

ORIGINAL ARTICLE

The normal tissue sparing obtained with simultaneous treatment of pelvic lymph nodes and bladder using intensity-modulated radiotherapy

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Abstract

Background. We have implemented an intensity-modulated radiotherapy (IMRT) protocol for simultaneous irradiation of bladder and lymph nodes. In this report, doses to normal tissue from IMRT and our previous conformal sequential boost technique are compared. **Material and methods.** Sixteen patients with urinary bladder cancer were treated using a six-field dynamic IMRT beam arrangement delivering 60 Gy to the bladder and 48 Gy to the pelvic lymph nodes. Dose-volume histogram (DVH) parameters for relevant normal tissues (bowel, bowel cavity, rectum and femoral heads) for the IMRT plans were compared with corresponding DVHs from our previous conformal sequential boost technique. Calculations of the generalized Equivalent Uniform Dose (gEUD) were performed for the bowel, with a reference volume of 200 cm³ and a volume effect parameter k=4, as well as for the rectum, using k=12. Acute gastrointestinal (GI) and genitourinary (GU) RTOG toxicity was recorded. **Results.** Statistical significant normal tissue sparing was obtained by IMRT. For the bowel, a significant reduction was obtained at all dose levels between 20 and 50 Gy (p < 0.05), e.g. from 180 to 121 cm³ at 50 Gy, while the gEUD was reduced from 58 to 53 Gy (p < 0.05). Similar patterns were seen for the bowel cavity. For the rectum, IMRT reduced the maximum dose as well as the volumes receiving more than 50 and 60 Gy (p < 0.05), e.g. from 72 to 48 cm³ at 50 Gy. The rectum gEUD was reduced from 55 to 53 Gy (p < 0.05). For the femoral heads, IMRT reduced the maximum dose as well as the volumes above all dose levels. The rate of acute peak Grade 2 GI RTOG complications was 38% after IMRT. **Conclusion.** IMRT to the urinary bladder and elective lymph nodes result in considerable normal tissue sparing compared to conformal sequential boost technique. This has paved the way for further studies combining IMRT with image-guided radiotherapy (IGRT) in bladder cancer.

The main challenge in radiotherapy (RT) is to deliver a tailored high radiation dose to the tumour while minimizing irradiation to surrounding healthy tissue. Recent technological development has considerably improved our possibilities to individualize RT dose distributions to match the 3-D tumour shape [1]. A major technological solution within this field, intensity-modulated RT (IMRT), applies beams with varying intensity across the fields. IMRT has shown great potential to spare normal tissue and to ensure tumour coverage and thus enable tumour dose escalation, also in bladder cancer [2–5].

Treatment outcome using traditional conformal RT of bladder cancer is modest [6]. In a study from

Aarhus University Hospital, the 5 year overall survival and local control was 21 and 37%, respectively. Furthermore, considerable acute and long term side-effects were observed [7,8]. Efforts to improve treatment plans have therefore been considered, with special focus on normal tissue sparing, in particular for the bowel and rectum. Because of considerable internal movement of the bladder, large safety margins around the clinical target volume are required. Consequently, this results in large volumes of normal tissues included in the high dose region. Detailed studies on bladder filling and interfractional movement of the bladder have enabled us to implement an anisotropic margin [9,10]. To safely reduce the margins, individualized

margins based on image-guided strategies have been explored [11].

As a starting point for our image-guided IMRT activities, we have implemented an IMRT protocol for simultaneous treatment of the bladder and the lymph nodes. The present study evaluates the normal tissue sparing effect of IMRT in comparison to a conventional sequential boost 3-field box technique which was previously the standard for RT of bladder cancer in our department.

Materials and methods

Patient material

Between June 2007 and February 2008, 16 consecutive patients were treated with IMRT for bladder cancer at Department of Oncology, Aarhus University Hospital. Diagnostic workup, staging and examination for metastatic disease including CT of the abdomen and CT or conventional x-ray of the thorax were performed in all patients. The patients had T2-T4a N0M0 disease and were considered inoperable due to severe co-morbidity. The mean age was 70 years (range 51–79) and the majority of patients were men. Patient and tumour characteristics are shown in Table I.

