has the potential to improve the therapeutic ratio in combination with smaller planning margins.

We also performed a test of the TCP and corresponding P with different surviving fraction (SF_2) parameters, and clonogenic cell density to evaluate the robustness of our results. Since standard fractionation was used in the treatment, α/β ratio was excluded for evaluation. The effect of δ on $P+$ was investigated by Liao *et al* (2010) and the impact of δ on P was negligible. When SF_2 was 0.5, there were undetectable differences in TCP and between the static and actual plans since TCP was 99% for all plans and was independent of cell density. When SF_2 was 0.6, TCP depended on cell density only when cell density increased from 10^5 to 10^6 cm^{-3} as shown in figure 6. The $P+$ values shown in figure 5 represented less responsive tumor cells ($SF_2 = 0.6$) and early stage prostate cancer (cell density 10^6 cm^{-3}). The $P+$ values predicted that the actual complication free tumor control possibility was inferior to the static one at each margin setting in general. The results demonstrated that current radiobiological evaluation based on the static treatment planning could not accurately predict the treatment outcome. Reducing the margin to 5/3 mm showed systematic improvement on the actual $P+$ values for all patients. Further reducing the margin to 3 mm did not provide any gain on $P+$. And the $P+$ value was significantly degraded for

patient 7 with 3 mm margin. By combining TCP and NTCP, $P+$ provides a useful guidance to understand the clinical results in the relative ranking of the margins.

A similar radiobiological analysis was performed for the bladder. Data published by Cheung was used for NTCP calculation ($TD_{50} = 77.6$ Gy, $n = 0.00995$, $m = 0.022$) to evaluate late GU toxicity with grade equal or greater than 1. Since n is small, the bladder is considered a serial organ when the risk of low grade GU toxicities is included. Therefore the complication is directly related to the bladder D_{max} . The effectiveness of margin reduction to reduce the mild GU toxicity depends heavily on the prescription dose and the maximum bladder dose. No direct correlation was found in this study between the planning margin and NTCP, because even though the mean dose decreased with smaller margins, the maximum bladder dose showed no predictable variation as a function of margin. A future study will focus on the correlation between PTV margin and severe GU toxicity.

We applied a uniform margin to all patients. However, even with a cohort of eight patients, we noticed large inter-patient variation in NTCP. Patient compliance with regard to bladder and rectal physiology prior to treatment was found to be an important factor. All eight patients were instructed on proper bowel preparation, and how to maintain bladder filling at each treatment. If the rectum showed large deformational changes, the patient was taken off the table and given time to ensure that the bladder and bowel physiology closely resembled that at the time of simulation. Patient 2 had difficulty complying with the instructions; therefore there was large deformation in the rectum which could not be corrected by rigid transformation. Even though patient 7 did not have significant difficulty complying with bowel and bladder preparation instructions, the systematic geometric errors caused by deformation through the treatment course could lead to a treatment failure if 3 mm margin was applied. The benefit of margin reduction was dependent on the individual patient, which has been reported by other studies as well (Song *et al* 2006, Ghilezan *et al* 2004). Moreover, the lack of consistent physiologic conditions in the bladder and rectum on a daily basis, due in part to lack of preparation, produces intra- and inter- patient variability. Huang *et al* quantified the dosimetric and radiobiological impact by reducing PTV margin from 7 mm to 3 mm for IMRT plans (Huang *et al* 2008). However, their results were also subject to large inter-patient variability. This suggests that individualizing patient margins may be helpful in achieving the best clinical outcome and may facilitate better plan re-optimization, as necessary during the treatment course. The assessment of the re-planning/re-optimization is a subject of future investigation.

Conclusion

We applied an ‘in-house’ developed framework to determine the actual doses delivered to a cohort of eight patients with early stage prostate cancer. We demonstrated that margin reduction is an effective method to improve the therapeutic ratio but has to be implemented with extreme caution. A prospective study with a large patient population is warranted to produce more conclusive results.

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Figure 1.

Comparisons of CTV minimum (left), mean (middle) and maximum (right) doses between static and actual plans. Vertical bars represent the average value of all eight patients at each margin setting. The bar on the left-hand side shows the static dose while the right-hand side shows the actual dose. Error bars represent the minimum and maximum values for all patients.

Figure 2.

Comparisons of minimum (left), mean (middle) and maximum (right) rectal doses between static and actual plans. Vertical bars represent the average value of all eight patients at each margin setting. The bar on the left-hand side shows the static dose while the right-hand side shows the actual dose. Error bars represent the minimum and maximum values for all patients.

Figure 3.

Comparisons of minimum (left), mean (middle) and maximum (right) bladder doses between static and actual plans. Vertical bars represent the average value of all eight patients at each margin setting. The bar on the left-hand side shows the static dose while the right-hand side shows the actual dose. Error bars represent the minimum and maximum values for all patients.

Figure 4. NTCP comparison of late rectal bleeding between the static (solid line) and actual (dashed line) plans at the three margins. Markers with filled square showed NTCP of real grade 2/3 bleeding. Markers with filled triangle represented NTCP of real grade 3 bleeding only.

Figure 5.
 $P+$ comparison between static (solid line) and actual (dash line) plans at three margins 10/6, 5/3, and 3 mm.

Figure 6. TCP versus N_0 evaluation between static (solid line) and actual (dash line) plans at three different margins 10/6 (markers with circle), 5/3 (markers with triangle) and 3 mm (markers with diamond). N_0 is in log scale, ranging from 10^3 to 10^6 .