Clinical Investigations

Original paper

Effect of constipation on dosimetry after permanent seed brachytherapy for prostate cancer

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Abstract

Purpose: A major concern in prostate brachytherapy is rectal toxicity, which mainly depends on the dose and volume of rectum involved by radiation. We hypothesize that the rectal distension, as produced by constipation, influences the dosimetric parameters of the rectum and other pelvic organs.

Material and methods: An open, controlled, prospective, paired trial (pre-post test) was designed and conducted. Twenty-three patients treated with prostate brachytherapy were recruited, of which 21 were evaluated. All of them underwent two CT scans, the first one with empty rectum and the second with rectum distended by a catheter balloon. Target volumes and organs at risk were delineated, and dosimetric parameters were calculated and then compared for each patient between both CT.

Results: For rectum, D_{2cc} increased 15.8% ($p < 0.001$) and $D_{0.1cc}$ 24.05% ($p = 0.002$) when the rectum was full. A significant difference was also found in dose distribution to prostate, when rectum is distended, a 1% decrease in V_{100} ($p = 0.031$) and a 3.25% in D_{90} ($p = 0.033$) was registered.

Conclusions: The status of rectal distension, as occurs in constipation, has a deleterious influence on prostate brachytherapy dosimetry. This situation increases the radiation to rectum and modifies dose distribution to prostate. We recommend prevention of constipation for at least two half lives of the radioactive seeds.

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Key words: brachytherapy, constipation, LDR, prostate cancer, rectal toxicity, seeds.

Purpose

Brachytherapy has become a first-line option in the treatment of localized prostate cancer [1,2]. One of the main concerns of the brachytherapist when performing a seed implant is rectal toxicity. A predictor of this toxicity is the radiation dose received by the rectum, and its relation to the irradiated volume [3-8]. In brachytherapy, this rectal dose can be inferred from the dosimetric study of intra or postoperative images. However, these images are only able to provide a dose value for a given anatomical situation. Physiological variations such as occurring in defecation cycle can produce anatomical changes that alter the planned distribution. The incidence of constipation increases with age and is particularly prevalent in patients 65 years of age or older [9], and at least 70% of patients with idiopathic chronic constipation show anorectal dilatation via barium enema [10]. Narcotic analgesics, often prescribed in the postoperative period, may also promote retention of stool in the rectum during the period of highest activity of the radioactive sources. It is assumed that rectal distension influences dosimetry in external radiation for prostate cancer [11,12]. Some specialists recommend avoiding constipation after permanent implant brachytherapy, while the activity of the seeds remains significant [13] but there are no objective data to support these recommendations. Only the results published by Merrick *et al.*, although based on a single case report, highlight the possible relationship between rectal content and rectal dosimetry in brachytherapy [14]. In this chronically constipated patient, they found a substantially higher rectal dose for the full versus the empty rectum.

We aimed to determine, through a prospective controlled study, whether there was a relationship between the rectal content and dosimetry in permanent seed prostate brachytherapy, as well as quantify its importance.

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Material and methods

An open controlled prospective paired trial (pre-post test) was conducted to investigate the dosimetric changes induced by rectal filling. Study was approved by the local Ethics Committee for Clinical Trials.

Inclusion and exclusion criteria

Inclusion criteria: Patients diagnosed with low-risk prostate adenocarcinoma undergoing prostate brachytherapy with ^{125}I permanent seeds, for a prescribed dose of 145 Gy in real-time dosimetry by transrectal ultrasonography imaging. We considered ineligible the following: 1) patients in whom intraoperative dosimetry, as seen by transrectal ultrasonography, was not optimal (V_{100} > 95%, V_{150} < 65%, D_{90} > 100% of CTV); 2) patients suffering fecal incontinence or previous severe rectal diseases.

In addition, we excluded the following patients after recruitment: 1) patients who experienced deviations in study method; 2) patients who, despite enema administration, still presented rectal feces at first CT scan; 3) patients in whom radiographic or anatomical abnormalities at first CT scan made the images unusable.

All patients were recruited the day after seed implant. All patients were fully informed by the researchers, and a written informed consent was obtained before inclusion.

Twenty three patients were recruited from March to June 2013. Mean age was 68 years (55-78). Mean number of seeds implanted was 55.7 (37-77). Seed activity ranged from 0.552 to 0.599 U.