Dose planning CT and definitions of targets and organs at risk

Patients were immobilized in supine position using a heel and knee fixation system. The CT scans were performed using a spiral scanner (Siemens Somatom Plus 4) with 3 mm slice thickness (6 mm/s) and reconstructed with 512×512 pixels and 3 mm interslice distance. Before CT planning and treatment the patient was instructed to empty the bladder. Delineation was performed in collaboration between a radiation oncologist and a diagnostic radiologist by use of the Eclipse treatment planning system (Varian

Oncology Systems, Palo Alto, CA, USA). Two planning target volumes (PTV) were contoured: PTV1 included the bladder with margins and PTV2 included both the bladder and lymph nodes with margins. The bladder included bladderwall as well as its content. The lymph nodes were contoured from the level of the promontory, with the internal iliac included to the obturator fossa and the external iliac to the level of the femoral heads. Para-rectal and pre-sacral lymph nodes below the sacro-iliac joint were excluded. An-isotropic wide margins were used around the bladder to account for the considerable geometrical uncertainties present in bladder cancer (superior 25 mm, inferior 15 mm, lateral 20 mm, anterior 25mm and posterior 20mm) whereas a uniform 10 mm margin was added between the lymph nodes and the PTV2 to account for delineation and geometrical uncertainties. Electronic portal images were acquired at setup of the first treatment, and repeated whenever required according to a standard protocol. Daily image-guidance was not performed.

Organs at Risk (ORs) (bowel, bowel cavity, rectum and femoral heads) were contoured. The bowel volume included all segments of contrast and non-contrast enhanced small intestine and colon as seen on the planning scan (superior border 12 mm above the PTV2). For the rectum, the recto-sigmoid flexure was applied as the superior/cranial limit and the anal verge as the inferior/caudal limit. Both the bowel and rectum were outlined as wall with contents. The femoral heads were outlined from the most cranial part to the inferior part of minor trochanter on both sides.

Field arrangements and optimization criteria

An IMRT plan with simultaneous integrated boost delivering 48 Gy to PTV2 and 60 Gy to PTV1 in 30 fractions (2 Gy daily fractions, 5 days a week) was used for all patients. A six-field beam arrangement with standard gantry angles of 45° , 82° , 168° , 192° , 278° , 315° was applied for all patients using 15 MV photon beam. A collimator angle of 5° was used for all beam to reduce tongue-and-groove effects. Patients were treated on Varian Clinacs equipped with the Millennium MLC-120 multi leaf collimator (MLC). Intensity-modulation was obtained using the sliding window technique.

Treatment planning and optimization were performed in ARIA (Varian Oncology Systems, Palo Alto, CA, USA) using locally defined clinical protocols including structure templates, field arrangement, prescription and optimization criteria. Four virtual volumes were defined for optimization purposes: oPTV60, oPTV48, oBowel and oRectum. The

Table I. Patient characteristics.

Gender (female/male)	4/12
Mean age (years)	70 (50–79)
Clinical stage	
T1	0
T2	10
T3	4
T4	1
Tx	1
Total no. of patients	16
Planning CT scans	
Mean bladder volume (cm ³)	208 (70–413)
Mean bowel volume (cm ³)	514 (164–1079)
Mean rectal volume (cm ³)	121 (32–276)

oPTV60 was a copy of PTV1 reduced with 5 mm from the skin surface. The oPTV48 was a copy of PTV2 reduced with 5 mm from the skin surface and oPTV60 subtracted so that only one dose level was prescribed to the volume. The oBowel was defined as the content of the bowel more than 5 mm from PTV1 and PTV2 in the cranio-caudal extension of the PTV1 and PTV2. The oRectum was the part of rectum with at distance of more than 8 mm from PTV2. PTV constraints were hard whereas the constraints on the rectum, oRectum and oBowel were soft.

