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Overview of patient preparation strategies to manage internal organ motion during radiotherapy in the pelvis

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Abstract

Introduction

Pelvic internal organs change in volume and position during radiotherapy. This may compromise the efficacy of treatment or worsen its toxicity. There may be limitations to fully correcting these changes using online image guidance, therefore effective and consistent patient preparation and positioning remains important. This review aims to provide an overview of the extent of pelvic organ motion and strategies to manage this motion.

Methods and Materials

Given the breadth of this topic a systematic review was not undertaken. Instead, existing systematic reviews and individual high-quality studies addressing strategies to manage pelvic organ motion have been discussed. Suggested levels of evidence and grades of recommendation for each strategy have been applied.

Results

Various strategies to manage rectal changes have been investigated including diet and laxatives, enemas and rectal emptying tubes and rectal displacement with endorectal balloons and rectal spacers. Bladder filling protocols and bladder ultrasound have been used to try to standardise bladder volume. Positioning the patient supine, using a full bladder and positioning prone with or without a belly board have been examined in an attempt to reduce the volume of irradiated small bowel. Some randomised trials have been performed, with evidence to support the use of endorectal balloons, rectal spacers, bladder filling protocols and the supine over prone position in prostate radiotherapy. However, there was

a lack of consistent high-quality evidence that would be applicable to different disease sites within the pelvis. Many studies included small numbers of patients, were non-randomised, used less conformal radiotherapy techniques or did not report clinical outcomes such as toxicity.

Conclusions

There is uncertainty as to the clinical benefit of many of the commonly adopted interventions to minimise pelvic organ motion. Given this and the limitations in online image guidance compensation, further investigation of adaptive radiotherapy strategies is required.

Introduction

Pelvic organs including rectum, bowel, bladder and uterus are subject to physiological changes in position, shape and volume[1, 2]. During radiotherapy, these variations result in discrepancies between the planned and actual treatment delivered, which can lead to geographical miss of the tumour, and/or variable dose delivery to adjacent organs at risk (OAR). Day-to-day and during treatment delivery variability is referred to as inter-fraction and intra-fraction motion respectively. On-treatment image guidance using cone beam computed tomography (CBCT) and/or fiducial markers can guide couch shifts to correct for simple translations in organ position, but correcting for organ rotation and deformation remains challenging using current technology[3-5]. This means that appropriate and consistent patient preparation and positioning strategies remain important[6]. Organ motion may be of greater significance during intensity modulated radiotherapy (IMRT),

since more complex dose distributions and steeper dose gradients are used than during three dimensional conformal radiotherapy (3D-CRT)[2]. This is especially relevant for the safe and effective delivery of highly conformal and hypofractionated treatments such as stereotactic ablative radiotherapy (SABR)[7]. This review aims to provide an overview of the extent of pelvic organ motion and patient preparation and positioning methods for managing organ motion in the pelvis.

Methods

Literature searches were performed using PubMed (NCBI) for terms relating to pelvic organ motion and strategies to manage this motion. Further relevant articles were found by manually searching reference lists of relevant publications. Given the breadth of this topic, a systematic review was purposely not undertaken. Instead, to bring the best existing evidence into one article, systematic reviews which focus on one or more areas within the subject of managing internal pelvic organ motion are discussed, where these are available. In addition, individual higher quality studies, such as randomised controlled trials (RCTs) or well-conducted cohort studies, are specifically mentioned.

Additional individual studies addressing strategies for managing pelvic organ motion, judged to be of lower quality (see below), are included as an appendix (see Supplementary Material).

A hierarchy of evidence and recommendations grading scheme was applied using the Oxford Centre for Evidence-based Medicine- Levels of Evidence[8]. Studies allocated level 1b included well-conducted randomised controlled trials (RCTs) (e.g. Mariados *et al*[9]). Individual cohort studies (e.g. Krol *et al*[10]) were allocated level 2b, unless judged to be of lower quality. We allocated a level of 2c for studies with small patient numbers (taken as <20 patients), studies that were retrospective or treatment planning studies without reference to clinical outcomes such as toxicity. Grade recommendation A was applied where level 1 studies were available and grade B where evidence was provided by level 2 studies.

Results

Extent of pelvic organ motion is described below for rectum, bladder and bowel. Strategies to manage this motion are then described. Motion management strategies were separated into similar themes, and the available evidence for each strategy considered. In total, four systematic reviews and seven RCTs were identified that addressed different methods of managing pelvic organ motion. Best level of evidence, alongside grade of evidence, is presented for each pelvic organ motion management strategy (see Table 1). Level and grade of evidence for individual studies, including those contained within the cited systematic reviews, are included in Supplementary Material.

Extent of pelvic internal organ motion

Rectum

Rectal filling with faeces and gas is the predominant factor influencing rectal distension (see Figure 1). In prostate radiotherapy, rectal distension can result in significant and predominantly anterior-posterior displacements of the prostate gland[11, 12]. Presence of rectal gas may also affect the delivered dose distribution during prostate IMRT[13]. Retrospective studies have observed inferior biochemical and local control for patients with a distended rectum at the time of prostate radiotherapy planning[14-16]. In rectal cancer radiotherapy, a systematic review of studies of mesorectal (containing the rectum and perirectal fat) motion found that the greatest displacements were anteriorly in the upper mesorectum[17]. For hypofractionated courses of radiotherapy, such as short-course pre-operative radiotherapy in rectal cancer, an error on even a single fraction could potentially be significant[18]. A systematic review of pelvic organ motion in cervical radiotherapy observed that movement of the cervix and upper vagina is mainly related to rectal filling[2].

