(Un-)certainties in radiotherapy of rectal cancer
Nijkamp, J.A.
Bowel exposure in rectal cancer IMRT using prone, supine, or a belly board

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Abstract

Purpose
To investigate bowel exposure using prone, supine, or two different belly boards for rectal cancer intensity modulated RT plans using a full bladder protocol.

Material and methods
For 11 volunteers four MR scans were acquired, on a flat table in prone, supine, and on two different belly boards (IT-V Medizintechnik GmbH (BB1) and CIVCO (BB2)), using a full bladder protocol. On each scan a 25 x 2 Gy IMRT plan was calculated.

Results
BB2 led to an average bowel area volume reduction of 20–30% at any dose level compared to prone. BB1 showed a smaller dose reduction effect, while no differences between prone and supine were found. Differences between BB2 and prone, supine or BB1 were significant up to a level of respectively, 45, 35, and 30 Gy, respectively. The reducing effect varied among individuals, except for the 50 Gy regions, where no effect was found. An increase in bladder volume of 100 cc led to a significant bowel area V15 reduction of 16% independent of scan type.

Conclusions
In the low and intermediate dose region a belly board still attributes to a significant bowel dose reduction when using IMRT and a full bladder protocol. A larger bladder volume resulted in a significant decreased bowel area dose.
Introduction

The standard of care for primary resectable rectal cancer has evolved to total mesorectal excision (TME) surgery mostly in combination with pre-operative (chemo-) radiation [1–5]. This treatment is associated with acute and late gastro-intestinal toxicity, such as diarrhea, faecal incontinence and late small bowel obstruction requiring surgery [6–16]. The occurrence of diarrhea and small bowel obstruction is primarily dependent on the dose and volume parameters of the small bowel.

Baglan et al. [12] showed that a cut-off at 150 cc of small bowel receiving more than 15 Gy divided a group of 40 patients into 0% and 50% chance of developing acute grade 3 diarrhea. This was later confirmed in a larger study by Robertson et al. [13], who showed that a cut-off point of 120 cc and 15 Gy divided the group into 9% vs. 38% risk of developing grade 3 diarrhea. Gallagher et al. [14] found a critical level of 45 Gy to 78 cc and 50 Gy to 17 cc of the small bowel predictive for late toxicity in post-operative RT. Letschert et al. [15] showed afterward, at a dose range of 45–50 Gy, that if the small bowel volume is increased by a factor of 2, then a total dose reduction of 17% is required for the same complication rate.

Full bladder protocols, prone positioning, and belly boards have been used to reduce the volume of small bowel in the radiation field by pushing the small bowel away from the high dose region [17–22]. A disadvantage of full bladder instructions is the large day-to-day variation of the bladder volume [23]. This can potentially lead to large systematic differences between planned and delivered dose to the small bowel. The downside of treating patients in prone position is that compared to supine, the setup is less reproducible between and during fractions [20, 24]. This can be partly compensated by online setup correction or by an increase of the PTV margin. The latter, however, will reduce the benefit of prone positioning on the small-bowel dose. Besides the described anatomy based steps to spare organs at risk, modern treatment delivery techniques such as intensity modulated radiotherapy (IMRT) can be used to create more conformal treatment plans, also reducing the dose to the small bowel [25–27].

Several planning studies have shown the benefit of a belly board in terms of small bowel exposure [17–19]. In these studies the effect of belly board and bladder distension has not been tested separately in the same subjects, while these factors are largely dependent of each other. Also patients in pre- and post-operative setting were compared. Only Kim et al. [22] compared prone on a flat table with usage of a belly board in the same subjects, while having an empty bladder, but they also stated that an empty bladder is clinically not feasible to use. Furthermore, the use of IMRT and a full bladder protocol has never extensively tested.

The aim of this study was to compare bowel exposure when using prone, supine, or two different belly boards for rectal cancer IMRT plans with a full bladder protocol. In order to establish comparable data a planning study was performed based on multi-MR scans of healthy volunteers.
**Material and methods**

**Volunteer selection and scanning positions**

Since acquiring multiple scans is a big burden for any patient in terms of time and dose, we decided to obtain scans of healthy volunteers. The use of volunteers obviously demanded for MR-scans instead of CT-scans, due to imaging dose.

