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Towards an evidence based treatment technique in prostate radiotherapy

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Abstract

There is a large evidence base around prostate cancer. Most of this concentrates on which stages of the disease to treat with which modality. The purpose of this study is to try and determine from the literature an evidence based radiotherapy treatment technique. The evidence is examined on prostate and patient motion, the effect of bladder and rectum filling, patient positioning and error detection with portal imaging. The technique derived is patient supine or prone with empty bladder and bowel. A simple leg immobilisation device is recommended, with set-up to couch height. The required margins are 13.2 mm laterally, 18 mm anterior-posteriorly and 21.3 mm cranio-caudally using a three-dimensional margin recipe. It is shown that an intensive portal imaging routine is required to demonstrate that systematic set-up errors are below 5 mm.

Keywords

Prostate radiotherapy technique; evidence based medicine; portal imaging

INTRODUCTION

Whenever possible, practice should be evidence based although implementation of the evidence may prove problematic[1,2] with even the collecting and analysing of the evidence being a difficult task.[3] As part of a review of our current technique for prostate radiotherapy we tried to glean from the literature an evidence-based treatment protocol for external beam prostate radiotherapy. Prostate radiotherapy has been intensively studied with an increasing number of papers per year being published on the subject. A literature search on evidence based prostate radiotherapy found only one[4] reference addressed treatment planning issues, and none dealt with the entirety of the treatment delivery technique. A wider search on prostate radiotherapy did find numerous studies looking at specific elements of treatment delivery. These included studies of the motion of the prostate within the pelvis and the pelvis itself during treatment; the effects of immobilisation and bladder and rectum filling on prostate movement; and studies on detection of set-up errors.

Given the size and diversity of the literature on this subject we have been unable to perform an exhaustive and unbiased search of the evidence, so the protocol derived here is not evidence-based in the strictest sense.[3] This study tries to answer six questions pertinent to prostate radiotherapy technique using the literature. These questions are: what state should the bladder and rectum be in for planning and treatment; is the supine or prone position better for treatment reproducibility; what, if any, form of immobilisation is required; what margins are required to ensure adequate irradiation of the prostate; is setting up to tattoos best; how many portal images are required to quantify systematic displacements? It also highlights areas where further studies would be useful.

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PROSTATE MOTIONS

Effect of rectal and bladder filling

Most studies looking at the effect of bladder and rectal filling use multiple CT scans throughout treatment. These are summarised in Table 1.[5–13]

All nine studies show that rectal filling significantly effects prostate position. Only 5 of the 9 studies show that bladder filling is correlated with prostate position. This may be a reflection of the fact that this correlation is less than that found for rectum.

Three studies looked at the question of the importance of initial volumes of the bladder and rectum. Zelfsky et al.[5] found prostate displacement during a course of radiotherapy to be more pronounced for patients with large initial rectal and bladder volumes. Zellars[9] found that large bladder volumes late in therapy are strongly associated with posterior prostate displacement and were worried that this prostate displacement may result in marginal miss and hence cautioned against the practice of treating patients with full bladders. Beard et al.[12] found neither the initial rectal volume nor the initial rectal diameter could be used to predict subsequent target motion when evaluated either singly or as part of a multiple regression model.

As acute treatment toxicity can affect bladder and rectum filling and this in turn can effect prostate position, we looked for evidence that the planning scan is representative of the prostate position during treatment. Dawson et al.[10] studied six patients and found that prostate position variations were evenly distributed around the initial position for some patients studied, but unpredictable patterns were seen in others. Antolak et al.[11] found that bladder and rectal volumes decreased between the pre-treatment CT scan and the first on-treatment CT scan for 17 patients, but were constant for all on-treatment CT scans and stated the need for more consistent methods (e.g. empty rectum) for reproducing prostate position. This consistency of rectal and bladder volumes has not been reproduced in other studies. Roeske et al.[7] found that bladder and rectal volumes varied by 30% during radiotherapy of 10 patients. Similarly Zellars et al.[9] found on average, bladder and rectal volumes decreased to 51% (±29%) and 82% (±45%) of their pre-treatment values on 24 patients.

Table 1. CT observational studies that look at effect of bladder and rectal filling on prostate position.