Bladder

The main factor influencing bladder motion is bladder filling (see Figure 1). This causes more movement in the anterior and superior directions since expansion laterally and posteriorly is limited by the pelvic bones and rectum[19]. Filling may differ between diseased and healthy bladders, with cancer infiltration causing greater wall rigidity, resulting in asymmetry of bladder distension and smaller bladder capacity. Greater variation and magnitudes of motion are also noted in patients with bladder cancer[20, 21]. In prostate radiotherapy, deformation of the prostate by bladder (and rectal) filling is limited. However, significant deformations of seminal vesicles by the bladder may occur[5, 22]. In cervical radiotherapy,

bladder filling may alter the position of the tip of the uterus in both superior-inferior and anterior-posterior directions. In addition, bladder volume may be altered towards the end of a course of radiotherapy as a result of early radiation toxicities[2].

Bowel

Bowel motion is under neurological and hormonal control and results in complex peristaltic waves of dilatation and relaxation[23]. Small bowel peristaltic waves have been shown to occur 11 times per minute with average amplitude of 7 mm. In addition to this oscillating motion, large changes in small bowel position and volume occur as a consequence of faeces and gas within the bowel and also vary with bladder filling[24]. Large bowel exhibits considerable variation in luminal diameter and is predominantly gas-filled in the absence of faeces. Peristaltic movements may be less frequent for large than small bowel, but differences have also been observed between proximal and distal large bowel. In a cine magnetic resonance imaging (MRI) study, Buhmann *et al* found peristaltic waves occurring 6 times per minute in the ascending colon compared with 3 times per minute in the descending and sigmoid colon[25]. There is considerable variation in the appearance of bowel both within and between patients and a single CT image represents only an arbitrary shape and position of a mobile and distensible organ. It may be that only 20 % of bowel occupies the same position throughout treatment compared with at planning[26, 27].

Strategies to manage pelvic organ motion

Levels of evidence

For each of the interventions discussed below, the best level of evidence is presented in Table 1. Individual studies have also been allocated a suggested level of evidence and are presented in Supplementary Material. While some high quality evidence does exist, for example RCTs, cohort studies form the majority of published evidence.

Patient preparation

To try to achieve reproducibility in the volume and position of pelvic organs, use of consistent patient preparation strategies to reduce organ motion should be applied both at planning and during treatment. Patient compliance with protocols may be greater at the time of planning with more directed patient education[6]. In addition, radiotherapy toxicity may alter organ volume and position towards the end of treatment[2]. Much of the published literature relating to rectal and bladder filling concerns prostate radiotherapy.

Diet and laxatives

McNair *et al* performed a systematic review of interventions to empty the rectum or stabilise its volume[6]. Low fibre diets and reduced dietary consumption of fermentable carbohydrates (such as beans and pulses) to reduce rectal gas and diarrhoea in prostate radiotherapy did not appear successful. Several studies in the review examined the laxative milk of magnesia (MoM; magnesium hydroxide) in combination with dietary advice. There

was some evidence to support reduction in rectal gas with use of MoM but this did not always correlate with reduced prostatic motion. In addition, MoM appeared to be poorly tolerated by patients. An RCT of the laxative magnesium oxide compared with placebo concluded that magnesium oxide did not reduce prostatic motion and there was a trend to worse quality of life with the laxative[28]. Oates *et al* investigated the effect of dietary intervention with a bulk-forming laxative in an RCT, and found a non-significant trend to more consistent rectal volumes[29]. At the level of the prostate, the combination therapy was associated with reduced rectal faeces and gas. However, this relationship was not observed in the superior rectum, where the greatest changes in volume occur[6, 29].

Other methods of altering bowel gas

The anti-foaming drug simeticone has been used to try to reduce rectal gas in prostate radiotherapy patients, although there is limited evidence for its benefit. While Madsen *et* al described little intra-fraction prostatic motion when using simeticone, a rectal catheter was also inserted when rectal gas was seen which limited interpretation of the benefit from simeticone[30].

Ki *et al* performed a randomised study of probiotics containing *Lactobacillus acidophilus* compared to placebo in prostate radiotherapy. They found that the probiotic reduced rectal gas and variation in rectal volume from planning to treatment imaging. However, some patients had excessive rectal distension suggesting variability in outcome using this particular probiotic[31].

Rectal emptying strategies

Rectal emptying tubes

McNair *et al* also reviewed studies of rectal emptying, which has been advocated as a method of reducing variation in rectal filling[6]. There was some evidence that rectal emptying tubes reduced rectal volume variation and prostatic motion during prostate radiotherapy. No RCTs have been performed. Disadvantages of rectal emptying tubes include the additional time taken for the procedure, staff training and patient compliance. Manual evacuation of the rectum, although found in one study to reduce rectal volume and prostatic motion, is unlikely to be tolerated during routine clinical practice.