The mean dose to PTV1 was normalised to 60 Gy. The optimisation strategy was to increase the priorities to oPTV60 and oPTV48 until at least 99% of PTV1 were covered by 95% of 60 Gy and at least 99% of PTV2 were covered by 95% of 48 Gy while keeping the global maximum less than 107% of

60 Gy. Next, the soft constraints to oBowel and oRectum were modified until the 50 Gy isodose line never circumscribed the whole circumference of the rectum at any CT-slice and $V_{35\text{ Gy}} < 20\%$ for the bowel without violating the target coverage. A smoothing factor of 60 was used for all fields.

For the purpose of this study, patients were re-planned with the traditional sequential boost 3-field box technique using two opposing lateral fields and one anterior field (gantry angles 90° , 270° , 0°) using 15 MV photon beams. Fields were individually shaped with MLCs. Margins and constraints to targets and ORs were the same as for the original treatment plan. The prescribed dose to the PTV2 was 46 Gy in 23 fractions followed by a sequential boost to the PTV1 of 14 Gy in 7 fractions (2 Gy daily fractions, 5 days a week).

Analysis of dose-volume histograms

DVH parameters (in 10 Gy steps) were derived for bowel, bowel cavity, rectum and femoral heads as well as median dose, dose to specified percent volume of PTVs (e.g. near minimum $D_{98\%}$, near maximum $D_{2\%}$) and standard deviation of the dose to the PTVs. Since PTV2 encompasses PTV1 in the IMRT treatment plan, we subtracted the PTV1 volume in the analysis of PTV2 related parameters. IMRT DVH parameters were compared with corresponding DVH parameters resulting from the summed plans of our previous conformal sequential boost technique.

Calculations of the bowel generalized Equivalent Uniform Dose (gEUD) were performed to supplement the comparisons of the DVHs for the IMRT and CRT technique. Bowel gEUDs were also

calculated for CRT plans with a prescribed dose to the PTV1 of 60 Gy and 64 Gy, respectively. For the bowel, we followed the method by Hysing et al., extending the Niemierko EUD equation by introducing an absolute reference volume, V_{ref} , and by replacing the volume fraction with the absolute volume at the i^{th} differential DVH dose bin [12,13].

$$gEUD = \left(\frac{1}{V_{ref}} \sum_i v_i D_i^k \right)^{\frac{1}{k}}$$

A volume dependency parameter $k=4$ and a $V_{ref} = 200\text{ cm}^3$ was used for the bowel [14]. For the rectum, the standard gEUD equation was used (with fractional volumes) and with $k=12$ [15]. The choice of parameters (k -value, V_{ref}) for the different ORs in the extended Niemierko formula (gEUD) was derived from available literature to make comparison with similar studies feasible.

To describe the homogeneity of the dose distribution of the plans, we calculated the Homogeneity Index (HI) [16].

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{median}} \times 100\%$$

Finally, to compare the conformity of the various plan alternatives, the Dice Similarity Coefficient (DSC) was calculated [17]. Treated volume (TV) was the volume enclosed within the 95% isodose level.

$$DSC = \frac{(PTV1 \cap TV_{95\%})}{(PTV1 \cup TV_{95\%})}$$

Scoring of toxicity

Acute toxicity was evaluated retrospectively from patient charts using the Radiation Therapy Oncology Group (RTOG) scoring system [18], to grade peak lower gastrointestinal (GI) and genitourinary (GU) morbidity before, during and at the last day of treatment. Patients were scheduled for regular assessments of toxicity during the course of therapy. Anal symptoms were scored using the modified scoring system of Koper et al. [19] together with the GI score. First cystoscopy follow-up was scheduled 3 months after RT.

Results

Normal tissue DVHs

Using IMRT we obtained considerable normal tissue sparing (Table II). For the bowel, a statistical significant reduction was obtained at all dose levels

Table II. Mean volume of organs (OARs) at risk receiving step-vice increased radiation doses.