Organ	Associated with prostate movement	Not associated with prostate movement
Bladder	5–9	10–13
Rectum	5–13	

Apart from these observational studies looking at the correlation of bladder and rectum volume with changes in prostate position, there is one experimental study that has measured changes in prostate position by filling the bladder and rectum. Schild, Casale and Bellefontaine[14] found the posterior margin of the prostate shifted anteriorly from 0 to 9 mm. (median = 1 mm) on distension of the rectum in 18 men. The posterior border of the prostate was displaced anteriorly by more than 5 mm in 17% of these. Distension of the bladder shifted the posterior border of the prostate posteriorly from 0 to 8 mm. (median = 2 mm) in 11 men. The posterior border of the prostate was shifted more than 5 mm in 9% of these. Again the rectal filling seems to have more influence than the bladder filling, but they act in opposite directions. So if a patient was planned with a relatively empty bladder and a full rectum, but treated with a full bladder and an empty rectum then a large (possibly 17 mm) posterior shift in the posterior border of prostate could occur. This may result in a geometric miss of the target.

There is also an intriguing study by Padhani et al.[15] looking at prostate motion in real time using cine MRI. They imaged 55 patients with biopsy-proven or suspected prostate cancer every 10 seconds for 7 minutes and found 86 rectal movements resulting in 33 anterior-posterior prostate movements. In 16% of patients this movement was greater than 5 mm. The maximum displacement observed was 14 mm anteriorly. This indicates that significant displacements of the prostate gland can occur during a single fraction of radiotherapy and needs to be accounted for in the size of the margins.

Range of prostate motions

There are many studies reporting the range of motion of the prostate, the pelvis (bony anatomy), and the combination of these two factors under a variety of conditions. Booth and Zavagorodni[16] have attempted to combine these studies and have

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produced a limited meta-analysis. We will summarise results for the prostate alone and in combination with the set-up error to illustrate the range of reported values. The set-up error is dealt with in a later section.

We looked at six studies that measured the prostate displacement using multiple CT scans.[5–7,11,12,17] These indicate that the motion along the left-right (L-R) axis is less than the motion about either the superior-inferior (S-I) or anterior-posterior (A-P) axes. These studies find the mean and standard deviation of the L-R motion to be about 1 mm. For the S-I and A-P axes the mean and standard deviation of the motions are similar at about 4 mm, but for the A-P axis deviations up to 20 mm are observed.[12] Also Mellian et al.[6] note that movements are significantly greater above the bladder base than below it. This probably reflects changes in the anatomical restrictions to motion.

We found three papers reporting studies of prostate motion alone using implanted radio-opaque markers.[8,18,19] The results are similar to the above CT studies with Vigneault et al.[18] finding inter-fractional displacements up to 16 mm (but no intra-fractional motion) and Crook et al.[8] finding the prostate displaced more than 10 mm posteriorly in 30% of patients. These motions are secondary to changes in rectal and bladder filling.

The combined uncertainty of prostate motion and set-up error has also been investigated using multiple CTs.[10,20–22] Stroom et al.[20] looked at both prone and supine patients, using a laxative before the planning scan to minimise the rectal content. For both positions they recommend a lateral planning margin of 5 mm and a margin of 10 mm for the other directions. This is similar to Dawson et al.,[10] who quote 95 % confidence margins as 12.4 mm (A-P), 10.3 mm (S-I), and 5.6 mm (L-R) and Tinger et al.[21] at 7–11 mm. Although for complete (99%) coverage margins of 10–16 mm are required.[21] Lattanzi et al.[22] manage to reduce the daily field placement error on 6 patients to 3 mm using a daily CT localisation technique.

PATIENT SET-UP

Patient position

We used two criteria to judge between patient positions: dose to critical structures and reproducibility of set-up taking into account both organ motion and set-up error. A position that maximises reproducibility while minimising dose to critical structures (by maximising the distance between the prostate and adjacent organs) would be ideal. The advantage of increasing reproducibility is the ability to decrease margins, hence possibly reducing the amount of normal tissue in the treatment volume.