Rectal enemas and suppositories

McNair *et al* concluded that some studies using glycerine suppositories and microenemas demonstrated reduced anterior displacement of the rectum (and therefore anterior-posterior prostatic motion)[6]. However, most studies included only small numbers of patients and did not prospectively compare enemas to alternative interventions. Sabater *et al* performed a prospective trial of 59 patients using enemas in vaginal brachytherapy for post-operative endometrial cancer, with the patient acting as their own control[32]. Despite an overall 15% reduction in mean rectal volume following an enema, over one third of patients had an increase in rectal volume, and no improvement in rectal dosimetry was observed. In external beam radiotherapy, the extent of rectal emptying, especially from

patient self-administration of enemas or suppositories, may vary, with some patients requiring further rectal emptying[6]. Superior rectal volume may have the greatest impact on prostatic displacement, but in some studies reviewed by McNair *et al* rectal volume was measured at the level of the prostate gland (corresponding to the level of the mid rectum). Therefore, it is possible that superior rectal volume may not be reduced through the use of an enema or suppository, which acts more distally. Self-administration of enemas or suppositories was well tolerated by patients[6].

Rectal displacement strategies

Endorectal balloons/devices

Previous studies of endorectal balloons (ERB) in prostate radiotherapy, including one RCT, have demonstrated reduced anorectal toxicity through reduction in the volume irradiated and dose delivered to the anal and rectal walls[10, 33]. Wortel *et al* suggested that patients tolerate ERBs[33]. However, ERB insertion may deform the prostate gland and increase treatment time. Therefore, outside of a clinical trial it is possible that patient acceptance for daily insertion of an ERB might be lower. An RCT is currently investigating use of a daily inserted rectal obturator (ProSpare) in prostate bed radiotherapy (ClinicalTrials.gov Identifier: NCT02978014). The trial is using smaller planning target volume (PTV) margins for patients allocated ProSpare to determine if this reduces rectal toxicity. In addition, steel markers within the device mean it can be used for treatment verification as an alternative to implanted fiducial markers.

Rectal spacers

The vast majority of the evidence for rectal spacers concerns prostate radiotherapy. Mok *et al* performed a systematic review of rectal spacers inserted between the prostate and rectum[34]. Spacers are used to increase the distance between these structures and reduce both dose to the rectum and the volume of rectum irradiated to a significant dose. These are made from biodegradable materials such as polyethylene-glycol, hyaluronic acid or collagen and can be injected using ultrasound guidance under local, epidural or general anaesthesia. Biodegradable balloons made of polyatic acid have also been used. Biodegradation occurs after around 6 months for polyethylene-glycol spacers and polyatic acid balloons and 12 months for hyaluronic acid and collagen spacers. In the review by Mok *et al*, studies of spacers and balloons demonstrated good safety profiles and improvements in rectal dosimetry[34]. One RCT, comparing a hydrogel spacer with no spacer in prostate radiotherapy, found that spacer insertion was well tolerated and late rectal toxicity was reduced from 7 % to 2 % for patients in the spacer group[9]. Further analysis of the trial at 3 years, including patient reported outcomes, was also reported[35]. In addition to the improvements in late rectal toxicity, statistically significant differences in favour of the spacer group for urinary toxicity and minimally important differences in bowel, urinary and sexual quality of life domains were found. Potential disadvantages of spacers may include complications from insertion, patient discomfort and infection (although in the RCT by Mariados *et al*, the only procedure-related complication was mild transient perianal discomfort reported in 10 % of patients). In addition, spacers have mainly been used in localised (T1 and T2) prostate cancers and their role in locally advanced tumours remains uncertain[9, 34]. Nevertheless, it was recently reported that hydrogel spacer will be funded

for patients in the United Kingdom as part of an NHS innovation and technology programme[36].

Electromagnetic transponders

In prostate radiotherapy, implanted electromagnetic transponders such as the Calypso 4D localisation system (Calypso Medical Technologies, Seattle, USA) can monitor for inter-fractional changes in prostate position[37]. In addition, these also permit real time tracking, providing the potential to correct for intra-fractional prostate motion and gating of the radiation beam if intra-fraction motion exceeds a certain threshold. This could be especially useful for treatments requiring a high degree of conformality such as SABR or boosting of dominant intra-prostatic lesions. A retrospective study of electromagnetic transponders in 236 patients undergoing prostate radiotherapy observed that changes in intra-fractional prostate position were more likely the longer the treatment delivery time [38]. Variations of >3 mm were seen for 12 % of the time taken to deliver fixed-field IMRT delivered within 10 minutes, compared to only 4 % for more rapidly-delivered volumetric modulated arc therapy (VMAT) treatments completed within 5 minutes. Using the real time tracking system, the authors also observed changes in prostate position within 1 minute of patient set up. They speculated that this may occur due to patient relaxation on the treatment couch or passage of rectal gas. Since VMAT could be delivered within a few minutes, the group therefore suggested that there could be a benefit in watching for any initial prostate displacement before commencing treatment delivery. Potential drawbacks of electromagnetic transponders include need for implantation and specialist equipment and

staff training. In addition, significant image artefacts are produced on MRI which could limit their use within an MRI-based planning pathway. Patients with pacemakers, hip prostheses and larger patients are also unsuitable[37].

