Potential benefit and clinical implementation of adaptive radiotherapy

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CHAPTER 3

Evaluation of delivered dose for a clinical daily adaptive plan selection strategy for bladder cancer radiotherapy

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Abstract

Purpose: To account for variable bladder size during bladder cancer radiotherapy, a daily plan selection strategy was implemented. The aim of this study was to calculate the actually delivered dose using an adaptive strategy, compared to a non-adaptive approach.

Methods: Ten patients were treated to the bladder and lymph nodes with an adaptive full bladder strategy. Interpolated delineations of bladder and tumor on a full and empty bladder CT scan resulted in five PTVs for which VMAT plans were created. Daily cone beam CT (CBCT) scans were used for plan selection. Bowel, rectum and target volumes were delineated on these CBCTs, and delivered dose for these was calculated using both the adaptive plan, and a non-adaptive plan.

Results: Target coverage for lymph nodes improved using an adaptive strategy. The full bladder strategy spared the healthy part of the bladder from a high dose. Average bowel cavity V30Gy and V40Gy significantly reduced with 60 and 69 ml, respectively (p < 0.01). Other parameters for bowel and rectum remained unchanged.

Conclusions: Daily plan selection compared to a non-adaptive strategy yielded similar bladder coverage and improved coverage for lymph nodes, with a significant reduction in bowel cavity V30Gy and V40Gy only, while other sparing was limited.

Keywords: Adaptive radiotherapy; Bladder cancer; Plan of the day; Plan selection; Normal tissue sparing
**Introduction**

As a bladder-conserving alternative to cystectomy, external beam radiotherapy provides an effective treatment option for muscle-invasive bladder cancer [91]. For focal tumors, combining whole bladder irradiation with a tumor boost and chemotherapy, local control rates of 67% were achieved [89]. In our department, when such a tumor boost is given, patients are treated with a full bladder which is expected to spare more of the healthy bladder from the boost dose [33]. To compensate for variations between fractions in bladder filling, size and position, large target volume margins are required to ensure target coverage, even with the use of a strict drinking protocol [31, 32]. These margins result in a high dose to the organs at risk (OARs).

The introduction of pre-treatment cone beam CT (CBCT) for daily patient set-up, has enabled soft-tissue visualization during the treatment course. This allows adapting the radiation delivery according to anatomical changes during the treatment course, which is known as adaptive radiotherapy (ART). Multiple ART strategies for bladder cancer have been described, based on daily plan selection, which comprises the creation of multiple treatment plans for different bladder volumes, and daily selection of the plan best fitting the bladder volume as seen on the CBCT [40, 42, 44, 113–116]. To obtain target volumes for the multiple plans, variable target margins, multiple CT scans or the CBCT scans acquired during the first week can be used [40, 42, 113–116]. Interpolating a registration between a full and an empty bladder delineation to generate intermediate bladder volumes, for the creation of multiple treatment plans, was also described previously [44]. This method was implemented in 2013 at our institute.

The dosimetric analyses for these adaptive strategies imply that target coverage is maintained or improved, while reducing dose to the organs at risk [40, 42, 44, 113–116]. These dosimetric analyses are usually performed by summating the weighted dose calculations of the used plans during treatment. In this case, the changed anatomy of the organs of interest, i.e. bladder, rectum and bowel, are not taken into account. To understand the value of an adaptive strategy and investigate the areas of improvement, dose delivery to the target and separate OARs should be evaluated. Even though this has been investigated earlier, either for specific organs [10,11], or for the normal tissue as a whole [15], it is currently unknown whether OAR sparing is also seen in patients treated with a full bladder including pelvic lymph nodes in the target, and whether target coverage of bladder and lymph nodes is not compromised using an adaptive strategy, taking daily anatomical changes into account.