Methods

Twenty eight days after brachytherapy implant, patients underwent a double CT study, the first with empty rectum and the second with the rectum distended by a catheter balloon, to compare differences in dosimetry. One hour before CT scan, a 250 cc enema was applied to each patient, who had to retain it for ten minutes before defecation, to ensure complete rectal emptying. Then, with the patient supine on the scanner table, a 20 gauge Foley type catheter was inserted in the rectum, without expanding the balloon. The catheter was placed at the beginning of the procedure and for both CT scans in order to avoid having to move the patient and to enhance the comparability between the two series of images.

In this position, the first set of images was collected using standardized helical computed tomography at 120 kV and 100 mA. Images included from the upper edge of the sacroiliac joint to the penile bulb. Reconstructions were performed 3 mm thick and 3 mm of spacing between slices. In this first set of images, the investigator ensured that the rectum was completely empty, and that there was no abnormality, which could invalidate the data. These CT images correspond to the *empty rectum* status (Figure 1A). Then, preventing any movement of the patient, the rectum was dilated by inflating the balloon of the catheter with 30 cc of air. Gently pulling the catheter, the balloon was displaced to lodge in the lowest part of the rectum. One second CT scan was then performed in the same conditions as the first. This second set of images corresponds to the *full rectum* status (Figure 1B).

Images were exported to a computer using the software VariSeed v7.2 (Varian Medical Systems, Inc., Palo Alto, CA, USA) for dosimetric clinical use. In each series of images of each patient, the following structures were defined: prostate, urethra, seminal vesicles, rectum, bladder, and PTV (defined as prostate +3 mm avoiding rectum). The structure balloon was only considered in the full rectum series. Except for the rectum structure, volume measures were remarkably similar between the two series of each patient.

Subsequently, we proceeded to dosimetric study, calculating for: 1) rectum: volume, $V_{145\%}$, $V_{100\%}$, $V_{75\%}$, $V_{50\%}$, D_{2cc}, D_{1cc}, $D_{0,1cc}$, 2) PTV: volume, $V_{150\%}$, $V_{100\%}$, D_{90}, D_{50}, 3) prostate: volume, $V_{150\%}$, $V_{100\%}$, D_{90}, D_{50}.

Statistical analysis

A Kolmogorov-Smirnov study was performed to verify that all variables followed a normal distribution. Subsequently, the differences of dose to structures for the status full versus empty rectum were compared in each patient, calculating their significance with Student's *t* for paired samples.

Finally, we analyzed whether a correlation existed between prostate volume and dose difference at full or empty rectum. To do this we calculated the correlation coefficient (Pearson's *r*).

Differences with a p value ≤ 0.05 were considered statistically significant.

Results

Twenty three patients had signed informed consent and were included in the study. Two were subsequently excluded: one patient voluntarily withdrew from the trial before CT completion and one patient showed significant artifacts in the first CT (hip replacement), which made the images unusable. The results relate to the remaining 21 cases.

Dose to rectum

As shown in Table 1, dose to rectum, represented by D_{2cc}, D_{1cc}, and $D_{0.1cc}$, increased in the status full rectum compared with empty rectum. These differences were statistically significant. D_{2cc} increased in 20 out of 21 cases, ranging from –3 to + 29%, which means between –4 and +42 Gy with an average increment of 23 Gy. $D_{0.1cc}$ also increased an average of 24%, which means 35 Gy.

$V_{145\%}$, $V_{100\%}$, $V_{75\%}$, and $V_{50\%}$ also increased significantly, despite the fact that prostate brachytherapy involves a very circumscribed area of the rectum and V_{50} represents the dose delivered to greater volumes of the rectum.

The structure balloon yielded a mean volume of 27 cc, which means that the pressure of the rectum and the balloon itself slightly compressed the 30 cc of injected air.

Dose to other structures

Doses to PTV decreased with rectal filling, albeit modestly (Table 1). D_{90} was reduced in 17/21 cases when the rectum was full, with an average of 2.8%, which means 4 Gy.

For the structure prostate, $V_{100\%}$ decreased by 1% while D_{90} nearly 5 Gy. These differences between empty and full rectum, though small, were statistically significant.