Bladder filling protocols

Wiesendanger-Wittmer *et al* performed a systematic review of strategies to reduce irradiated small bowel volume during pelvic radiotherapy, including patient positioning and bladder filling[39]. They concluded that use of a drinking protocol to achieve a full bladder reduced the volume of small bowel irradiated during external beam radiotherapy for various pelvic cancers, especially for whole pelvis treatments. Many of the studies included in this review, however, did not specify the exact drinking protocol, which limited definition of the optimal bladder volume/drinking protocol. In a retrospective cohort study of 1080 patients treated with 3D-CRT to the prostate, use of both an empty rectum and comfortably full bladder was associated with reduced biochemical and clinical relapse and risk of dying from prostate cancer[40]. However, some full bladder protocols used for prostate radiotherapy have been shown to result in greater inter-fraction variation in prostate position compared to empty bladder protocols, especially in the superior and anterior directions, and therefore may be less reproducible[41]. Jadon *et al* reviewed studies in cervical cancer and observed that daily variation in bladder volume was common and maintaining a consistently large bladder volume may become more difficult later in a course of radiotherapy because of early radiation cystitis and intravenous fluid administered with chemotherapy[2]. This may alter the position of the target and OAR. Because of this, the advice frequently given to

patients is to maintain a comfortably full bladder. Since this statement is ambiguous, more specific instructions regarding bladder emptying and filling could help minimise differences in daily bladder volume[39]. This approach is supported by an RCT by Mullaney *et al* of two different drinking protocols in prostate radiotherapy. The group found that 540 ml (3 cups of water over 10 minutes) was associated with better reproducibility of bladder volume as assessed by bladder ultrasound than 1080 ml (6 cups of water over 10 minutes)[42]. Studies of ultrasound bladder scanning have reported improved consistency of bladder volume during prostate radiotherapy[43-45]. This might be because measuring bladder volume encourages better patient compliance with drinking protocols[43]. A cohort study of 190 patients by Mullaney *et al* found that bladder volume measured by ultrasound was strongly positively correlated with the bladder volume delineated on the radiotherapy planning CT scan[44]. Different bladder filling strategies may be necessary for whole pelvis treatments compared to the more limited volumes treated during prostate radiotherapy. Eminowicz *et* al performed a cohort study comparing bladder volume measured at planning and on cone beam computed tomographies (CBCTs) performed during treatment for cervical cancer[46]. They recommended that the ideal bladder volume at planning was 150-300 ml, since larger volumes were not reproducible throughout treatment. Shorter waiting times prior to delivery of radiotherapy on chemotherapy and post-chemotherapy were also proposed to minimise bladder volume variation. Bladder ultrasound could be beneficial in maintaining consistency of bladder volumes throughout the course of whole pelvis treatments. Umesh *et* al performed a cohort study of patients treated with cervical radiotherapy[47]. They found that a 300 ml bladder volume was tolerable throughout treatment, and was achieved after a mean time of 65 minutes following bladder emptying and administration of 1000 ml of water. A further benefit from ultrasound is the potential to reduce radiation dose from

additional CBCT scans[44]. Limitations to the use of ultrasound, however, may include imprecision of volume measurements, inter-operator variability in use and additional time needed within the patient pathway to perform the scan (especially if ultrasound were to be used to determine when a fixed bladder volume had been achieved).

Patient position and immobilisation

Belly board and prone position

Prone position has been used to displace small bowel superiorly out of the irradiated volume, however evidence is less clear as to the clinical benefit for different tumour sites within the pelvis. The systematic review by Wiesendanger-Wittmer *et al* examined the impact of patient positioning (supine, prone or prone with belly board) on irradiated small bowel volume[39]. The authors concluded that prone position without a belly board could reduce the volume of irradiated small bowel compared to supine position. They reported that the addition of a belly board led to further reductions in irradiated small bowel volume for both 3D-CRT and IMRT techniques. IMRT has been shown to result in better normal tissue sparing of small bowel, rectum and bladder in whole pelvis radiotherapy compared to 3D-CRT[48]. Addition of a belly board to IMRT allowed a further reduction in irradiated small bowel volume[39]. This bowel-sparing benefit may also be observed in post-surgical patients where it might be expected that small bowel could be displaced inferiorly into a pelvic radiation field. The clinical benefit derived from small bowel sparing likely depends on the treatment indication. Extended whole pelvis treatments, such as those used in cervical

cancer radiotherapy, would be expected to include larger volumes of small bowel than radiotherapy to the prostate or pre-operative rectum. It is known that for conventionally fractionated radiotherapy, acute and late bowel toxicity is related to the volume of bowel irradiated. However, since many of the studies examined by Wiesendanger-Wittmer *et al* were retrospective, included small numbers of patients, used less conformal radiotherapy techniques and reported dosimetric rather than clinical endpoints such as rates of bowel toxicity, it is therefore difficult to be certain about the absolute clinical benefit from prone position and belly board[39]. The major concerns about prone position relate to patient comfort, stability of patient position and reproducibility of set up[2]. An RCT by Bayley *et al* of prone versus supine position in 28 patients treated with prostate radiotherapy found that supine position was significantly more comfortable for patients and easier to set up [49]. Based on the studies reviewed, Wiesendanger-Wittmer found that prone position was associated with greater set up errors. The group concluded that modern image guided radiotherapy (IGRT) techniques, such as online correction protocols, may help identify and permit correction of changes in internal anatomy and patient position[39]. As Jadon *et al* acknowledge in their review, however, application of simple translational shifts may be insufficient to account for internal motion organs within complex treatment volumes such as in cervical radiotherapy and rotational errors are also not well compensated for by on-line correction protocols[2]. Simply increasing PTV margins to account for this may negate the bowel-sparing benefits of IMRT. In the RCT performed by Bayley *et al*, prone position was associated with significantly greater anterior prostate inter-fraction motion and a larger PTV margin was therefore required to account for this[49]. Greater volumes of rectum, bladder and bowel were seen within the 50-95 % isodoses as a result, although this study was performed using 3D-CRT rather than IMRT.