There are three studies[23–25] that find the prone position reduces the rectal dose compared to the supine position, with two of these[24,25] also finding reduced bladder doses. Weber et al.[25] however do note that their results may be artifactual due to the positional-dependent rectal air volume that may vary from day to day. None of these studies considered the time dependence of this dose advantage, but McLaughlin et al.[23] do think that the dose advantage in the prone position is due to the paradoxical retraction of the rectum away from the prostate in this position. Also Bentel et al.[26] find that it is not only gravity, but also pressure from the tabletop that influences the relative positions of the pelvic organs.

Neither position is found to be advantageous with regard to reproducibility.[20,23,25] This is due to the slight gain in internal prostate stability in the prone position being countered by an increase set-up error.

Immobilisation

There are many devices that have been used to immobilise patients. Most of these are externally fitted devices, although one study[35] reports the effective use of a rectal balloon for internal immobilisation. The criteria we used to judge external immobilisation devices were reduction of set-up error and degree of customisation. A simple, non-customised device that could be used by many patients was judged better than a single use customised device giving the same degree of immobilisation due to its reduced cost.

Tables 2[27–33] and 3[30–34] summarise those studies that quantify set-up errors as "% displacements > 5 mm". We have added data from our own studies at Addenbrooke's as a comparison. Table 2 shows that without immobilisation between 15% and 66% of patients may have displacements greater

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Table 2. Summary of studies reporting displacements measured from portal images of prostate patients (no immobilisation).

Study	Percentage with displacement > 5mm		
	Sup-Inf	Rt-Left	Unspecified
Addenbrooke's			15%
Hanna[27]	33%	21%	
Gildersleve[28]	24%	15%	
Huddart[29]	29%		
Bijhold[30]		17%	
Rosenthal[31]			66%
Italia[32]			24%
Mubata[33]			16%

than 5 mm. Table 3 indicates that some form of immobilisation can improve this figure, and leg/ankle immobilisation seems most effective reducing displacements > 5 mm to between 4% and 8%.

There have been several comparative studies reported. Catton et al.[36] found the use of a soft immobilisation device supporting the lower legs was significantly better than no immobilisation. Soffen et al.[37] found that rigid whole body immobilisation was better than no immobilisation. Bentel et al.[38] did find a statistically significant reduction in the A-P set-up uncertainty in patients immobilised with an individualised hemi-body cast compared to no cast, but no change in the other two axes. Two studies compare a wide variety of immobilisation techniques.[39,40] One[39] compares no immobilisation with four types of immobilisation (alpha cradle from waist to upper thigh, alpha cradle from waist to below knee, a below knee Styrofoam leg immobiliser, aquaplast cast covering abdomen to mid-thigh with alpha cradle to lower legs and feet). This study found no significant

Table 3. Summary of studies reporting displacement from portal images of prostate patients immobilised with a variety of devices.

Study	Immobilisation	% with displacements > 5mm
Addenbrooke's	Knee-fix	14%
Addenbrooke's	Legstocks	8%
Bijhold[30]	Legstocks	8%
Rosenthal[31]	VacFix	43%
Italia[32]	Shell	24%
Fiorino[34]	VacFix – Pelvis	21.60%
Fiorino[34]	VacFix – Legs	4.40%
Mubata[33]	VacFix and ankle support	4%

reduction in overall patient movement (greater than 5 mm) with any of these devices compared to no immobilisation. A recent study[40] compares a below knee to ankle foam rubber leg cushion, a whole body alpha cradle, and the Hipfix system (which consists of a thermoplastic sheet attached to rigid board under the pelvis). This found that the leg cushion gave 15–18% (depending on axis) of fraction with displacements greater than 5 mm. For the alpha cradle this was 7% to 17%, and 2% to 6% for the Hipfix system. The Hipfix system reduced errors greater than 10 mm to 0.25% of fractions. Given the marked variation in reported efficacy of the various immobilisation devices, the question of which, if any, system is best is still open. The data in Table 3 seems to indicate that some form of leg immobilisation does decrease the percentage of displacements over 5 mm, but until further comparative studies have been completed each institution needs to determine which form of immobilisation it finds most acceptable.

