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Modelling second malignancy risks from Low Dose Rate and High Dose Rate brachytherapy as monotherapy for localized prostate cancer.

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Short title: Brachytherapy second cancer risks

Abstract

Background and Purpose

To estimate the risks of radiation-induced rectal and bladder cancers following low dose rate (LDR) and high dose rate (HDR) brachytherapy as monotherapy for localized prostate cancer and compare to external beam radiotherapy techniques.

Materials and Methods

LDR and HDR brachytherapy monotherapy plans were generated for three prostate CT datasets. Second cancer risks were assessed using Schneider's concept of organ equivalent dose. LDR risks were assessed according to a mechanistic model and a bell-shaped model. HDR risks were assessed according to a bell-shaped model. Relative risks and excess absolute risks were estimated and compared to external beam techniques.

Results

Excess absolute risks of second rectal or bladder cancer were low for both LDR (irrespective of the model used for calculation) and HDR techniques. Average excess absolute risks of rectal cancer for LDR brachytherapy according to the mechanistic model were 0.71 per 10,000 person-years (PY) and 0.84 per 10,000 PY respectively, and according to the bell-shaped model, were 0.47 and 0.78 per 10,000 PY respectively. For HDR, the average excess absolute risks for second rectal and bladder cancers were 0.74 and 1.62 per 10,000 PY respectively. The absolute differences between techniques were very low and clinically irrelevant. Compared to external beam prostate radiotherapy techniques, LDR and HDR brachytherapy resulted in the lowest risks of second rectal and bladder cancer.

Conclusions

This study shows both LDR and HDR brachytherapy monotherapy result in low estimated risks of radiation-induced rectal and bladder cancer. LDR resulted in lower bladder cancer risks than HDR, and lower or similar risks of rectal cancer. In absolute terms these differences between techniques were very small. Compared to external beam techniques, second rectal and bladder cancer risks were lowest for brachytherapy.

Keywords: High Dose Rate Brachytherapy, Localised prostate cancer, Low Dose Rate Brachytherapy, Second Cancer Risks

Introduction

The diagnosis of a radiation-induced second primary cancer is a recognised late complication following radiotherapy treatment. Patients who survive for many years following radiotherapy are thought to be at greatest risk, and so for younger prostate cancer patients, the risk of second malignancy is a relevant issue, particularly when a range of treatment modalities are available. Clinical studies have attempted to address the second cancer risks associated with the traditional external beam techniques used in prostate cancer [1]. For more modern radiation techniques such as brachytherapy and IMRT, where insufficient clinical follow-up and lower patient numbers mean that valid conclusions cannot yet be drawn, planning studies and theoretical modelling have attempted to provide answers instead[2]. There is, however, very little data, clinical or theoretical, which address the risks of second malignancy following brachytherapy monotherapy. Brachytherapy monotherapy is a possible treatment option for many patients with early prostate cancer, and so assessments of the risk of radiation-induced second malignancy would help inform the decision making process when patients are considering which treatment option to undertake.

This paper aims to investigate second malignancy risks associated with both low dose rate (LDR) and high dose rate (HDR) brachytherapy monotherapy using Schneider's concept of organ equivalent dose[3]. Risks are compared with previously published work regarding second malignancy risk from external beam techniques[4]. This study was undertaken in the framework of the GEC ESTRO UroGEC/BRAPHYQS group.

Methods

Contouring

Three prostate CT datasets for patients originally treated using external beam radiotherapy were selected at random. All patients had enemas prior to scanning to ensure that rectums were empty. The prostate, bladder, and rectum were contoured. A 5mm shrink margin was created within the bladder and the subtraction of this structure from the bladder structure

was used to represent the bladder wall for assessment of radiation-induced bladder cancer. The risk of radiation-induced rectal cancer was calculated form the whole (empty) rectal structure.