	Bowel		Bowel cavity		Rectum		Femoral heads	
	CRT	IMRT	CRT	IMRT	CRT	IMRT	CRT	IMRT
Vol. >10 Gy (cm ³)	425	458*	1108	1179*	118	115*	271	245*
Vol. >20 Gy (cm ³)	394	356*	1024	930*	115	105	248	192*
Vol. >30 Gy (cm ³)	329	263*	882	704*	96	103	230	123*
Vol. >40 Gy (cm ³)	270	201*	713	554*	87	81	85	24*
Vol. >50 Gy (cm ³)	170	121*	465	319*	72	48*	14	1*
Vol. >60 Gy (cm ³)	44	43	123	100	14	4*	–	–
Max dose (Gy)	63	63	63	63	61	61*	57	52*
gEUD (Gy)	58	53*	–	–	55	53*	–	–

Data are means (range).

*p-value from the paired two-sided nonparametric Wilcoxon-signed rank test. A $p < 0.05$ was considered statistically significant.

between 20 and 50 Gy ($p < 0.05$), e.g. from 180 to 121 cm³ at 50 Gy. Similar patterns were observed for the bowel cavity, e.g. a reduction from 465 cm³ to 319 cm³ at 50 Gy ($p < 0.05$). For the rectum, IMRT reduced the maximum dose as well as the volumes receiving more than 50 and 60 Gy ($p < 0.05$), e.g. from 72 to 48 cm³ at 50 Gy. For the femoral heads, IMRT reduced the maximum dose as well as the volumes above all dose levels. Figure 1 illustrates an iso-dose distribution comparing CRT and IMRT in one patient. This demonstrates the

ability of IMRT to deliver a high dose to the PTV1 and PTV2 while sparing the surrounding healthy tissue, in particular the bowel.

Normal tissue EUDs

Use of IMRT instead of the sequential boost CRT technique reduced the average bowel gEUD from 58 to 53 Gy ($p < 0.05$). Calculation on the CRT plan treating the bladder (PTV1) alone resulted in an average bowel gEUD of 52 and 55 Gy for a

