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ORIGINAL ARTICLE

External beam radiotherapy of bladder carcinoma: considerations in determining the irradiation field margins

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Summary

Purpose: *Motions of the bladder and rectum during pelvic irradiation are considered as major causes of geometrical uncertainties. As a result, the volume status of these organs is changed and the definition of the treatment margins is imperative. The aim of this study was, firstly, to determine these margins, comparing series of CT scans, performed at simulation time, with empty (EB) and full bladder (FB) and, secondly, to evaluate the dose volume histograms (DVHs) of tumor and rectum using standard treatment margins.*

Methods: *Fifteen patients with muscle-invading urinary bladder carcinoma underwent two scan series with EB and FB bladder during radiotherapy (RT) simulation. Gross tumor volume (GTV), clinical target volume (CTV), planning treatment volume (PTV) and organs at risk (OAR) were contoured. Displacements of the bladder wall were determined at all directions. Cumulative DVHs were generated for the volumes of interest. Using the same beam arrangements for both the EB and FB CT series, DVHs were also produced.*

Results: *The mean bladder volume was 119.3±55.9 cm^3 and 264.3±145.7 cm^3 for EB and FB CT series, respectively ($p < 0.001$). The maximum bladder wall displacement was observed at cranial direction (2.2±0.6 cm for the EB vs. 3.4±1.0 cm for the FB series; $p < 0.001$) and at caudal direction (2.3±0.6 cm for the EB vs. 3.6±1.0 cm for the FB series; $p < 0.001$). Standard anisotropic margins of 2 cm in craniocaudal and posterior-anterior directions and 1.2 cm in lateral direction gave coverage to 75% of all bladder movements caused by FB. Analysis of DVHs and tumor control probability (TCP) calculations gave same results (74%), while normal tissue complication probability (NTCP) of the rectum showed no significant changes.*

Conclusion: *CT scans series with empty and full bladder, performed at simulation time, could offer a potential advantage to evaluate the target expansion necessary to cover the bladder wall for each patient, giving more information about safe margining.*

Key words: bladder cancer, margin widths, radiotherapy, treatment planning, tumor motion

Introduction

External beam radiotherapy (EBRT) plays an important role in the management of muscle-invading bladder cancer, given that contraindications for cystectomy (e.g. old age, heart disease and general arteriosclerosis) are frequently observed among bladder cancer patients [1,2]. The majority of studies on organ motion and patient positioning accuracy in pelvic irradiation have focused on prostate irradiation and only a few studies have investigated patients with bladder cancer [3,4].

In RT of bladder cancer, the various organ positions create special problems. The bladder is a mobile and hollow organ that varies in volume and position because of differences of its filling status [5]. This potentially leads to spatial variability of the tumor site and, as a consequence, may lead to errors throughout the course of RT, resulting in tumor under- or overdosing [6].

The use of inadequate treatment margins (i.e. causing geographical misses) in bladder irradiation has been shown to compromise the overall survival [7].

Bladder motion has usually been measured in patients planned and treated with an empty bladder, and in the most recent studies, this motion has been measured in relation to bony anatomy [5].

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Methods for quantification of organ motion include primarily CT scanning, ultrasound imaging and MRI [8]. CT scan remains the most useful imaging modality in RT, and has adequate soft tissue contrast for contouring and RT treatment planning. In previously published studies, paying attention to organ motion during EBRT for bladder cancer, anisotropic margins of 1.2 - 2.3 cm were necessary to encompass all bladder displacements [9]. The rectum and surrounding small bowel are OAR included in the treatment fields of bladder carcinoma so the dose that they receive must be minimized to reduce adverse effects. This leads to additional planning considerations for determining the irradiation field margins to be used during pelvic RT for muscle-invading bladder carcinoma.

The aim of this study was, firstly, to determine these margins, comparing series of CT scans, performed at simulation, with EB and FB and, secondly, to evaluate the DVHs of tumor and rectum using standard treatment margins.

Methods

Patient selection

Between March and August 2008, 15 patients (13 male and 2 female, aged 73.4±7.6 years) with muscle-invading transitional cell bladder carcinoma were included in this study. All patients provided written consent before entering the study.