Discussion

Pelvic organ motion presents a challenge to safe and effective delivery of radiotherapy to a variety of primary sites both in terms of tumour control and toxicity. IGRT using online verification and volumetric imaging such as CBCT and/or fiducial markers may compensate for certain inter-fractional changes in volume or position, although this process remains a balance between PTV coverage and avoiding excess dose to OAR. In addition, certain movements including rotations and organ deformation as well as intra-fractional changes are not well corrected for using standard IGRT strategies[3-5].

Organ motion may be more detrimental during IMRT than 3D-CRT because of the greater conformality and complex dose distributions used with IMRT. This is especially relevant to whole pelvis treatments such as those used in radical and post-operative gynaecological cancers, rectal cancers and node positive prostate cancers[17, 50-52]. In whole pelvis IMRT, the large and complicated target volumes used may be impacted by motion of multiple pelvic organs which could result in undercoverage of the planning target volumes (PTVs) or overdose of OAR. Simply increasing internal target volume margins to account for organ motion may negate the conformality benefits of an IMRT-delivered treatment. Moreover, for cervical cancer, such large variations in uterine position may occur that even with relatively large margins there remains the potential for target volume undercoverage[50]. Even for smaller target volumes, such as those used in localised prostate IMRT, organ motion may be detrimental given the small margins used. This would be particularly

important for simultaneous integrated boost treatments, for example boosting a dominant intraprostatic lesion[53].

Concerns about pelvic organ motion are especially relevant to SABR treatments where a high dose of radiation is given to a highly conformed volume in only a few fractions. A small margin from the GTV to PTV is used with steep dose gradients and any deviation from this risks undercoverage of the tumour and/or overdose of adjacent critical OAR[7]. The unpredictability of pelvic organ motion, especially bowel with its potential for intra-fractional changes in position, could compromise the safe delivery of SABR. Further research is needed to establish the extent of inter and intra-fractional bowel motion, its impact on delivery of SABR and strategies to best manage this motion.

Given the need to balance tumour control with normal tissue toxicity, there is considerable interest in adaptive radiotherapy. Various techniques have been described including reactive re-planning based on tumour shrinkage or other internal/external changes, selection of the most suitable plan from a library of plans and daily plan re-optimisation. Appropriate and consistent patient preparation and positioning, however, will still remain important in the era of adaptive radiotherapy, since widely different variations in internal anatomy would present a challenge to accurate and timely delivery of consistent treatments. In addition, organ motion artefacts, especially streak artefacts on CBCT resulting from moving bowel gas while the scan is acquired, may limit the identification of the target and adjacent OAR and thus make adapting the plan based on position of these structures difficult[54, 55].

Addressing intra-fractional changes in organ position will require real time monitoring. Treatment could be interrupted or adapted if intra-fraction motion exceeded a certain threshold. This could be addressed by electromagnetic transponders, for example using the Calypso system for prostate radiotherapy, or by MRI-delivered treatments such as the MR-Linac[37, 56]. However, the additional equipment and need for implantation may limit more general use of electromagnetic transponders and the complexities of rapid daily adaptive replanning at present represents a challenge to the routine use of the MR-Linac. An alternative could be Kilovoltage Intra-fraction Monitoring (KIM), which permits intra-fraction tracking of position of implanted prostate fiducial markers using the CBCT mounted on a standard linear accelerator without the need for additional equipment[57]. KIM is being evaluated in a phase 2 trial of prostate SABR (ClinicalTrials.gov Identifier: NCT02397317).

Ensuring more consistent bladder and rectal volumes might appear a more straightforward approach to reducing organ motion. Despite significant interest and effort in investigating different methods of addressing variation in rectal and bladder filling, however, there is often conflicting evidence regarding the benefits of commonly undertaken interventions including bladder filling protocols and rectal enemas[6, 39]. Levels of evidence and grades of recommendation for interventions to improve bladder, rectal and bowel motion have been allocated in this review (see Supplementary Material). While some RCTs were available, the majority of studies included in this review would be classed as cohort studies. Many of these are limited to a single centre and have included small patient numbers without randomisation, meaning that findings may not be more generally applicable.

While there may be some evidence to support more complex interventions, including rectal emptying tubes or use of ERBs and rectal spacers, the potential benefits have to be balanced against patient discomfort and acceptability, the need for additional procedures and increased treatment times. This may be especially relevant in the setting of prostate radiotherapy, where use of IMRT has already resulted in low rates of rectal and urinary toxicities[58].

Bowel motion remains a concern, and may not be reduced by interventions directed towards the bladder and rectum. Some studies of bladder filling and use of prone patient positioning (with or without a belly board) have observed reduced dose to small bowel but have not necessarily demonstrated definitive clinical improvements in bowel toxicity[39]. For SABR treatments of oligometastatic pelvic nodal disease, the node (and adjacent bowel) might be sufficiently distant to the bladder that bladder filling does not displace bowel away from the treatment volume. In addition, given the ablative doses used with SABR, the maximum dose to any loop of bowel close to the PTV is likely to be a more relevant constraint than the volume of bowel receiving a certain dose. Issues of stability and reproducibility of patient position when prone would also be of concern, given the highly conformal treatment volumes and high dose per fraction used with SABR.