The aim of this study was therefore to calculate the actually delivered dose to the target and OARs when patients are irradiated with a full bladder, using a daily plan selection strategy for bladder cancer radiotherapy, and to compare this to the dose that would have been delivered with a non-adaptive approach.
Methods

Patients and imaging

Between March 2013 and September 2014, 11 of the 16 consecutive patients with muscle-invasive bladder cancer were treated with an adaptive strategy, of which 10 were included in this study. Patients with multiple tumors or carcinoma in situ were excluded, as well as patients with two metal hip prostheses. Patient characteristics are presented in table 1. Patients were treated in 20 fractions to the bladder and pelvic lymph nodes, combined with a simultaneously integrated boost to the tumor.

Prior to treatment, two planning CT scans with a full and empty bladder were acquired in supine position. Patients were eligible for our plan selection approach if the full bladder volume on the planning CT scan was at least twice the empty bladder volume. On both scans, the radiation oncologist contoured the bladder and GTV, which was aided by cystoscopically placed fiducial markers. On the full bladder scan, the draining pelvic lymph nodes, rectum, bowel cavity and both femur heads were delineated.

Creation of library of structures

The bladder and GTV structures as delineated on the full bladder CT were registered to the bladder and GTV structures from the empty bladder CT, using a structure-based deformable registration algorithm as implemented in Erasmus RTStudio (part of Erasmus MatterhornRT, software platform for radiotherapy research and advanced treatment). This algorithm was described previously [117]. In short, the algorithm found corresponding points between two structures. By connecting these pairs of corresponding points, deformation vectors were obtained. Linear scaling of these deformation vectors resulted in a library of structures. To represent different filling states, the following scale factors were used: 0%, 33%, 67%, 100% and 133%, with 0% and 100% structures corresponding to the empty and full bladder, respectively.

Treatment planning and delivery

The full bladder CT scan and bladder and GTV structures were imported in Oncentra treatment planning system (version 4.3, Elekta, Stockholm, Sweden). For each filling state two planning target volume (PTV) structures were created: PTV_{elective} consisting of the lymph nodes and one of the five bladder volumes, with a uniform margin of 7 mm, and PTV_{boost}, consisting of one of the five GTV volumes and a 9 mm uniform margin (figure 1). The margins are applied to account for residual errors, such as shape changes, delineation errors and intrafraction motion. The PTV_{boost} margin is larger than the PTV_{elective}
Evaluation of delivered dose for adaptive bladder cancer radiotherapy

margin, due to larger delineation uncertainties for the tumor. Five dual arc VMAT plans were created on the full bladder CT, with a separate optimization for each combination of PTVs. Standard planning objectives were used to aim for a homogeneous fractional dose of 2 Gy in PTV_{elective} (i.e. 40 Gy in 20 fractions), and 2.75 or 3 Gy in PTV_{boost} (i.e. 55–60 Gy in 20 fractions), while keeping dose to the OARs as low as possible. A prescription of 3 Gy to PTV_{boost} is preferable, but for ventrally and caudally located tumors 2.75 Gy is chosen, to spare the bowel cavity from a 3 Gy fraction dose.

Before each fraction, patients were asked to drink 0.5 liter of water 1.5 hours prior to treatment, and refrain from voiding. A CBCT scan was acquired daily, and registered to the pelvic bony anatomy (XVI, Elekta). Subsequently, the five bladder contours were projected on the CBCT scan, and the smallest bladder contour encompassing the entire bladder on CBCT was selected. The plan corresponding to the chosen bladder contour was

<table>
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<tr>
<th>Pt</th>
<th>Age</th>
<th>Sex</th>
<th>Tumor stage</th>
<th>Pre-RT treatment</th>
<th>Cx</th>
<th>GTV location</th>
<th>Markers</th>
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<td>TURT</td>
<td>Left wall</td>
<td>Hydrogel</td>
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</tr>
</tbody>
</table>