Eleven healthy volunteers of the RT department were asked to participate in this study. Each volunteer was scanned with four different scan types, being: (1) supine on a flat table (supine), (2) prone on a flat table (prone), (3) prone on a BellyStep (IT-V Medizintechnik GmbH, Innsbruck, Austria) belly board (BB1), and (4) prone on a Perspex copy of a Contoura (CIVCO medical solutions, Orange City, Iowa) belly board (BB2). A Perspex copy was made because it was uncertain at that time if the belly board was MR compatible.

**MR scans**

In accordance to clinical protocols, all volunteers were instructed to empty the bladder and drink 350 ml of water 1 h prior to the scans. All four MR scans per volunteer were taken on a Philips Achieva 3T machine (Philips Medical Systems, Best, The Netherlands) in one session, as fast as possible. To minimize the effect of urinary inflow on the study, the order of the four scans was randomized per volunteer. To establish an optimal balance between scan speed and image quality, T1 weighted MR images were acquired. Because of the height of BB1 it was physically not possible to use a body coil to improve the image quality. Therefore none of the four scans were performed with a body coil. The scans in prone position were acquired using a rotated knee support (CIVCO medical solutions, Orange City, Iowa) as ankle support to increase comfort and stability. The forehead was positioned on a specially designed head pillow (Pron Pillo, CIVCO medical solutions, Orange City, Iowa), with a cut out aperture and support for the shoulders. During the supine scans only the knee support was used. For the scans on BB1 and BB2 the volunteer position with respect to the aperture of the belly board was checked on the scout view. Repositioning was performed if necessary. All scans were taken by the same team of technologists.

Each scan was taken from the L2–L3 junction to the perineum with 5 mm slice spacing.

**Treatment plans**

For each scan a clinical target volume (CTV) was delineated. The CTV encompassed the mesorectal fat, pre-sacral lymph nodes, and the lymph node regions along the internal iliac arteries, superior rectal artery, and internal obturator vessels. The bladder and bowel area were delineated and used as organs at risk. The bowel area was defined as the abdominal region encompassing the small bowel and colon, excluding the large vessels, uterus, and bladder, with the cranial border at 3 cm from the CTV. All CTV’s were delineated by one observer (B.D.) and approved by a radiation oncologist (C.M.). A uniform CTV to PTV margin of 10 mm was used for all scans. An example of the delineated volumes for one volunteer can be found in Fig. 2.1.
Subsequently, for each scan an external contour was generated. The volume inside this contour was assigned with water equivalent Hounsfield units for dose calculation on the MR images.

For each scan a 7-field IMRT plan of 25 x 2 Gy was calculated using Pinnacle (Philips Medical Systems, Eindhoven, The Netherlands version 8.0 h). Plans were optimized using direct machine parameter optimization (DMPO) with a maximum of 35 segments, 10 and/or 18 MV, a minimum field size of 25 cm² and a minimum of 4 MU per segment, which is daily practice in our clinic. For prone, BB1, and BB2 field angles of 0°, 50°, 100°, 150°, 210°, 260°, and 310° were used, while for supine the field angles were mirrored. For the sparing of the bowel area two maximum equivalent uniform dose (EUD) constraints were used at a dose level of 28 and 17.5 Gy with an α of 7 and 1 and a weight of 10 and 5, respectively. These constraints were optimized per volunteer if possible.

All treatment plans had to satisfy ICRU-62 conditions, such that 99% of the PTV volume receives at least 95% of the prescribed dose of 50 Gy. Hot spots up to 107% of the prescribed dose were allowed. Besides comparable PTV doses for all scan types, treatment plans were also kept similar by putting constraints on the dose to the body outside the bowel area. Doing so, scan type differences only affected the dose in the bowel area, and treatments plans were assumed to be clinically acceptable and mutually comparable.

**Scan type comparison and statistical analysis**

Although the scanning order was randomized, and the average bladder volume was not statistically different between the different scan types, large intra-volunteer differences in bladder volume were present (see Results). To take both the bladder volume effect and scan type effect into account, a mixed effects model was constructed with bowel area volume dose in steps of 5 Gy as outcome. In the model a square-root transform was applied to the outcome data, to ensure normally distributed residuals. All results are presented back-transformed into the original scale. To fit the shape of the bowel area dose volume histograms a cubic polynomial was used in the model. The fixed effects in the model are scan type, interaction between scan type and bowel area dose, and the volume of the bladder in the scans. Intra-volunteer correlation in the data was accounted for by including random effects, one for each fixed effect.