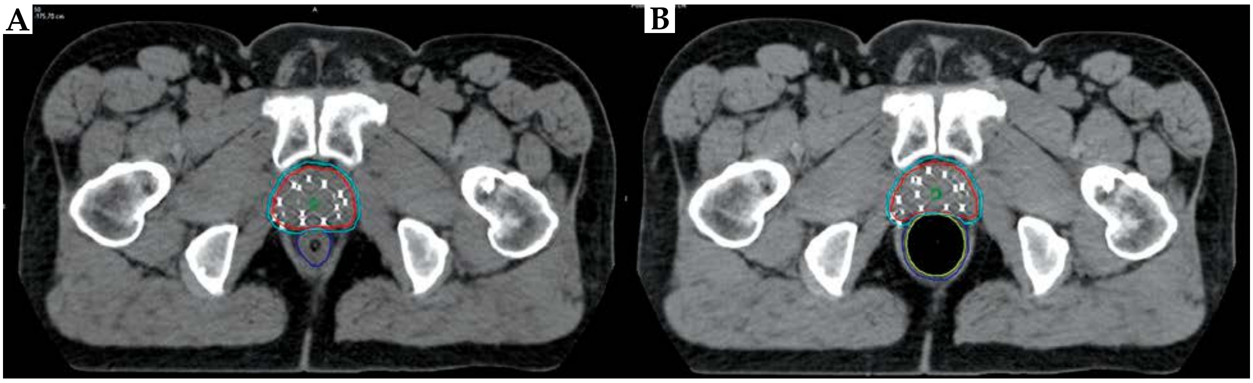

Fig. 1. A) Computed tomography image with "empty rectum" status. B) Same patient, same slice with "full rectum" status: balloon filled with air. Note differences not only in rectum but also in prostate shape

Table 1. Differences in dosimetry between full rectum status and empty rectum status. The difference was calculated for each patient as full minus empty. The mean of these differences is reported. Positive values for rectum indicate that this organ receives more radiation in the full rectum status. Negative values for PTV and prostate indicate that this structures receive less radiation in the full rectum status. Statistically significant values ($p \leq 0.05$) appear in bold

Rectum	Mean of differences between full vs. empty (SD)	*p*
Volume in cc	+27.99 (3.85)	**0.000**
$V_{145\%}$	+0.70 (0.68)	**0.000**
$V_{100\%}$	+1.87 (1.16)	**0.000**
$V_{75\%}$	+2.96 (1.51)	**0.000**
$V_{50\%}$	+5,01 (2.09)	**0.000**
D_{2cc} in Gy	+22.93 (13.92)	**0.000**
D_{1cc} in Gy	+24.06 (17.57)	**0.000**
$D_{0.1cc}$ in Gy	+34.88 (45.99)	**0.002**

PTV	Mean of differences between full vs. empty (SD)	*p*
Volume in cc	–0.87 (3.86)	0.287
$V_{150\%}$	–0.11 (1.66)	0.870
$V_{100\%}$	–1.01 (1.61)	0.110
$D_{90\%}$ in Gy	–4.09 (7.19)	**0.015**
$D_{50\%}$ in Gy	–0.91 (6.61)	0.597

Prostate	Mean of differences between full vs. empty (s.d)	*p*
Volume in cc	–0.77 (3.16)	0.249
$V_{150\%}$	–0.48 (2.38)	0.467
$V_{100\%}$	–1.08 (2.16)	**0.031**
$D_{90\%}$ in Gy	–4.85 (9.67)	**0.033**
$D_{50\%}$ in Gy	–1.51 (6.35)	0.354

PTV – planning target volume, cc – cubic centimeter: Gy – Grey; $V_{145\%}$, $V_{100\%}$, $V_{75\%}$, $V_{50\%}$ – target volume receiving at least 145%, 100%, 75% or 50% of prescription dose, $D_{0.1cc}$, D_{1cc}, D_{2cc} – minimum dose to the most exposed 0.1 cm^3, 1 cm^3, 2 cm^3; D_{90}, D_{50} – the minimum dose to 90%, 50% of the CTV

Correlation with prostatic volume

We wished to determine whether the volume of the prostate, usually known at the time of the implant, could affect the dose differences that had shown significance. Results can be seen in Table 2.

Decreased dose to both prostate and to PTV, correlated negatively with the prostate volume. This means that, the smaller the prostate, the greater the change of prostate dose with rectal filling. By contrast, dose escalation in the rectum when it was full, correlated positively with the volume of the prostate; i.e., patients with larger prostates receive more rectal dose when the rectum is full. In any case, although the trend was stable, it was not statistically significant.