Pt = patient. Cx = chemotherapy. TURT = transurethral resection of the tumor. Chemotherapy regimen: weekly administration of cisplatin or carboplatin. Lipiodol and hydrogel: fluid contrast agents, injected during cystoscopy procedure prior to planning CT scans, to indicate border of the tumor [37,38]. Patient 12 was excluded from analysis, since quality of CBCT scans was not sufficient.
selected for treatment. The corresponding $\text{PTV}_{\text{elective}}$ and $\text{PTV}_{\text{boost}}$ contours were projected on the CBCT. If needed, these contours were shifted manually, until maximum tumor coverage was obtained, based on the location of the tumor markers relative to $\text{PTV}_{\text{boost}}$, ensuring that the bladder was still located inside $\text{PTV}_{\text{elective}}$ (summarized data regarding these shifts in supplementary table). The resulting setup correction was applied before starting treatment. Irradiation time per fraction was 140–160 sec.

**Simulation of non-adaptive procedure**

To compare the dose delivered with the daily plan selection protocol to a non-adaptive approach, a non-adaptive $\text{PTV}_{\text{elective}}$ was created. This consisted of the full bladder and lymph node delineations, with 13 mm margin ventrally and cranially to the bladder, and 7 mm margin in all other directions. To obtain a non-adaptive VMAT plan, a separate optimization was performed for this PTV and the full bladder $\text{PTV}_{\text{boost}}$ (i.e. GTV from the full bladder CT with a 9 mm uniform margin). This plan was not used clinically.

Using this non-adaptive plan, a second treatment regimen was simulated according to our non-adaptive clinical protocol. Using XVI software, each CBCT was registered to the full bladder CT based on tumor markers to ensure maximum tumor coverage, and setup correction was recorded. The non-adaptive VMAT plan was selected for every fraction.
Dose calculation and comparison to non-adaptive strategy

Each CBCT was imported in either Oncentra (first eight patients) or VelocityAI (version 3.1.0, Velocity Medical Solutions, Atlanta, USA). The bladder, rectum and bowel cavity were delineated by a single observer, using RTOG delineation guidelines [118]. Due to limited visibility of lymph nodes on CBCT, the lymph node delineations were copied from the full bladder CT scan, using a bony anatomy registration including translations and rotations [119]. To minimize variability, delineations were performed by a single observer. Intraobserver variation was assessed by re-delineation of three CBCT scans for four patients, at least one month after initial delineation. Volume variation between every contour combination was < 5% in all cases, mean overlap was 96% for bladder and bowel cavity, and 90% for rectum. This is higher than the previously reported interobserver delineation variability (i.e. overlap values of 75-81%), which was assessed to be sufficiently small for use in adaptive strategies [120, 121].

Dose calculation on CBCT requires calibration of CBCT voxel values, which is subject to uncertainties [122]. Therefore, the dose distribution calculated on the full bladder CT during treatment planning was used for calculation of the DVHs. For each day, the dose distribution corresponding to the delivered plan was selected. Daily delineated structures were propagated to the full bladder CT using a translation vector which is determined by the isocenter position of the selected plan and the setup correction applied that day. This enabled calculation of the daily DVH for each structure, using Matlab (version R2012a, MathWorks, Natick). For the bowel cavity, an absolute volume scale was used since the CBCTs did not include the entire organ.

Dose calculation and DVH creation was repeated for the non-adaptive approach, using the same CBCTs and delineations, but applying the non-adaptive plan and the setup correction based on marker position.

Evaluation of irradiated volumes and statistical analysis

Bladder and lymph node coverage was assessed by calculating the daily V95%, i.e. the volume receiving at least 95% of the prescribed daily dose. The relative bladder volume receiving more than the elective dose, but less than the boost dose, i.e. V2.25Gy – V2.75Gy, was calculated for each fraction. The irradiated volume of rectum and bowel cavity was calculated for each separate fraction. Low, intermediate and high dose levels were assessed by extracting the V0.5Gy, V1.5Gy and V2Gy from the daily DVHs for rectum and bowel cavity. These correspond to dose levels of 10 Gy, 30 Gy and 40 Gy for the entire treatment course, and will therefore be referred to as their fractionated substitutes, i.e. V10Gy-fx, V30Gy-fx and V40Gy-fx.
Differences in target coverage between the adaptive versus the non-adaptive strategy were tested using the McNemar chi-square test, and for OAR dose with the Wilcoxon signed-rank test. The daily difference in irradiated volume for the three dose levels was calculated by subtracting the irradiated volumes for the non-adaptive from those of the adaptive strategy. Statistical analysis was performed using R version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria).