Scan type effect was analyzed by estimation of the bowel area dose using the mixed effects model with a fixed bladder volume equal to the average of the first scans for all patients. The average volume of the first scans was used, since the first scan was made 1 h after voiding and drinking, similar to our clinical protocol.

The separate influence of bladder filling on bowel area dose was evaluated by estimating the bowel area volume receiving 15 Gy (V15) at different bladder volumes ranging from 100 to 400 cc for each scan type with the mixed effects model.

The level of significance for all comparisons was chosen at p < 0.05. The mixed effects model was constructed using R (version 2.10.1; The R Foundation for Statistical Computing).
Fig. 2.1: Transversal (left) and sagittal (right) example of a female volunteer in supine (top) prone (second), BB1 (third), and on BB2 (Bottom) with the PTV (thick white), bladder (thick yellow) bowel area (thick pink) and the planned isodose lines of 15, 30, 47.5, and 50 Gy in blue, lime, orange, and red, respectively.
Results

MR scans

The four different scans were acquired for 4 male and 7 female volunteers. The scanning sessions per volunteer took on average 46 min from the first to the last scan (range 40–54 min). For six BB2 scans the volunteer was repositioned based on the scout view and for one scan the volunteer was repositioned and rescanned after immediate scan evaluation. On average the prone and supine scans took 10 min including setup, while the belly board scans needed on average 12 min.

Although the setup was checked for each scan type on the scout view, two of the female volunteers were retrospectively determined to be positioned too far caudally on the BB2 scan. Despite this suboptimal volunteer position, all scans were taken into account in the evaluation in order to adhere to the intention to treat principle.

Fig. 2.2: Cumulative bowel area dose volume histograms for each volunteer and each orientation. The original data are represented by the symbols, the mixed effects model fits by the smooth lines. On the left y-axis the bowel area volume (cc) is shown, on the right y-axis the bladder volumes (cc) are shown in the same scale. The bladder volume for M1 using BB2 was 684 cc.
The average bladder volumes were 274 (114), 288 (132), 291 (138), and 324 (139) cc (1SD) for supine, prone, BB1, and BB2, respectively. There was a large variation in urinary inflow between the volunteers, with an average of 4.4 cc per min and a range of 0.7–10.7 cc per min.

The average delineated bowel area volumes were 460 (226), 464 (217), 389 (204), and 363 (206) cc (1SD) for supine, prone, BB1, and BB2, respectively. None of the average volumes were significantly different between the scan types.

Treatment plans
Clinically acceptable plans could be achieved for all volunteers and for all treatment positions (Fig. 2.1). The differences in organ at risk position and volume mainly led to variation in low dose distribution.

Fig. 2.3: Predicted bowel area dose volume histograms for each volunteer and each orientation when the bladder volume is fixed to 216 cc (average of the first scan over all volunteers) in the mixed effects model.
Dose to the bowel area
The bowel area dose volume histograms were calculated in steps of 5 Gy for each volunteer and each of the four scans (Fig. 2.2). The DVH estimates using the mixed effects model are shown by the smooth lines. All accompanying bladder volumes per volunteer are shown on the right y-axis. Note the large variation in bowel area exposure and bladder filling between the volunteers.

The mixed effects model was used to present the data for each volunteer corrected for bladder volume differences (Fig. 2.3). For each subject and scan type the DVH was estimated with a fixed bladder volume of 216 cc. The overall effect was summarized by the estimated dose volume numbers for each scan type averaged over the volunteers (Table 2.1). No significant differences between prone and supine were found. With BB1 significantly lower bowel area exposure was reached compared to prone and supine in the lower dose regions up to 30 and 20 Gy, respectively. BB2 outperformed all other scan types. Differences between BB2 and prone, supine or BB1 were significant up to a level of respectively, 45, 35, and 30 Gy. At higher dose levels differences were small and not significant.

The effect of bladder volume changes on bowel area V15 was estimated for each scan type (Fig. 2.4). As expected, with an increase in bladder volume a decrease in bowel area volume exposure was found (p < 0.0001), independent of scan type. The modelled effect of scan type on the V15 can be appreciated by the distance between the lines. There were no significant differences between the slopes of the different lines, indicating that bladder volume increase up to a level of 400 cc has the same relative effect for all scan types.