Range of motion of the pelvis during prostate treatments

Several authors have studied pelvic motion. Jones et al.[41] found mean displacements about each axis to be less than 2 mm, with standard deviations around 3 mm. They suggest Gross Tumour Volume (GTV) to field margins of 13 mm laterally and 21 mm in the A-P direction. Other authors[42,43] have reported similar results. An excellent study by Stryker, Shafer and Beatty[44] compared digitally reconstructed radiographs (DRRs) from planning CTs with electronic portal images. They found mean and standard deviations in displacements of about 2 mm, with 98% of S-I and 95% of L-R and A-P positions to be within 5 mm. Four of their 25 patients had DRR to first treatment displacements greater than 5 mm, 3 being in the L-R axis. They find their 20 mm GTV to field edge margins adequate.

The use of couch height for patient set-up

The two set-up methods commonly used to determine the anterior-posterior isocentre location in pelvic radiotherapy are to align lateral localization lasers with lateral skin tattoos on the patient, or to set the couch height so that the isocentre is at a fixed height (determined during simulation or treatment planning) above the couch top. It has been found[45,46] that the fixed height technique gives much more accurate localization of the anterior-posterior isocentre in pelvic radiotherapy than lateral skin tattoos. This result would have to be confirmed at individual centres as different equipment could produce a different result.

MARGINS

ICRU 50[47] defines the GTV is the palpable or visible extent of the malignant tumour and the Clinical Target Volume (CTV) as the GTV plus a margin for sub-clinical disease. These volumes are based entirely on anatomical, topographic and biological factors and do not consider any technical factors (such as patient set-up). As patients are not rigid, immobile objects further margins are required around the CTV to ensure that it is irradiated during treatment. The resulting volume is the Planning Target Volume (PTV). It is the PTV that is used in treatment planning. ICRU 62[48] split the CTV to PTV margins into two portions. The internal margin takes into account the general motion of an organ, breathing and other "biological" movements and increases the CTV to the Internal Target Volume (ITV). Technical factors, such as daily set-up uncertainty, increase the ITV to the PTV by the addition of a set-up margin. ICRU 62 notes that margins may be combined in quadrature but, in practice, the PTV must be delineated by the radiation oncology team based on experience and judgement drawn from observation and evaluation of the risk of failure and complications.[48]

It has been argued that the splitting of the CTV to PTV margin into biological and technical portions is not helpful and a better division would be between preparation and execution errors.[49,50] Preparation errors have three components: set-up error at planning imaging; uncertainties in delineation of the target; and the fact that it is unlikely that the position of the CTV at the time of planning imaging coincides with its mean position during treatment. These errors result in the planned CTV being systematically displaced from the CTV at time of treatment. It is assumed that each of these components, although fixed for a particular patient, is randomly distributed over a population of patients. Hence, large preparation errors can lead to a large under-dosage for some patients. Execution errors are due to random set-up errors and organ motions during treatment and have the effect of blurring the dose distribution over the CTV. This results in a slight reduction in the dose for most patients. Preparation errors have more impact than execution errors and thus require a larger margin factor.[50] This formalism emphasises the statistical nature of the uncertainties in target definition and requires the choice of a percentage of the patient population for which a given dose level is to be achieved (e.g. for 90% of the patient population, the minimum dose to the CTV must be 95%, or higher, of the nominal dose). It is not possible to guarantee that the CTV is within the PTV at every fraction using finite margins.

The margin factor is the factor the standard deviation (SD) of errors is multiplied by to obtain a particular probability of the CTV being inside the PTV (e.g. if the distribution of the errors follow a one-dimensional normal distribution, the CTV will be inside the PTV 95% of the time if the margins were set at 2 SD). There has been discussion in the literature as to the type of distribution to use for the various errors.[49–51] For preparation errors margin factors of 2 to 2.5 have been proposed.[49,50] For execution errors the recommended factor ranges from 0.7[49,50] to 1.65.[50,51]

To determine the required margins each source of uncertainty needs to be quantified and combined. Specifically organ motion and set-up errors both contribute to preparation and execution errors, whilst uncertainties target delineation are part of the preparation error. The prostate itself seems to have a very limited motion in the L-R axis (about 1 mm standard deviation), but a larger freedom in the other two principle axes (about 4 mm standard deviation) (see previous section on 'Range of prostate motions'). This freedom increases above the bladder base.[6] The standard deviations of set-up errors are the same in all directions at about 3 mm. There is some evidence that the S-I direction may be slightly more reproducible.[44] There is limited work on target delineation error in the prostate.[52] This shows that the S-I extent of the prostate can be particularly difficult to determine from CT scans. This can lead to differences in CTV length of 10 mm between clinicians. The delineation error also varies from level to level within the prostate.