**Results**

Of the 16 patients treated with radiotherapy, 10 were eligible for inclusion. Four patients did not have a large enough difference between full and empty bladder on planning CTs. One patient could not enter the ART-protocol due to logistic reasons. For one patient, CBCT quality was not suitable for analysis.

Most often a 67% or 100% plan was chosen, in 47% and 22% of the cases, respectively. During treatment, in 85% of fractions the bladder was at least 10% smaller than on full bladder planning CT, and at least 10% larger in 6% of fractions. Patients complied with drinking instructions in a majority of cases, although actual fluid intake was not

**Figure 2:** Bladder volume change during treatment. Left: Selected plans per week, for all patients. Right: Relative bladder volume, i.e. the bladder volume on CBCT divided by full bladder volume on CT, for each treatment week. The horizontal line represents the median, the box represents the first and third quartile. Whiskers extend to 1.5 times the interquartile range from the box and the dots represent outliers.
monitored. The full bladder protocol was well tolerated, although in one fraction the patient voided during treatment.

The bladder volume decreased significantly during treatment, with a median bladder volume of 228 ml during the first week, and a median volume of 175 ml during the fourth week (p < 0.01). This is reflected in the selected plans during the course of treatment (figure 2).

Figure 3 shows that for smaller bladder volumes, a larger part of the bladder receives a dose between 2.25 and 2.75 Gy. Therefore, our full bladder approach is beneficial for the healthy part of the bladder.

**Target coverage**

Adequate target coverage, as expressed in percentage of all fractions where V95% was larger than 99%, was 98% for bladder for both strategies. For lymph nodes, a difference was found, with 93% of the cases with adequate coverage for the adaptive strategy, versus 80% for the non-adaptive strategy (p < 0.01).

Figure 3: Bladder volume receiving a dose between 2.25 and 2.75 Gy (denoted: V[2.25-2.75Gy]), as a function of relative bladder volume (as percentage of the full bladder on CT), for each daily fraction, for all ten patients. The V[2.25-2.75Gy] is normalized to the V[2.25-2.75Gy] on the full bladder CT scan with the 100% plan, to account for inherent differences in tumor volume. The reference line indicates a value of 1 (i.e. the daily V[2.25-2.75Gy] equals the V[2.25-2.75Gy] on the full bladder CT with the 100% plan). A value > 1 represents a larger area of the bladder receiving a dose between 2.25 and 2.75 Gy than on planning CT.
OAR sparing

Figure 4 illustrates the difference in daily DVHs for the adaptive and non-adaptive strategies. Figure 5 shows the fractionated substitutes of the median $V_{10}\text{Gy}$, $V_{30}\text{Gy}$ and $V_{40}\text{Gy}$, for all fractions of all patients, for both bowel cavity and rectum. The differences in $V_{30}\text{Gy}$-fx and $V_{40}\text{Gy}$-fx for bowel cavity were significant. The median $V_{30}\text{Gy}$ was 572 ml for the adaptive strategy, and 632 ml for the non-adaptive strategy ($p < 0.01$). For the $V_{40}\text{Gy}$, these values were 246 ml and 315 ml, respectively ($p < 0.01$). In general, sparing of the OARs is larger when smaller plans are chosen (supplementary figure 1). Using ART, sparing of bowel volume from the elective dose of 40 Gy appeared to be larger for patients with a dorsally located tumor (supplementary figure 2), but this difference was not statistically significant, probably due to the small sample size.