Conclusion

There is considerable variation in pelvic organ motion and this can impact on the safe and effective delivery of radiotherapy treatments in the pelvis. Much of the evidence base to

support strategies to manage motion of the rectum, bladder and bowel is limited by absence of high-quality studies and direct comparison between interventions. Further investigation of adaptive radiotherapy strategies is likely to be required to compensate for daily variation in organ motion.

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Conflicts of Interest

None.

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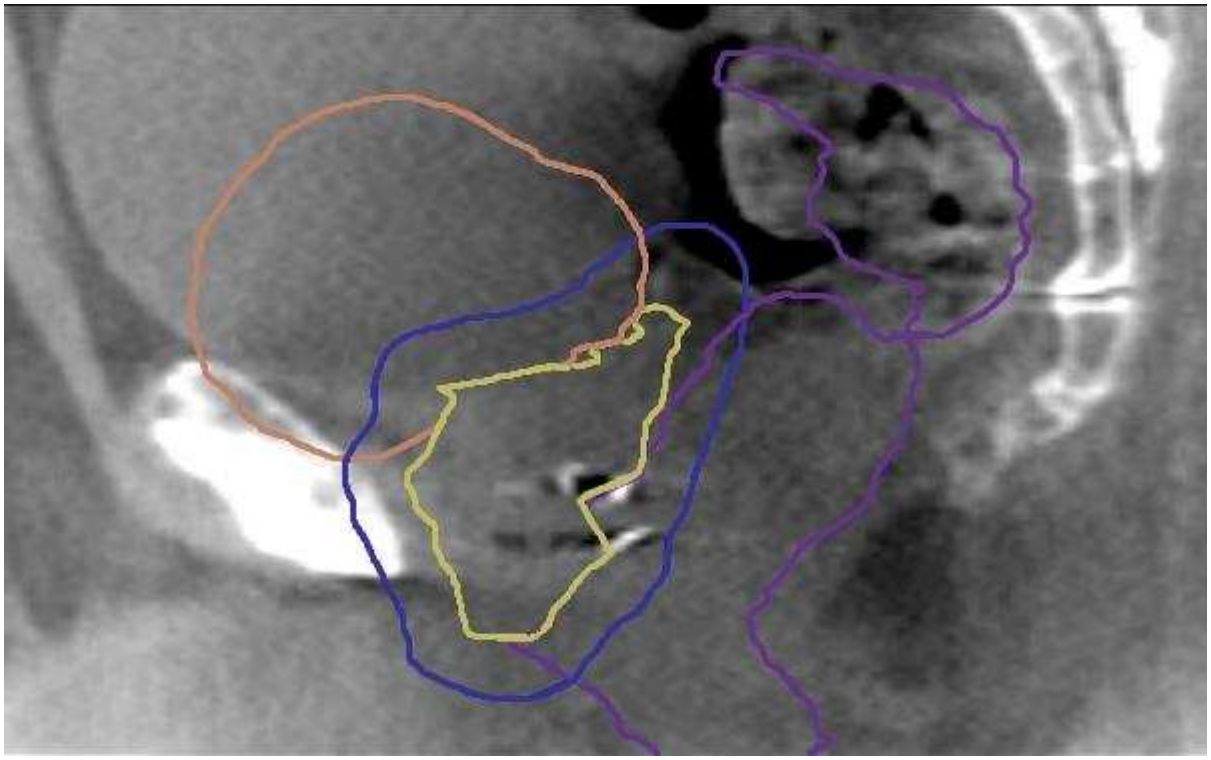
Table 1: Summary of strategies to manage pelvic organ motion and accompanying level of evidence and grade recommendation.

Organ	**Intervention**	**Best level of evidence**	**Grade recommendation**
Bladder	Bladder filling	1b	A
Bladder	Ultrasound	2b	B
Rectum	Diet/laxatives	2b	B
Rectum	Enema/suppositories	2b	B
Rectum	Rectal emptying tube	2b	B
Rectum	Endorectal balloon	1b	A
Rectum	Rectal spacer	1b	A
Bowel	Supine versus prone position	1b	A
Bowel	Prone position/belly board	2b	B
Prostate	Electromagnetic transponder	2b	B

Figure 1:



Sagittal CBCT on-treatment image with contours from planning CT overlaid (clinical target volume (CTV) prostate and seminal vesicles (yellow), planning target volume (PTV) (blue), bladder (orange) and rectum (purple)). Increase in bladder volume seen compared to planning with expansion superiorly and anteriorly. Increase in mid/upper rectal volume seen compared to planning due to faeces and gas with expansion anteriorly. Motion results in shift in prostate position compared to planning identified by displacement of fiducial markers.

Supplementary Material

The following data tables group individual studies examining strategies to address pelvic internal organ motion with a suggested level of evidence and grade recommendation. A reference list for these individual studies is included.