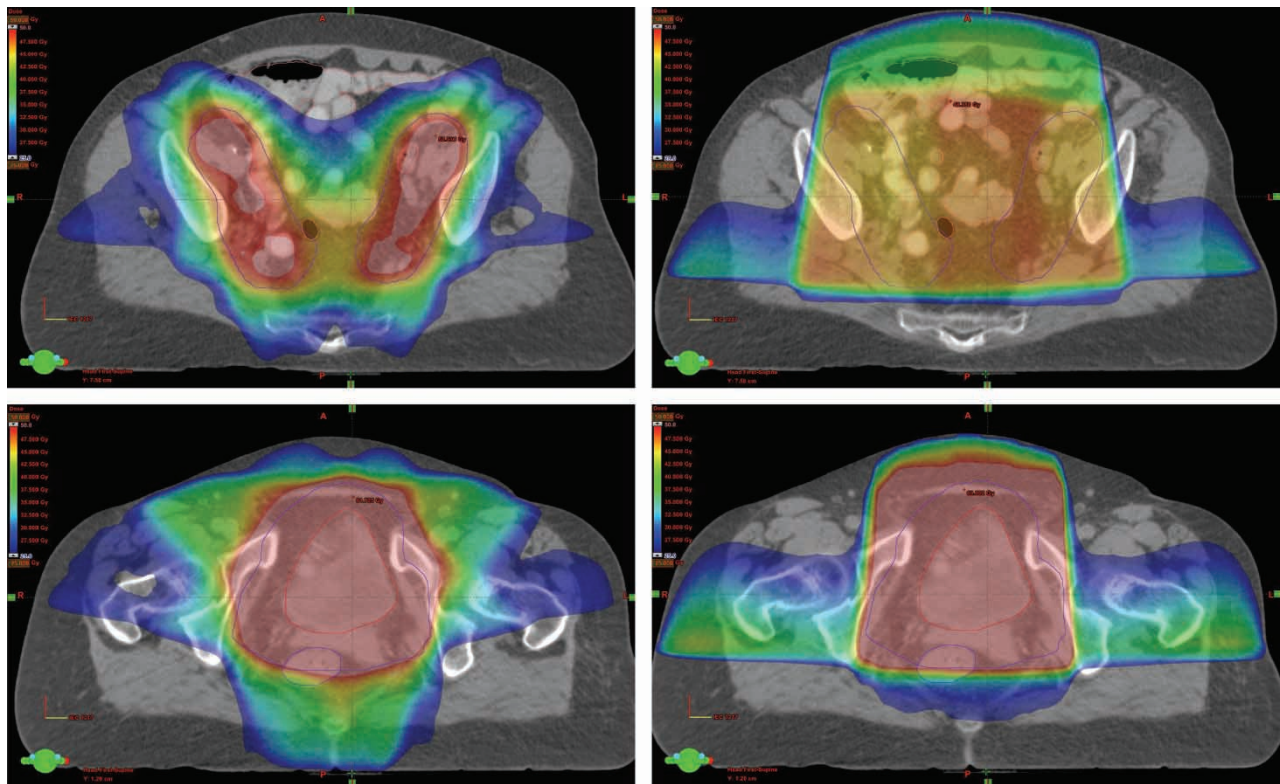


Figure 1. Example of a treatment plan for RT of bladder cancer including the lymph nodes with IMRT (left) and the summed sequential CRT (right) in the upper (upper) and lower (lower) pelvis. Target volumes shown in red, intestine in pink, bladder in yellow and rectum in blue. Dose colour wash is from 25 Gy (dark blue) to 50 Gy (red).

prescription dose of 60 and 64 Gy respectively. For the rectum, the average gEUD was reduced from 55 to 53 Gy using IMRT instead of CRT ($p < 0.05$).

We found no correlation between the reductions in bowel gEUD and individual planning parameters such as bladder volume, the volume overlap between bowel and PTVs or the ratio between high- and low-dose PTV.

Target coverage

IMRT and CRT were similar with respect to the average dose homogeneity, standard deviation of the dose, median, D2% and D98% doses for the PTV1. However, IMRT showed improved DSC compared to CRT (from 0.62 to 0.88, $p < 0.05$). In PTV2, the prescription dose differed (e.g. IMRT 48 Gy, CRT 46 Gy), and still the use of IMRT reduced the average median dose from 52.5 to 49.6 Gy ($p < 0.05$). The average homogeneity index was improved from 29% to 22% ($p < 0.05$), the average D2% from 60.8 to 57.5 Gy ($p < 0.05$) and the average standard deviation of the dose decreased from 4.6 to 2.8 Gy ($p < 0.05$). No difference in D98% was observed for PTV2 between IMRT and CRT treatment plans.

Acute effects

Acute Grade 2 GI effects were reported by 6 of 16 patients (38%), while Grade 1 was the highest GI adverse effect in 6 patients (38%). No Grade 3-4 GI toxicity occurred. None of the patients had GI symptoms before start of RT. The symptoms generally consisted of increased frequency of bowel movement and change in stool consistency (diarrhea). Four patients (25%) did not experience any GI adverse effects during treatment. Acute Grade 2 GU toxicity were reported by 8 (50%), while Grade 1 was the highest GU toxicity reported by 7. One patient experienced Grade 3 GU toxicity because of the need for a urinary catheter. 50% of the patients with a peak Grade 2 or higher toxicity score had the same toxicity score before start of RT. The GU symptoms generally consisted of increased urinary frequency and dysuria.

Discussion

In this report we have presented our planning procedures as well as our early clinical experiences from a study of integrated bladder and lymph node IMRT. The main finding was that use of IMRT reduced the doses and gEUD to important ORs such as the bowel and rectum. At the same time, target conformity and homogeneity were improved. The

early clinical outcome in terms of acute toxicity was also promising.