Reasonable values of the standard deviation of these errors are 3 mm in the L-R and A-P directions and 5 mm in the S-I direction. Using the margin recipe from van Herk et al.[50] the required margins are L-R 13.2 mm, A-P 18 mm, S-I 21.3 mm. These figures are larger than those derived by van Herk (9.5 mm, 11 mm, and 13 mm respectively[50]) mainly as we have used inter-operator delineation variability rather than intra-operator delineation variability and slightly larger values for both organ motion and set-up errors in the margin calculation. If we remove the contribution of the delineation error to the preparation uncertainty our margin dimensions are reduced to 10.2 mm L-R and 16 mm in the other directions. These are larger than other margin figures found in the literature. This is because we have not used the one-dimensional recipe of "two standard deviations equals 95% confidence limits" used in these studies, but have used the recently published three dimensional recipes.[49,50] It must be emphasised that these margins have been arrived at using data from the literature and individual centres must determine their own set-up uncertainties and hence their own margins. The radiation oncology team delineating the PTV must also balance any risk of complications that may be caused by the use of large margins.[48] Margins may be reduced if special set-up techniques are employed.[22, 53]

DETECTING SYSTEMATIC DISPLACEMENTS

When a portal image is obtained from a treatment field the treatment isocentre will generally differ from the planned isocentre (as taken from a simulator film or CT planning DRR). Some of this displacement may be due to random error and some due to systematic error. There is no way of differentiating between the two types of error based on one film. To find a systematic error one requires more than one film. The more films obtained, the better defined are the random and systematic errors. Any systematic error should be corrected as quickly as possible in a course of treatment. So we need to determine the minimum number of films to be taken that identifies a systematic error with reasonable accuracy.

Considering this problem as an exercise in statistics, it can be reformulated as a simple null hypothesis that the mean of the portal film isocentre positions is the same as the planned isocentre position. To test this hypothesis for small sample numbers (less than 10 films) one uses a Student's t-test.[54] This can be formulated as:

$$\text{Detectable isocentre displacement} = t \times s / \sqrt{n}$$

Where t is value of the 95% confidence level of the Student's t-distribution with (n-1) degrees of freedom, s is the standard deviation of the displacements calculated from n films. For 2 films $t = 13$, for 3 films $t = 4$ and for 4 films $t = 3.2$. This means that 3 films are 4 times more sensitive at detecting systematic isocentre shifts than 2 films, and 4 films are 7.4 times more sensitive than 2 films. It also means that 6 films are required to reliably detect systematic errors the same size as the random errors. So if s is about 3 mm for pelvic motions,[39] 2 films will only detect (with 95% confidence) systematic errors around 28 mm, three films 7 mm, four films 4 mm, and six films 3 mm. So four films are required to detect systematic errors of 5 mm if the random error is 3 mm. The greater the random error, the more films are required to detect systematic errors of a given magnitude.

Denham et al.[55] have suggested a method for detecting systematic errors based on Hotelling's t^2 statistic. This is a two dimensional version of Student's t test. They have tested it against other models for detecting systematic errors and found it to be more sensitive.[56] Bel et al. have used a shrinking action level technique to reduce mean deviations greater than 5 mm from over 25% of patient to fewer than 2% of patients in 3 centres.[57] The detection of this size of error depends on computer-aided analysis rather than a visual inspection of the films.[58]

CONCLUSIONS – AN EVIDENCE-BASED PROTOCOL?