CT procedure

A dedicated CT simulator (Siemens Somatom Sensation Open) was used to generate all scans. All patients underwent two scan series during RT simulation at the Department of Radiotherapy, University Hospital of Ioannina, Greece. At first, patients were invited to void the bladder and a CT scan with EB was obtained for every patient. Afterward, they were instructed to drink enough water and to refrain from voiding the bladder about 2 hours before a new CT scan with FB was carried out. No special protocol (i.e., drinking a certain amount of fluid a certain time before the CT scan) was applied. The feeling of the patient to have a FB was the single relevant criterion before the FB CT scan.

All CT scans were acquired in supine position using a leg immobilisation device, the slice thickness was 5 mm and the distance between the centres of the slices was 5 mm. No bowel or intravenous contrast enhancement was used.

Organ definition

All CT images were transferred to a virtual simulation workstation (Siemens, Vsim) and GTV, CTV and PTV were outlined. The GTV consisted of the tumor in the bladder. The CTV was defined as the whole bladder while standard non-isotropic margins of 1.2 cm laterally and 2.0 cm anterior-posterior and cranial-caudal were used to generate the PTV, as described elsewhere [5].

At all acquired slices the OAR, i.e. the rectum, was also contoured using the definition applied in a range of recent publications (superior/cranial limit: first slice below the recto-sigmoid flexure, inferior/caudal limit: first slice above the anal verge), including the rectal wall and the rectum contents [10]. The anatomy, size and internal mobility of the intestine makes this organ difficult to handle. The intestine was not contoured.

Bladder wall displacement

Displacements of the bladder wall were determined at the anterior, posterior, cranial, caudal, and lateral borders. The FB CT series were compared to the respective EB CT series. Anterior-posterior and cranial-caudal displacements were measured in the mid-sagittal plane. The lateral displacements were determined in the mid-axial plane. All displacements were presented as distances from a standard reference point (i.e. the isocenter) to the bladder wall border. The isocenter point was kept stable in the FB and EB CT series.

Treatment planning and generation of dose volume histogram

A standard four-field box technique with 6 MV photons was used to deliver 2 Gy per fraction to the isocenter. The total prescribed dose was 64 Gy. Field weights, use of beam wedges, beam modulation and arrangement were chosen to satisfy the ICRU 50 recommendations. All calculations were made using a Pinnacle (Philips Medical Systems, Andover, MA) commercial treatment planning system.

Cumulative DVHs were generated for the CTV, PTV and the rectum volumes corresponding to the EB and FB volumes. Using the exact beam arrangements for both the EB CT series and the FB CT series, DVHs were also produced.

Tumor control probability (TCP) calculation

To calculate the TCP, the fractional volume for each DVH bin is initially computed by dividing the bin

volume by the total DVH volume. The TCP for the bin is computed based only on the dose level for the bin. The current TCP value is multiplied by the returned TCP raised to a power equal to the fractional volume, according to the following equation:

$$TCP_{(DVH)} = \prod_i TCP(dose_i)^{+vol_i}$$

This model obligates the following tumor response parameterisation to deliver TCP predictions: D_{50}, the mean tumor dose giving 50% tumor control and m, a slope factor defined as $m = \frac{1}{\sqrt{2\pi} \cdot \gamma_{50}}$, where γ_{50} is the maximum normalized gradient of the tumor control response curve. The model parameters for the bladder used for this study are given in Table 1 [11].

Normal tissue complication probability (NTCP) calculation

NTCP calculation for non-uniformly irradiated volumes is based on the histogram reduction method described by Kutcher et al. [12].