Diet/laxatives

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade recommendation
Lips[1]	Prostate cancer	Diet + laxative versus (vs) diet plus placebo	46+46	RCT	Magnesium oxide did not reduce intra-fraction prostatic motion	1b	A
Smitsmans[2]	Prostate cancer	Diet + laxative vs none	23+26	Prospective vs retrospective cohort	Reduction in rectal faeces and moving gas with dietary protocol/laxative	2b	B
Oates[3]	Prostate cancer	Diet + laxative vs none	15+15	RCT	Trend to improved consistency of rectal volume with diet/laxative	1b	A
Nichol[4]	Prostate cancer	Diet + laxative vs none	42+42	Internal control prospective cohort	Anti-flatulent diet/milk of magnesia did not reduce rectal volume/intra-	2b	B

					fraction prostatic motion		
Darud[5]	Prostate cancer	Diet + laxative vs none	17+15	Prospective cohort	Diet/laxative did not reduce variation in inter-fraction prostate position	2b	B
Stillie[6]	Prostate cancer	Laxative (rescan if distended rectum)	89	Prospective cohort	No relationship between rectal distension at planning and prostatic inter/intra-fraction motion if rescanned for distended rectum	2b	B
McNair[7]	Prostate cancer	Diet	22	Internal control prospective cohort	No improvement in consistency of rectal filling	2b	B

Anti-foaming medication

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence
Madsen[8]	Prostate cancer	Simeticone	47	Phase 1 study	Use of rectal catheter to remove gas confounded potential benefit from simeticone	2b	B

Probiotics

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence
Ki[9]	Prostate cancer	Probiotic	20+20	RCT	Reduced variation in inter-fraction rectal volume but some patients demonstrated excessive rectal distension	1b	A

Rectal emptying

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence
Fuji[10]	Prostate cancer	Rectal emptying tube	21	Internal control prospective cohort	Reduced variation in rectal volume and prostatic motion	2b	B
Stasi[11]	Prostate cancer	Emptying bowel before scan	10	Prospective cohort	Improved rectal dosimetry with rectal emptying	2c	B
Ogino[12]	Prostate cancer	Manual evacuation	42+34	Prospective cohort	Reduced rectal volume and prostatic motion	2b	B

Enemas

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence

Fiorino[13]	Prostate cancer	Enema	21	Prospective cohort	Limited prostatic motion with use of enema	2b	B
Graf[14]	Prostate cancer	Enema + diet	38	Prospective cohort	Limited prostatic motion with use of enema/diet	2b	B
Seo[15]	Prostate cancer	Enema	15	Prospective cohort	Reduced prostatic motion with enema	2c	B
Villeirs[16]	Prostate cancer	Enema	7	Internal control cohort	PTV coverage maintained with use of enema/bladder filling	2c	B
Yahya[17]	Prostate cancer	Diet, enema or nothing	10+10+10	Retrospective cohort	Reduced rectal volume and prostatic motion with enema	2c	B
Sabater[18]	Endometrial cancer	Enema	59	Internal control prospective cohort	No reduction in rectal dosimetry with enema	2b	B

Endorectal balloons

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence
Krol[19]	Prostate cancer	Endorectal balloon	60	Prospective cohort	Rectal capacity and sensory function post IMRT/ERB	2b	B
Smeenk[20]	Prostate cancer	Endorectal balloon	24	Internal control planning study	Reduced anal wall dose with	2c	B

					ERB for CRT and IMRT		
van Lin[21]	Prostate cancer	Endorectal balloon	22+30	Prospective cohort	ERB did not reduce random inter-fraction prostatic motion	2b	B
Wortel[22]	Prostate cancer	Endorectal balloon	85	RCT	ERB associated with reduced rectal dose and toxicity	1b	A
van Lin[23]	Prostate cancer	Endorectal balloon	24+24	Randomised cohort study	ERB associated with reduced rectal dose and toxicity	2b	B
van Lin[24]	Prostate cancer	Endorectal balloon	20	Internal control planning study	ERB associated with reduced rectal dose for CRT	2c	B

Rectal spacers

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence
Chapet[25]	Prostate cancer	Hyaluronic acid injection	16	Internal control planning study	Hyaluronic acid reduced dose to rectal wall	2c	B
Noyes[26]	Prostate cancer	Collagen injection	11	Internal control planning study	Collagen reduced dose to rectal wall	2c	B
Pinkawa[27]	Prostate cancer	Spacer gel injection	18	Internal control planning study	Spacer gel reduced dose to rectal wall	2c	B

Mariados[28]	Prostate cancer	Spacer gel injection	222	RCT	Spacer gel reduced dose to rectal wall and rectal toxicity	1b	A

Electromagnetic transponders

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence
Tong[29]	Prostate cancer	Electromagnetic transponder	236	Retrospective cohort	Generally limited intra-fraction prostate motion	2b	B

Bladder filling

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence
Kim[30]	Rectal cancer pre-operative	Distended bladder/belly board	20	Internal control planning study	Distended bladder alone and combined with belly board reduced volume of irradiated small bowel	2c	B
Kim[31]	Rectal cancer post-operative	Distended bladder/belly board	20	Internal control planning study	Distended bladder alone and combined with belly board reduced volume of irradiated small bowel	2c	B
Pinkawa[32]	Prostate cancer	Full/empty	30	Internal control	Higher dose to	2c	B