![Influence of bladder filling on bowel exposure (V15)](image)

*Fig. 2.4:* Estimated average bowel area volume receiving 15 Gy (V15) for each orientation when having different bladder volumes.
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Discussion

To the best of our knowledge this is the first study to compare bowel exposure using prone, supine and belly board scans in the context of IMRT and a full bladder protocol for rectal cancer RT. Belly board 2 outperformed the other scan types by having statistically significant lower doses to the bowel area in the low and intermediate dose region. Positioning with respect to the compression verge of this belly board was, however, challenging and had to be corrected on multiple occasions.

Scan type effect on bowel area exposure

Both belly boards had a statistically significant effect on the bowel area exposure in the low and intermediate dose regions (Table 2.1). The V15, for example, reduced from 218 to 178 cc and 144 cc when comparing prone with BB1 and BB2, respectively. The effect of the belly boards varied among the different volunteers (Fig. 2.3), where for example a minimal effect was found for F1, F3, F5, and M4, and a large effect was found for F4, M1, M2, and M3. In the high dose regions, above 35 Gy for BB1 and above 45 Gy for BB2, differences with prone were small and not significant. This lack of effect in the high dose region was due to the overlap between the PTV and the bowel area, which was similar for all scan types (not shown).

The significant difference between both belly boards can be explained by the difference in compression. Some volunteers indicated that because of the small compression verge, BB2 was uncomfortable to lie on, especially in combination with a full bladder. BB1 had a broader compression verge and was therefore considered to be more comfortable.

The advantage on small bowel dose with a belly board in an IMRT setting was previously shown by Kim et al. [22] comparing prone on a flat table with a belly board.

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Table 2.1: The estimated bowel area volumes (cc) for different dose levels. These bowel area volumes are averaged estimates over all volunteers at a bladder volume equal to 216cc. Volume differences are all absolute differences with respect to Prone. Differences between the orientations were tested using a 2-tailed pairwise comparison (* p < 0.05; ** p < 0.01; *** p < 0.0001).
They found significant small bowel volume reduction at dose levels between 10 and 50 Gy, with relatively increasing effect with increasing dose levels. We did not find a significant effect at 50 Gy and also the relative belly board effect reduced with increasing dose. In their study an empty bladder protocol was used with average bladder volumes of 120 cc, which is significantly less compared to our study. As a consequence, they also reported much higher absolute small bowel DVH’s, such as V15 prone 304 cc and V15 BB 250 cc. These differences hamper the comparability between both studies.

There was no difference in bowel area exposure between prone and supine (Table 2.1), which is in accordance with Drzymala et al. [28]. Many centers, however, still treat patients in prone position on a flat table in order to reduce bowel dose. Since supine daily setup is more reproducible [20, 21, 28], and patients find it more comfortable, we suggest to use supine positioning when no belly board is used.

**Scan acquisition**

Setup of the volunteers on the belly boards was not obvious. As mentioned earlier, some volunteers indicated that BB2 was uncomfortable to lie on, due to the pressure on the lower abdomen. Furthermore, belly boards were initially developed for gynaecological RT, which resulted in our study in discomfort for the male volunteers. Adaptation to male anatomy might help to partly improve comfort.

For 9 of the 11 BB2 scans, repositioning was, or should have been done to establish the intended position on the belly board. Repositioning was needed throughout the study, showing that a learning curve of 11 volunteers was not enough to overcome setup problems on this belly board. The position of the patient/volunteer with respect to the belly board was shown to be important by Koelbl et al. [29]. They showed a significant change in small bowel exposure when comparing different patient positions with respect to the belly board aperture. Note that their results were based on conformal treatment fields and a post-operative treatment setting.

Several studies have shown that reproducibility of bony anatomy setup during treatment is worse when using a belly board [20, 21, 28]. This reduction in reproducibility can be diminished by online setup correction protocols.