According to this method, the volume of the non-uniformly irradiated structure is reduced to an effective volume of a uniformly irradiated structure. The effective volume is computed using the following equation:

$$Vol_{eff} = \frac{1}{Vol_{ref}} \sum Vol_i \cdot \frac{D_i^{1/N}}{D_{\max}},$$

where Vol_i is the volume of the DVH bin i, D_i is the dose for the DVH bin i, N is the volume factor and Vol_{ref} is the reference volume (typically the DVH volume). The NTCP is then calculated using the following equation:

$$NTCP(dose, volume) = 0.5 + \frac{erf(t/\sqrt{2})}{2},$$

where $t = \frac{[Dose - Dose50(volume)]}{[m \cdot Dose50(volume)]}$,

$Dose50(volume) = D50 \cdot volume^{-N}$, N the volume factor for the structure, D_{50} is the dose at 50% probability of complication of the structure, m is the slope factor, $m = \frac{1}{\sqrt{2\pi} \cdot \gamma_{50}}$, where γ_{50} is the maximum normalized gradient of the normal tissue complication probability response curve, *Dose* is the maximum dose anywhere in the structure and *volume* is the effective volume. The parameters that are necessary to compute the NTCP for the rectum are listed in Table 2 [13].

Table 1. Parameters applied for calculation of tumor control probability for the bladder [11]

Model parameter	*Parameter value*
D_{50} (Gy)	63.2
γ_{50}	2.1
m	0.19

For abbreviations see text (methods)

Statistical analysis

All continuous variables are presented as the mean ± standard deviation, unless stated otherwise. All comparisons were made using matched pair t-test, after confirming the normal distribution of the compared variables. All p-values reported were two-sided and $p<0.05$ was considered statistical significant.

Results

Bladder and rectal volumes

For each individual patient the bladder and rectum volumes measured on EB and FB CT series are illustrated in Figures 1 and 2, respectively. The mean values of bladder, PTV and rectal volumes are listed in Table 3. The mean bladder volume was 119.3±55.9 cm^3 and 264.3±145.7 cm^3 according to EB and FB CT series, respectively ($p<0.001$). Rectum volume was

Table 2. Parameters applied for calculation of normal tissue complication probability for the rectum [13]

Model parameter	*Parameter value*
D_{50} (Gy)	80
γ_{50}	2.66
M	0.15
N	0.12

For abbreviations see text (methods)

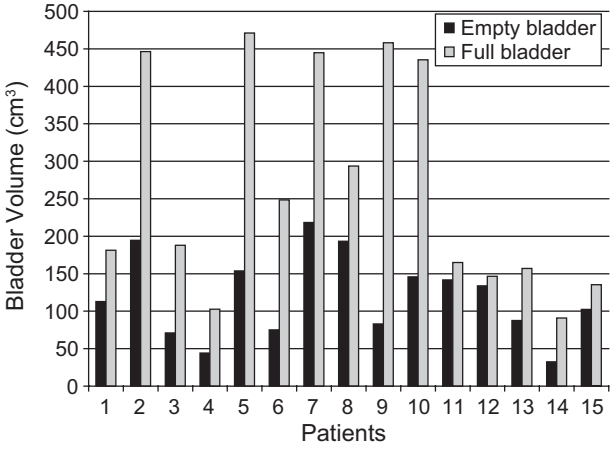

Figure 1. Full and empty bladder volumes.

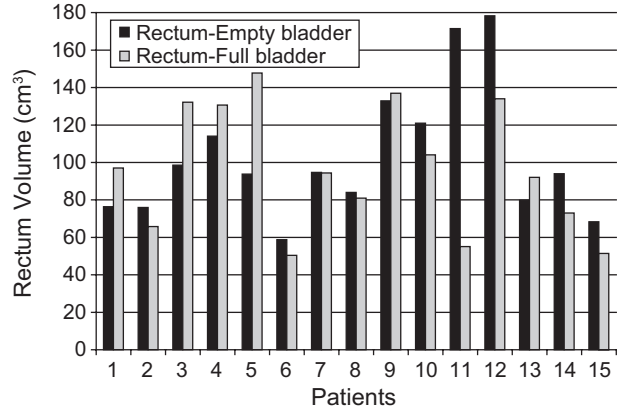

Figure 2. Rectum volumes with full and empty bladder.