		bladder		planning study	bladder and small bowel with empty bladder		
Pinkawa[33]	Cervical/endometrial cancer	Bladder filling/prone or supine position	20	Internal control planning study	Lower dose to bladder and post-operative bowel with bladder filling	2c	B
Czigner[34]	Prostate cancer	Supine/prone position + belly board with full/empty bladder	25	Internal control planning study	No significant difference found between supine/prone + belly board. Full bladder associated with lower doses to most OARs	2c	B
Zellars[35]	Prostate cancer	Full bladder	24	Prospective cohort	Prostate displacement with large bladder volumes late in treatment	2b	B
Roeske[36]	Prostate cancer	Full bladder	10	Prospective cohort	Bladder volume varied +-30% on weekly cone beam CT	2c	B
Casares-Magaz[37]	Prostate cancer	Full bladder	27	Prospective cohort	Considerable variation in bladder volume during course of RT	2b	B
Cramp[38]	Prostate cancer	Bladder scan/none	17+17	Prospective cohort	Greater consistency in	2b	B

					bladder volume using bladder scan		
Mullaney[39]	Prostate cancer	Two different drinking protocols	110	RCT	540ml water associated with better reproducibility of bladder volume than 1080ml	1b	A
Mullaney[40]	Prostate cancer	Bladder ultrasound measurements	190	Prospective cohort	Strong positive correlation between ultrasound and CT bladder volumes	2b	B
Eminowicz[41]	Cervical cancer	Drinking protocol	10	Retrospective cohort	Ideal planning bladder volume 150-300ml	2c	B
Umesh[42]	Cervical cancer	Bladder ultrasound measurements	46	Prospective cohort	Bladder filling to 300ml feasible throughout treatment	2b	B

Belly board/prone position

Author	Patient population	Intervention	Patient number	Type of study	Outcome	Suggested level of evidence	Suggested grade of evidence
Kim[30]	Rectal cancer pre-operative	Distended bladder/belly board	20	Internal control planning study	Distended bladder alone and combined with belly board reduced volume	2c	B

					of irradiated small bowel		
Kim[31]	Rectal cancer post-operative	Distended bladder/belly board	20	Internal control planning study	Distended bladder alone and combined with belly board reduced volume of irradiated small bowel	2c	B
Kim[43]	Rectal cancer pre-operative	Prone/prone + belly board	20	Internal control planning study	Reduced volume of irradiated small bowel with prone position + belly board	2c	B
Beriwal[44]	Endometrial cancer	Prone/supine position	21+26	Prospective cohort	No difference in bowel dosimetry or toxicity with supine position	2b	B
Martin[45]	Gynaecological cancer post-operative	Supine/prone + belly board	32	Prospective cohort	Reduced volume of small bowel irradiated using prone position + belly board plus low rates of acute toxicity	2b	B
Bayley[46]	Prostate cancer	Prone/supine position	28	RCT	Lower doses to rectum, bladder and bowel and reduced prostate motion in supine position	1b	A
Bajon[47]	Prostate cancer	Prone/supine	24	Internal control	Reduced doses	2c	B

		position		planning study	to rectum and bladder in prone position		
O'Neill[48]	Prostate cancer	Prone/supine position	26	Internal control planning study	Reduced doses to rectum and bladder in prone position	2c	B
Adli[49]	Cervical cancer	Prone + belly board/supine position	16	Internal control planning study	Lower small bowel doses with prone position plus belly board	2c	B
Huh[50]	Cervical cancer	Prone with/without belly board	10	Internal control planning study	Lower volume of small bowel received prescription dose	2c	B
Pinkawa[33]	Cervical/endometrial cancer	Bladder filling/prone or supine position	20	Internal control planning study	Lower dose to bladder and post-operative bowel with bladder filling	2c	B
Stromberger[51]	Cervical cancer	Prone + belly board/supine position	10	Internal control planning study	Lower volume of small bowel received higher doses	2c	B
Greer[52]	Prostate and rectal cancer	Prone/supine position	11+8	Prospective cohort	Larger average random and systematic errors in prone position	2c	B
Kitamura[53]	Prostate cancer	Prone/supine position	10	Internal control study	Larger intra-fraction	2c	B

					prostatic motion in prone position		
Shah[54]	Prostate cancer	Prone/supine position	20	Internal control study	Larger intra-fraction prostatic motion in prone position	2b	B
Weber[55]	Prostate cancer	Prone/supine position	18	Internal control study	Larger systematic errors in prone position	2c	B
White[56]	Rectal cancer pre-operative	Prone/supine position	25	Internal control planning study	Larger small and large bowel doses in supine position	2c	B
Heijkoop[57]	Gynaecological cancers pre/post-operative	Prone + belly board/supine position	26	Internal control planning study	Smaller small bowel and rectal doses in prone position + belly board only if larger nodal margins required	2c	B
Sawayanagi[58]	Prostate cancer post-operative	Prone + belly board/supine position	17	Internal control planning study	Volume of small bowel, rectum and bladder in or near PTV lower in prone position + belly board	2c	B
Koelbl[59]	Rectal cancer post-operative	Prone + belly board/supine	20	Internal control planning study	Irradiated volume and	2c	B

		position			total dose to bladder and small bowel lower in prone position + belly board		
Hollenhorst[60]	Rectal cancer pre/post-operative	Prone with/without belly board	20	Internal control planning study	Lower volumes of small bowel irradiated using prone position + belly board	2c	B
Czigner[34]	Prostate cancer	Supine/prone position + belly board with full/empty bladder	25	Internal control planning study	No significant difference found between supine/prone + belly board. Full bladder associated with lower doses to most OARs	2c	B
Estabrook							

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