We have attempted to derive an evidence based treatment protocol for prostate patients using the above evidence. The strength of evidence varies from question to question, with some areas requiring further study. We have adopted ICRU 62 formalism,[48] in that we have looked at prostate motion separate from set-up error, but for margin calculations we have used recently published three-dimensional margin recipes.[49,50] Preparation error due to systematic differences between the

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patient during planning imaging and the patient during treatment can be a major source of error. Our method for determining the "best" treatment protocol is to identify and minimise differences between the planning conditions and treatment conditions and minimise variation in treatment conditions. One source of preparation error not directly addressed here is that CT couches tend to be curved while treatment couches are flat. This can be overcome to some extent by using CT couch inserts to give the CT couch a flat top.

The bladder and rectum should be empty for planning and treatment

There is convincing evidence that degree of rectal filling significantly affects the position of the prostate. Therefore, attempts to keep this the same between planning scans and treatment and also throughout treatment should be encouraged. Rectal splinting[35] is effective, but may prove impractical in a busy treatment environment. A more acceptable approach is to have the patient empty their rectum before planning CTs and every treatment fraction.[59]

Bladder filling alters prostate position rather less than rectal filling. As bladder size has been found to decrease during treatment[7,9] and large bladder volumes may be associated with geographic misses,[9] it may be that scanning and treatment with empty bladder is best.[59] This analysis is assuming conformal fields, so any small bowel is likely to be shielded during treatment.

The patient may be either supine or prone

Neither the prone nor supine positions are found to be more reproducible. This is because although the prone position increases set-up errors, it decreases prostate motion within the pelvis. There is some evidence that the prone position reduces rectal and bladder doses compared to supine, but this requires further work. Until this issue is resolved, neither position can be regarded as superior.

An immobilisation device may improve reproducibility

There have been a wide variety of efficacies reported for a range of devices. It is possible that simple leg immobilisation may be as effective as any other method of immobilisation for prostate patients, but further studies are required to confirm this. Individual institutions need to determine the degree of immobilisation provided by their own methods.

Margins are required to allow for a variety of uncertainties

As discussed previously, margins are a statistical construct designed to account for random (execution) errors and systematic (preparation) errors that cannot be removed. The prostate moves as a result of bladder filling, rectal filling and rectal movements. To reduce preparation error these factors need to be controlled as far as practical. For example, if a patient is scanned with a full rectum but is treated with an empty rectum (possible due to treatment induced diarrhoea) then there will be a systematic difference in prostate position. The rectum has also been demonstrated to move the prostate significantly on a time scale similar to a treatment fraction.[15] This change in prostate position is not easily controlled and can be over 5 mm in the A-P direction.

To calculate adequate margins accurately much more work needs to be carried out in the areas of determining and minimising the uncertainties in CTV delineation. Current data suggests relatively large margins of 13.2 mm L-R, 18 mm A-P and 21.3 mm S-I are required. This may not be achievable in practice due to the proximity of dose limiting structures.

Set-up to couch height

Fixed height technique gives a more accurate localization of the anterior-posterior isocentre in pelvic radiotherapy than lateral skin tattoos.[45,46] This result would have to be confirmed at individual centres as different equipment could produce a different result.

Films and corrections

One portal image is not enough to verify a high accuracy treatment. A simple protocol would be to take an image on day one. If this shows an unacceptably large error, say greater than 10 mm, then it should be corrected. If not, then take three more images on subsequent days and determine the mean displacement. If this is greater than 5 mm then correct it. After any corrections obtain four more images to ensure the systematic error is less

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than 5 mm. Weekly images are not enough to monitor time trends in patient position. If a time trend in patient position is suspected then daily imaging, with a four day rolling average, is required to ensure that systematic errors of more than 5 mm do not occur. This is quite an intensive protocol and requires electronic portal imaging, computerised analysis tools, and dedicated imaging staff to be practical. If fewer images can be taken and analysed, then a greater systematic error will have to be tolerated.

CONCLUSION

So the prostate technique derived from the literature is patient supine or prone with empty bladder and bowel. A simple leg immobilisation device should be used, with set-up to couch height. The required CTV to PTV margins are 13.2 mm laterally, 18 mm anterior-posteriorly and 21.3 mm cranio-caudally using a three-dimensional margin recipe. An intensive portal imaging routine is required to ensure that systematic set-up errors are below 5 mm.

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