Table 3. Clinical target volume, planning target volume and rectum volume in empty and full bladder CT series

Parameter (cm^3)	*Empty bladder*	*Full bladder*	*p-value*
Bladder	119.3±55.9	264.3±145.7	<0.001
Planning target volume	414.1±126.9	689.6±259.5	<0.001
Rectum volume	102.8±35.3	96.4±33.6	0.53

102.8±35.3 cm^3 for EB CT series, and 96.4±33.6 cm^3 for the FB CT series (p=0.53). Despite the fact that similar drinking instructions were given to all patients, bladder variations were observed in the majority of patients. The difference in bladder volume fillings in

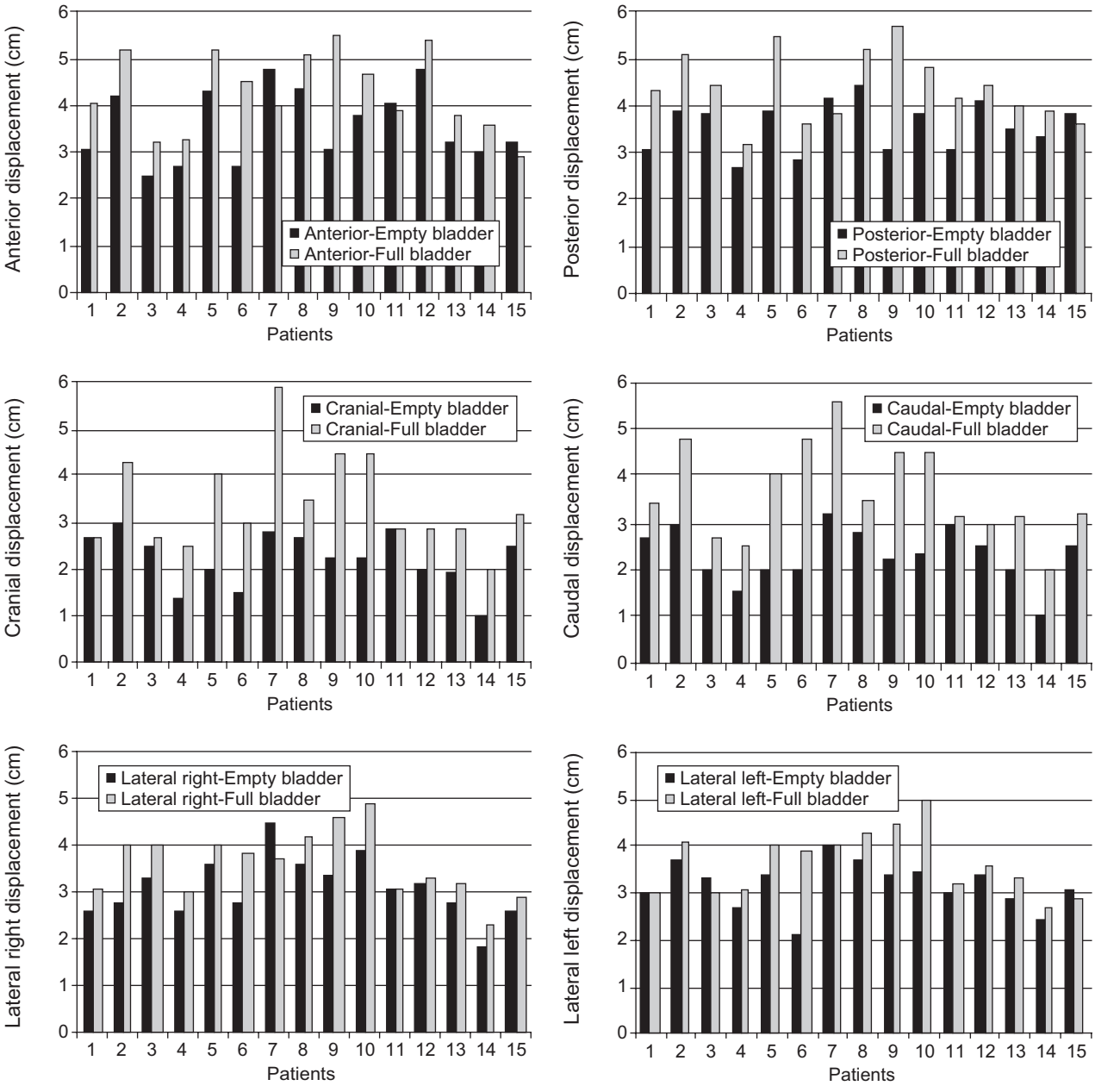

Figure 3. Bladder wall displacements with full and empty bladder.

patients numbered as 1, 11,12 and 15 was less than 30%. In all but one patient (no. 11), no statistically significant differences were observed in rectum volume variations.