In this study the regional lymph nodes were included in the treated target volume, due to high risk of lymph node metastasis. In patients treated by radical cystectomy, metastases to the lymph nodes were observed in 30%, increasing with tumour stage [20]. However, inclusion of the lymph nodes is not standard treatment in all countries and has never been tested in a randomized setting. Limited evidence exists on the performance of integrated IMRT for bladder and lymph nodes in terms of DVH dosimetrics and gEUD of the OARs. Most studies evaluating normal tissue sparing of IMRT versus CRT in the pelvis have been performed on prostate cancer. In a study by Muren et al., IMRT reduced the volume of intestine receiving more than 40 Gy from 139 to 89 cm³ and 50 Gy from 81 to 19 cm³, no Grade 3 toxicity and only 28% of patient's experienced Grade 2 GI toxicity [21]. Similar results were observed in a study from Ashman et al., were 13 of 27 prostate patients received IMRT to the regional lymph nodes (prescription dose 45 Gy). The volume of intestinal dose over 45 Gy was reduced from 23 to 9% and only one patient experienced acute Grade 2 GI toxicity [22].

The present study demonstrates a statistical significant reduction in gEUD for the bowel (from 58 to 53 Gy) and rectum (from 55 to 53 Gy). In a comparable study by Hysing et al. on prostate cancer where the target also included the regional lymph nodes, the gEUD using IMRT was 40 Gy and 46 Gy for the bowel and rectum, respectively [13]. The difference in gEUD between our study and the study by Hysing et al. reflects the different volumes of normal tissue included in the PTV for prostate and bladder RT, respectively. We also showed that a dose of 60 Gy prescribed to the PTV1 using CRT resulted in a bowel gEUD of 52 Gy, which compares well with that achieved by an IMRT plan covering both the PTV1 and PTV2 (gEUD 53 Gy). In terms of gEUD to the bowel, the lymph nodes can therefore be included as a secondary target at the expense of a 1 Gy increase in gEUD. It should, however, be mentioned that the gEUD calculations presented do not take the fractionation effects of simultaneous integrated boost (SIB) IMRT into account [23]. The actual normal tissue sparing of SIB IMRT when also including fractionation effects could therefore be even larger.

The acute toxicity presented in our study is limited by the small number of patient's and the short follow-up. Consequently, comparison with previous studies could be misleading. However, the results are encouraging since the acute GI toxicity is at least comparable to toxicity observed in a study

on conformal RT of bladder cancer were only the bladder was the target [24]. IMRT may allow the inclusion of the lymph nodes without increasing the acute toxicity as suggested in a study on treatment of prostate cancer [25].

In the present study, treatment planning as well as calculation of dose volume parameters to ORs was based on a single snap-shot dose planning CT scan. However, it is well known that the ORs, and especially the bowel will change position between treatment fractions [26]. In the study by Hysing et al., the IMRT sparing of the bowel and rectum persisted when the intra-fractional movements were analyzed on repeated CT scans [13]. Because of limited accuracy and definition of the targets and ORs, comparison with other studies is difficult, and the correlation between gEUD and clinical outcome may be problematic. Therefore, clinical studies with careful follow-up on tumour control, survival and toxicity outcomes using standardized scoring system along with data on the treatment plans are warranted.

The use of daily image guidance with on-board target correction may allow us to reduce the margins. A study by Redpath et al. using an image-guided RT (IGRT) strategy with setup correction of translational errors, demonstrated that this technique allowed a reduction of the safety margin around the bladder [11]. IGRT not only allow correction of setup-errors based on bone or soft tissue, but could also be used in an online/offline adaptive strategy where treatment is re-planned or adjusted according to the immediate position and conformity of the targets and OARs. With daily isocenter correction, it was possible to half the volume of OAR included by the PTV (Wright, P – personal communication). Using cone-beam CT and online adaptive RT strategies in bladder cancer may allow reduction of target margin and minimize the high dose volume to the OARs considerably [27,28].

We are currently developing strategies for adaptive RT of bladder cancer which includes a boost to the tumour. To visualize the tumour we are evaluating tumour demarcation using contrast enhancement with injection of Lipiodol into the bladder wall. This may allow on-line corrections based on actual tumour position.

In conclusion, a simultaneous treatment approach of bladder and lymph nodes using IMRT results in considerable sparing of the bowel and the rectum. Studies combining IMRT with image-guidance in bladder cancer, including adaptive strategies may allow us to reduce margins with subsequent increase of radiation dose. This may result in improved local control with the lowest possible toxicity.

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