Discussion

Doses to rectum

The main objective of this study was to establish if a plentiful rectal content distorts the dosimetry of prostate brachytherapy. The answer is yes. This proved true, even though in our study only 30 cc of air was introduced to simulate a distended rectum. In an interventional study, we did not dare to use large amounts of air or other substance to distend the rectum; it should be noted that

Table 2. Correlation between prostate volume ↔ differences in dose with empty or full rectum

Constraints	Correlation coefficient Pearson's *r*
Differences in prostate V_{100} (%)	–0.105
Differences in prostate V_{100} (cc)	–0.095
Differences in prostate D_{90} (Gy)	–0.109
Differences in PTV V_{100} (%)	0.034
Differences in PTV V_{100} (cc)	–0.063
Differences in PTV D_{90} (Gy)	–0.096
Differences in rectum D_{2cc} (Gy)	0.282
Differences in rectum $D_{0.1cc}$ (Gy)	0.206

PTV – planning target volume, cc – cubic centimeter: Gy – Grey; $V_{100\%}$ – target volume receiving at least 100 of prescription dose; D_{90} – the minimum dose to 90% of the CTV; $D_{0.1cc}$, D_{2cc} – minimum dose to the most exposed 0.1 cm^3,2 cm^3

a chronically constipated and dilated rectum can hold a much larger volume, probably multiplying the effects reported here. However, the balloon was placed at the lower part of the rectum, nearest the prostate, mimicking physiological rectal distension (Figure 1).

The amount of extra radiation that the rectum could receive if it is full, justifies our recommendation to prevent and treat constipation in any patient with this condition. Two or three half-lives of the radioactive source with fluent intestinal transit and adequate depositional frequency seems sufficient time to prevent the overdosing associated with rectal dilatation.

To our knowledge, most centers do not establish a standard rectal status when performing CT scan for control dosimetry. In view of these results, some advices may be recommended. For example, if the rectum is occupied by feces in CT dosimetry, the patient should be invited to defecate and then perform a second CT scan. This double measurement would allow a more accurate dosimetry.

Although the present study deals with low-dose-rate (LDR) brachytherapy, the results are applicable to high-dose-rate (HDR) brachytherapy to some extent. To keep the rectum empty when a patient is to receive prostate HDR-brachytherapy seems strongly recommended.

Doses to target/prostate

Surprisingly, the detrimental effect of rectal filling involves not only rectal dosimetry but also prostate and PTV dosimetry. The prostate is a deformable organ despite its hardness and a mere change from supine to prone position can modify its dosimetry [15]. It is feasible that the pressure exerted by the rectum changes prostate shape (Figure 1), thus modifying the planned dosimetry.

Whether this distortion in target dosimetry affects the prognosis of prostate cancer is unknown. It is likely that, in most cases, slight underdosing of the prostate does not increase the risk of recurrence. However, any target underdosage is undesirable. Note that, in external radiation therapy, an increased risk of biochemical failure has been demonstrated in patients with a distended rectum [16,17]. In brachytherapy, organ displacement do not need to have the same consequences but distortion in the shape of the prostate could create cold spots that worsen local control.

Correlations with prostate volume

It would be interesting to investigate whether the size of the prostate itself changes the effect of rectal filling on dosimetry and to what extent. The increase of dose to the rectum caused by rectal filling was higher for larger prostates. The reason might be that larger prostates are implanted with more activity and also offer a wider surface to rectum wall. Conversely, a small prostate is more affected by rectal filling than a large prostate in terms of target underdosage. This may be because any deformity of a smaller prostate induced by rectal filling produces higher dosimetric effect. Nevertheless, this small prostate underdosage is unlikely to be of any clinical relevance.

Neither of these correlations was statistically significant. In addition, the theoretical detriment applies to small or large prostates. In the case of small prostates, the target receives less radiation; in the case of large prostates, the rectum receives more. Hence, our recommendation is to deal with constipation regardless of prostate size.

Conclusions

The status of rectal distension, as occurs in constipation, has a deleterious influence on prostate brachytherapy dosimetry. This situation increases the radiation to rectum and modifies dose distribution to prostate. We recommend prevention of constipation for at least two half lives of the radioactive seeds.

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Disclosure

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