Bladder wall displacement

Figure 3 illustrates differences in distances from the standard isocenter point to the bladder wall concerning the anterior-posterior, cranial-caudal, lateral right-left borders, in EB and FB CT series for each patient. Apart from one patient (female, no. 9) all displacements in anterior-posterior direction were less than 2 cm. In the cranial direction we observed displacements that were higher than 2 cm in 3 patients and in caudal direction in 4 patients. In the lateral direction, all but one displacements were less that 1.2 cm (no 10. left lateral).

Table 4 shows the mean anterior-posterior and cranial-caudal distances for mid-sagittal plane, as well as the lateral right-left distances for mid-axial plane. The maximum bladder wall displacement was observed at cranial direction (2.2±0.6 cm for the EB series vs. 3.4±1.0 cm for the FB series; $p<0.001$) and at caudal direction (2.3±0.6 cm for the EB series vs. 3.6±1.0 cm for the FB series; $p<0.001$).

Dose volume histograms

DVH were produced for all EB and FB CT series. Figure 4 illustrates typical DVHs for the PTV, CTV and rectum for all beam arrangements used. DVH CTV and PTV dosimetric data were similar for EB and FB series. The mean DVH rectum dose was lower when bladder was emptied (Table 5, EB: 129.6±22.2 cGy/fraction vs. FB: 146.6±25.8 cGy/fraction; p=0.001).

According to the CT series planned with EB the TCP was lower (Table 6, EB: 53.9±1.2% vs. FB 55.2±1.8%; p=0.003). However, the NTCP for FB was higher than the NTCP for EB (EB: 1.6±2.2% vs. FB 3.7±3.3%; p=0.002).

When beam arrangements selected for EB CT series were used for FB CT series the TCP was 51.8±2.8 (p=0.011 vs. EB and p=0.001 vs. FB). Assuming that the status of the bladder is empty at simulation and full bladder is the extreme bladder position, TCP comparison between EB and FB using EB beam arrangement are illustrated at Figure 5. We observed that in patients no.5, 7, 9 and 10 TCP changes were higher than 2%. In this case, no significant variations were observed in NTCP calculations.