**Bladder volume and effect**

Due to randomization of the scan order, no significant differences in bladder volume were present between the scan types, minimizing a bias due to bladder filling on the comparison. The large variation in bladder volumes shows that even in healthy volunteers inter-individual variation is a significant problem when using a full bladder protocol [21, 23, 24]. Still, we demonstrated that usage of the full bladder protocol is very important (Fig. 2.4), with a 100 cc increase of the bladder volume resulting in a statistically significant reduction of the bowel area V15 of approximately 16% independent of the scan type. Kim et al. [21] showed, in a study comparing the effect of a belly board and the effect of a distended bladder separately, that small bowel exposure is more effectively reduced by a full bladder compared to the use of a belly board. In their study conventional treatment plans and much larger volumes to drink were used.
Effects on expected toxicity
In the current study bowel area is delineated, instead of small and large bowel loops separately. This was done because of the image quality, which was hampered by compromising between scan speed and quality and also by the lack of oral bowel contrast. Gunnlaugsson et al. [30] demonstrated, in a study comparing scan types between patients, that acute toxicity could only be correlated with the exposure to absolute volume of the small bowel, and not with large bowel or the bowel area. Also acute toxicity cut off values from Baglan et al. [12] and Robertson et al. [13] are based on dose to the small bowel. Translation of bowel area volume to small bowel volume is not easily done, since large anatomic differences between volunteers exist (Fig. 2.3). In a recent study on the possibilities to reduce the CTV [31] we have delineated small bowel and bowel area separately in a dataset of eight patients which were scanned with small bowel contrast. In this dataset the percentage of bowel area volume which was actually small bowel ranged from 11% to 48%. In that study IMRT plans were calculated in which the small bowel volume receiving a certain dose was on average 30% of bowel area volume receiving that same dose. A rough translation from bowel area volume to small bowel volume would therefore be a division by a factor between 2 and 3. The maximum bowel area V15, V45, and V50, which were 218, 59, and 28 cc for prone, could therefore be estimated to a small bowel V15, V45, and V50 range between 73 and 109, 20 and 25, and 9 and 14 cc. With the use of IMRT the average V15 for prone is therefore lower than the cut-off points for acute toxicity from Baglan et al. [12] (150 cc) and Robertson et al. [13] (120 cc). Also late toxicity cut-off points 78 cc V45 and 17 cc V50 [14, 15] were therefore on average not reached using IMRT and prone. Due to the large variation in bowel area exposure between volunteers (Fig. 2.3), usage of a belly board to lower the bowel dose below the cut-off points might be more effective in an individualized treatment setting. We therefore suggest using the belly board as an option when unacceptable small bowel exposure is found during planning on, for example, a supine scan. Patients who are already within tolerance limits would therefore not be subjected to a less reproducible [20, 21, 28] and comfortable belly board, while others can benefit significantly from the belly board. This approach would have been effective within the current study, except for volunteer F5 (Fig. 2.3), where a relatively large bowel exposure did not benefit from the belly board at all.

Limitations of the study
In our study we simulated IMRT plans for rectal cancer on multiple MR scans of healthy volunteers, instead of real patients. We have shown that there was a statically significant difference in bowel exposure in the low and intermediate dose regions, which is located at a distance from the CTV itself. We therefore assume that results acquired in the current volunteer study will also be applicable for patients, in which we speculate that the presence of a tumor mainly influences the anatomy within the CTV or PTV.

The aim of this study was to compare the effect of prone, supine, BB1, and BB2 on bowel exposure in IMRT plans for rectal cancer. To get a fair comparison we acquired all four scans within each individual, where the scanning order was randomized. Due to image quality, the bowel area was delineated, instead of the small bowel loops
separately for which the exposure is known to be more predictive for acute and late toxicity [12–15].

The bladder volumes for the different scans within each individual were not constant, due to the physiological process of bladder filling. To separate the bladder filling effect from the scanning procedure effect a mixed effects model was used. The mixed effects model is only applicable for the bladder volumes which occurred in this study. Extrapolation to larger or smaller volumes is not allowed.

**Conclusions**

In the presence of bowel dose reducing options as IMRT and a full bladder protocol the usage of a belly board still has a significant additional value. With BB2 a significant reduction of dose to the bowel area was established up to an intermediate dose level of 30, 35, and 45 Gy compared to BB1, supine, and prone, respectively. In the high dose region no difference between the scanning positions was present. On the other hand, the setup on BB2 had to be repeated multiple times for correct positioning on the aperture. Large inter-volunteer variation from almost no belly board effect to a large effect on bowel area exposure indicated that the use of a belly board should be on an individual basis for more clinical effectiveness. There was no significant difference in bowel area dose between prone and supine, making supine superior to prone because of reproducibility and comfort. Important independent factor was the volume of the bladder, where a larger bladder volume resulted in a significant decreased bowel area dose.
Chapter 2

References
Bowel exposure in rectal cancer IMRT using prone, supine, or a belly board