Discussion

In this first full dosimetric analysis for ten patients treated with a daily plan selection strategy based on full bladder irradiation for bladder cancer, we evaluated the actually delivered dose while taking into account the day-to-day anatomical variations. Compared to a non-adaptive strategy, we found a similar to improved coverage for bladder and
lymph nodes, but OAR sparing was limited, with a significant reduction in bowel cavity V30Gy and V40Gy only.

Previously conducted dosimetric studies report either bowel cavity or normal tissue sparing when an adaptive strategy is used [40, 42, 44, 113, 115, 116]. Most studies employ an empty bladder protocol. Only Meijer et al. use a full bladder protocol, however, no dosimetric data is reported [44]. The sparing we found is relatively small, due to the smaller margins for our non-adaptive strategy compared to others, and due to the inclusion of the lymph nodes in the treatment volume. Previous studies report that when only bladder is considered as target volume, the reduction in irradiated normal tissue volume receiving the prescribed elective dose, ranges from 155–219 ml [40, 116]. However, when the pelvic lymph nodes are included in the target, the sparing reduces to 65–100 ml [40, 42]. This is in line with our results, since with taking anatomical changes into account, we found a mean reduction in bowel cavity V40Gy of 69 ml. Selecting a plan for a smaller bladder does not yield a smaller treatment volume around the lymph nodes, which are in close proximity to the bowel cavity. A minimum bowel cavity dose will therefore always be present. Reducing target margins for the lymph nodes could lower this, but since lymph node coverage does not improve drastically with our ART strategy, this does not seem appropriate. To facilitate the clinical workflow, a single margin size was used for bladder and lymph nodes. Possible intrafraction movement is mainly caused by bladder filling between acquisition of CBCT and irradiation. For a full

![Graphs showing DVH parameters for rectum and bowel cavity.](image_url)

**Figure 5:** DVH parameters for all patients, derived from daily DVHs for rectum and bowel cavity. ART: adaptive strategy. Non-ART: non-adaptive strategy.
bladder this might be a smaller issue than for an empty bladder, since shape change for a
certain volume of urinary inflow is less dramatic. However, an optimal margin size for the
ART procedure still has to be determined.

Even though the margins used in our clinic are relatively small, our results regarding
bladder coverage are in line with Foroudi et al., who reported a non-significant difference
in coverage between their adaptive strategy and a non-adaptive strategy for bladder
cancer [115]. To our knowledge, this is the first study to report that coverage of the lymph
nodes improved using an adaptive strategy. This improvement occurred in cases where
the bladder was on average 50% smaller compared to the planning CT. This smaller
bladder volume required large setup corrections for the non-adaptive strategy, due to the
match on tumor markers, which impaired lymph node coverage. The adaptive strategy
allows for the use of a match on bony anatomy, since for each level of bladder filling, a
fitting boost PTV is available.

Assessment of tumor coverage is difficult since the tumor cannot be seen on the
CBCT. However, both assessed strategies are based on either a marker match, or a
sufficient coverage of the markers by PTV_{boost}, so differences in tumor coverage are not
expected.

Our dosimetric analysis is based solely on daily DVHs, from which we extracted the
median irradiated volumes. To summate the dose for all fractions, a method taking the
dose distribution within the delineated organs into account, i.e. dose warping based on
deformable image registration, would be preferable. This is difficult in the pelvic area,
since it exhibits large local deformations in combination with static bony anatomy. Currently available algorithms therefore generally perform poorly in terms of anatomical
correctness leading to incorrect dose distributions [123, 124]. Therefore we decided to
evaluate the daily DVHs separately, but statistical tests were applied pairwise, so the
reported difference for both strategies is consistently valid.

Analysis was limited by our small patient population. Dose to the OARs could not
reliably be correlated to tumor location. In addition, a wider range of bladder volumes
could have provided more insight into the maximum achievable OAR sparing or coverage
improvement.