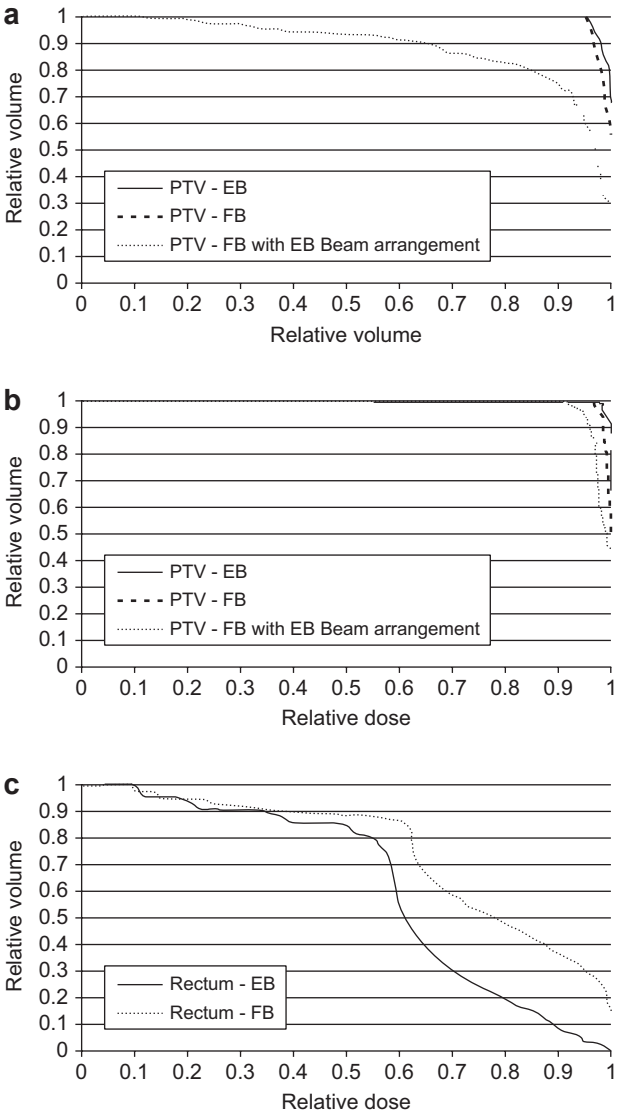

Figure 4. Typical dose volume histograms (DVHs): **(a)** planning treatment volume (PTV), **(b)** clinical target volume (CTV) and **(c)** rectum with empty bladder (EB) and full bladder (FB).

Table 4. Bladder wall displacements in empty and full bladder CT series

Direction (cm)	*Empty bladder*	*Full bladder*	*p-value*
Anterior	3.6±0.8	4.3±0.9	0.004
Posterior	3.6±0.5	4.4±0.7	0.001
Cranial	2.2±0.6	3.4±1.0	<0.001
Caudal	2.3±0.6	3.6±1.0	<0.001
Lateral right	3.1±0.7	3.6±0.7	0.002
Lateral left	3.2±0.5	3.6±0.7	0.010

Table 5. Dose volume histogram (DVH) rectum data

Parameter (cGy/fraction)	*Empty bladder*	*Full bladder*	*p-value*
Minimum DVH dose	23.9±15.4	37.9±34.3	0.11
Mean DVH dose	129.6±22.2	146.6±25.8	0.001
Maximum DVH dose	205.6±7.3	210.4±7.1	0.001

Table 6. Tumor control probability (TCP) and normal tissue complication probability (NTCP)

Parameter	*Empty bladder*	*Full bladder*	*p-value*
TCP	53.9±1.2	55.2±1.8	0.003
NTCP	1.6±2.2	3.7±3.3	0.002

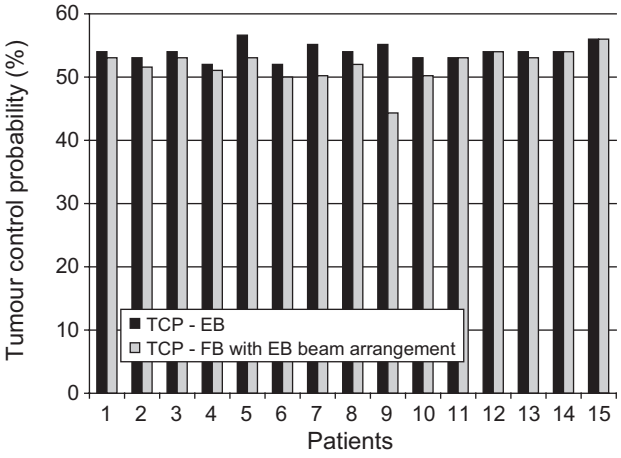

Figure 5. Tumor control probability (TCP) for empty bladder (EB) series at simulation vs. full bladder (FB) using EB beam arrangement.

Discussion

CTV for the treatment of muscle-invading bladder cancer is often considered to be the entire bladder. Presently, lack of local control is the major challenge in the treatment of bladder cancer, and this justifies the use of sufficient, and therefore, wide treatment margins. The choice of radiation treatment margin around the bladder volumes is likely to influence not only local control, but also toxicity [10].

The balance between hitting the tumor in each fraction and at the same time, avoiding as much as possible the involved OAR in practice becomes a question of the size of the safety margins around the CTV. If, during treatment, the bladder volume is smaller than that in the planning situation, there is certainly a good chance that the bladder CTV is adequately covered during treatment, but at the expense of irradiating a larger volume of the intestine [4].

In contrast to prostate, the spatial coordinates of bladder tumors depend not only on external pressure influences but also on random volume bladder changes making the treatment precision an even more difficult goal to achieve [14].

Based on current data, safety margins should be secured between the CTV and PTV, at least at the tumor-bearing parts of the bladder, and this recommendation applies when treating with a presumed empty bladder [5].