Many daily plan selection strategies employ CBCTs acquired in the first week
to obtain multiple bladder volumes to create the additional plans [42, 113, 115]. The
advantage of our method is having the plans ready before the start of the treatment,
which is convenient in terms of workflow, but is also a dosimetric advantage. In the
first week, in 29% of fractions a plan other than 67% or 100% was used, indicating the
need for adaptive plans from the first fraction onwards. Our strategy, however, does
not take into account the other anatomical changes that occur between fractions, such
as differences in rectal and bowel filling, whereas a strategy based on CBCT does have
this potential. Our strategy also requires a substantial difference between a full and an
empty bladder. When such a difference is not present, an adaptive strategy based on the first CBCTs could be beneficial. In addition, the workflow before treatment is currently quite elaborate and takes 5 hours additional treatment planning compared to the non-adaptive procedure.

Considering the minor differences found, and the increase in workflow for our daily plan selection strategy, an adjustment to the strategy could be proposed by using fewer plans, for example by combining the 0% and 33% plans. This will reduce the workload, render plan selection during treatment easier, and is likely to yield similar dosimetric results.

Our adaptive strategy employs a full bladder protocol with a tumor boost. Using a partial bladder boost reduces morbidity related to irradiation of the uninvolved bladder [125]. To also limit the risk of focal bladder toxicity, the area receiving the boost dose should be as small as possible. We showed that irradiating with a full bladder will spare the healthy bladder. However, compared to an empty bladder protocol, the dose to the bowel cavity will increase due to the larger treatment volume [32], which will mainly affect V2Gy. We showed that V2Gy decreases using ART, therefore the need for an adaptive strategy increases when a full bladder protocol is chosen.

Conclusion

Irradiating with a full bladder spares the healthy bladder from the boost dose, and by using an adaptive strategy the increased dose to the bowel cavity can be counteracted. Compared to a non-adaptive strategy, we found a similar coverage for bladder and an improved coverage for lymph nodes, but OAR sparing was limited, with a significant reduction in bowel cavity V30Gy and V40Gy only.
Supplementary materials

**Supplementary table:** Magnitude and direction of additional isocenter shifts performed after registration on bony anatomy for the plan selection. Shifts were performed in 74 of 196 evaluated fractions (37.8% of fractions), to obtain maximum tumor coverage.

<table>
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</tr>
<tr>
<td>Anteroposterior</td>
<td>2.3</td>
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Supplementary figure 1: OAR analysis of all separate fractions from all patients. Differences in volumes receiving the fractionated substitutes of 10, 30 or 40 Gy for small bowel and rectum. A difference smaller than zero (reference line) indicates that more volume is spared for the ART strategy. The rectum is spared most when the 0% and 33% plans are selected. For small bowel, the intermediate and high dose areas decrease most when the 0% and 33% plans are chosen. The low dose area, however, increases when smaller plans are chosen. For the non-adaptive strategy, in case of empty bladder volumes, the plan is often shifted inferiorly to match the tumor markers (data not shown). This shifts the low dose area outside of the small bowel volume, resulting in more low dose bowel sparing for the non-adaptive strategy.
Supplementary figure 2: Tumor locations were divided into mostly dorsally located, mostly cranially located and other locations. It was analyzed whether the sparing from the elective dose (40 Gy, i.e. 2 Gy per fraction) in the small bowel and rectum was different for these different locations, using a Wilcoxon signed-rank test. We only found differences for the small bowel, as depicted in this figure. It shows the difference in volume receiving 2 Gy for the adaptive, minus the non-adaptive strategy. The horizontal line represents the median, the box represents the first and third quartile. Whiskers extend to 1.5 times the interquartile range from the box and the dots represent outliers. Significant differences ($p < 0.05$) are indicated with an asterisk, however, these are based on a small sample size. Nevertheless, it does indicate that sparing from the elective dose is different for more dorsally located tumors, which implies that tumors located dorsally have the potential to benefit more from ART.