Because of the poor knowledge of the geometric uncertainties in bladder tumors, a wide range of margins (1.5-3 cm) between the CTV and PTV can be observed in current clinical practice [2].

Displacements of the bladder wall were analyzed at the anterior, posterior, cranial, caudal and lateral borders to solve the question, if and where a better bladder wall position stability can be achieved by treating the patient with an EB (assumingly best volume consistency) in comparison to a FB (assumingly always worse volume consistency) during a fractionated pelvic EBRT [15].

Previously published studies refer to the attention that should be paid to organ motion during RT for bladder cancer. Turner et al. in 1997 performed weekly limited CT scans through the course of RT. Outward bladder movements >1.5 cm were seen in 33% of the patients and the maximal displacement was 2.7 cm [16]. Miralbell et al. in 1998 chose to study tumor motion with bladder volume changes from 170 to 70 cc, assuming these to be representative extreme bladder volumes in a relatively old population undergoing curative RT for bladder cancer. They showed that a change in bladder volume of 100 ml resulted in significant displacement of the target volume and required at least 2 cm around the tumor to ensure acceptable dose coverage in case of maximum tumor displacements [17].

The organ motion of the bladder was quantified by Pos et al. in 2003, who measured tumor outside the PTV on weekly CT scans in 17 patients treated with FB. In this study a margin of 1.5 to 2 cm seemed to be inadequate in 65% of the patients with respect to spatial variability [6].

Meijer et al. in 2003 analyzed the bladder volumes at different moments during treatment. Apart from the initial planning CT scan, three follow-up scans were made for each of the patients. Anisotropy margins (1 cm anterior, 1.4 cm posterior, 2 cm cranial, 1.2 caudal and 1 cm lateral borders) between the CTV and PTV were needed in conformal RT of the bladder. Especially at the cranial side of the bladder, larger margins were needed because of the impact of bladder shape variation [18].

In 2004, Fockdal et al. studied the bladder motion caused by various filling amounts to the bladder and rectum. The mean bladder filling in this study was 192 ml independent of the rectal filling, and a 2 cm isotropic margin would encompass the bladder in all directions. The internal margins required to cover the bladder movements due to filling of the bladder and the rectum in 87% of the patients were 2.4 cm in the anterior, 1.1 in the posterior, 3.5 cm in the cranial, 0.5 in the

caudal and 1.3 in the lateral direction. The filling volumes of the bladder and rectum had a large impact on bladder movements, especially in the anterior and cranial directions [15].

Lotz et al. in 2006, showed that gross tumor translations were largest in the cranio-caudal and anterior-posterior direction and there was strong correlation with tumor location on the bladder wall [19].

In our study, during CT simulation each patient underwent two CT scans of the pelvis, one with EB followed by another one with FB. The bladder filling procedure was associated with voiding symptoms in most patients. The mean bladder volume before the start of treatment was 119.3 cm^3, while the mean bladder filling capacity was 263 cm^3 (range 90.8-471.2 ml). This value is small compared with a normal bladder capacity (usually >500 ml) [20]. However, it is well known that patients with invasive bladder tumors are known to have a low bladder capacity [20].

Rectal volumes showed no significant variability regarding the bladder volume changes. The 3D calculated beam arrangements and field sizes that were used for emptied bladders were also applied to simulate treatment for the maximally full bladders. The corresponding DVHs were obtained and calculations of TCP were performed. Bladder motion caused by changes in the bladder volumes was registered in all directions, especially in the cranial and caudal directions. We observed that standard anisotropic margins of 2 cm in cranio-caudal and posterior-anterior directions and 1.2 cm the in lateral direction gave coverage to 75% of all bladder movements caused by FB. Analysis of DVHs and TCP calculations gave the same result (74%), while NTCP showed no significant changes. In patients that exhibited excessive bladder movement, adequate margin would be defined from the start of treatment to allow for unpredictable movement.

In conclusion, CT scans series with EB and FB performed at the simulation time could offer a potential advantage to evaluate the target expansion necessary to geometrically cover the bladder wall for each patient at the beginning of RT.

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