Planning

For each of the three datasets, an LDR and HDR plan was created. The CT planning scans were rotated so that the position of the prostate approximated that used in trans-rectal ultrasound based treatment planning (flat posterior prostate capsule). LDR plans used stranded AgX100 (Theragenics Corporation, Buford, GA) iodine-125 seeds with air-kerma strength 0.453U and prescribed dose of 145Gy to the 100% isodose, as per ESTRO recommendations[5]. HDR plans used the iridium-192 Flexisource (Elekta AB, Stockholm, Sweden) with 2mm dwell spacing. HDR treatments are prescribed to the planned prostate D90 with 19Gy as the 100% isodose and delivered as a single fraction[6]. LDR plans were created in Variseed™ v8.0 (Varian Medical Systems, Inc., Palo Alto, CA) and HDR plans were created in Oncentra Prostate™ v4.1.3 (Elekta AB). Treatment planning algorithms using the TG-43 formalism were used[7]. The prostate volumes used in this study were 22.7, 32.8 and 34.5cm^3; although in practice a wider range of prostate volumes would be considered appropriate for HDR brachytherapy. Table 1 summarises the planning objectives and mean achieved plan DVH parameters for each plan type.

Differential dose volume-histograms (DVHs) for the rectum, and bladder wall were exported for second malignancy risk calculation using a bin width of 0.1Gy.

Second malignancy risk estimation

Schneider's concept of Organ Equivalent Dose (OED) was used to compare and estimate the risk of radiation-induced second malignancy from brachytherapy monotherapy [3,8]. The OED concept and calculation process has been described in detail elsewhere [3,8]. In brief, two different radiotherapy plans, which result in the same risk of second malignancy, have the same OED. The OED of one plan relative to another therefore gives the relative risk of second malignancy for those two techniques. The OED concept can be used to calculate

second malignancy risk using Schneider's mechanistic model which incorporates the impact of fractionation as well as a tissue specific repair/ repopulation factor, *R* [9]. The OED concept can also be used to demonstrate two extreme possibilities [8]:

i) the situation of no repair/ repopulation- this is a bell-shaped model of radiation-induced malignancy whereby the risk of second cancer initially increases with increasing doses but, after a certain point, cells become sterilised and no longer have the potential for malignant transformation, and so the risk of second cancer then begins to reduce (here the effect of fractionation is removed, i.e. *R*=0)

ii) the situation of full repair- this is a plateau model of radiation-induced malignancy whereby risk of second cancer initially increases with increasing dose, and then at some point levels off as all damaged cells are repaired, resulting in a constant second cancer risk above a certain threshold (in this situation *R*=1).

A bell-shaped model for OED calculation was used for the evaluation of the LDR and HDR brachytherapy plans assuming no repair or repopulation takes place, thereby removing the effect of fractionation or protraction[8]. To include the effects of long treatment duration, the alternative of the mechanistic model was used as well for the LDR plan.

For the bell-shaped model the OED is calculated according to Equation 1[8]:

1) $$\mathrm{OED} = \frac{1}{\mathrm{V_T}} \sum_i \mathrm{V_{D_i}}\, \mathrm{RED_{D_i}}$$

where V_T is the total volume of a structure, V_D is the volume of dose bin *i* receiving dose *D,* and the *RED* is the risk equivalent dose for that dose bin. For each dose bin using a bell-shaped model, *RED* is calculated according to Equations 2 and 3[8]:

2) $RED_D = D\exp\left(-\alpha' D\right)$, and

3) $\alpha' = \alpha + \beta d = \alpha + \beta(D/D_T)d_T$

where D is the dose received by the DVH bin, D_T is the dose prescribed to the target and d_T is the prescribed dose per fraction to the target. In the case of brachytherapy monotherapy, D_T and d_T were the same for each bin of the DVH since the number of fractions was one. Values for α were derived by Schneider et al[8], based on patients irradiated for Hodgkin's disease and atomic bomb survivors, and those used in this study are shown in Table 2. In all cases, β was such that α/β=3Gy.

Although LDR is delivered as a single fraction, since the dose rate is low, it is accepted that a degree of normal tissue repair occurs during LDR dose delivery[10] given the low dose rate of delivery (i.e. for I-125 LDR as used here, 90% of the dose is delivered over 204 days). Alternatively, to incorporate potential normal tissue repair during LDR delivery into the risk estimation, OED was also calculated using Schneider's mechanistic model [8,9]. Here using Equation 4:

4) $$RED_D = \frac{e^{-\alpha' D}}{\alpha' R}\left(1-2R+R^2 e^{\alpha' D}-(1-R)^2 e^{-\frac{\alpha' R}{1-R}D}\right)$$

where α' is calculated as above, and R is a tissue specific repair/ repopulation parameter (Table 2).

The excess absolute risk (EAR) of developing a radiation-induced cancer can be calculated using the RED according to Equation 5[8]:

5) $$EARorg = \frac{1}{V_T}\sum_i V_{D_i} \bullet RED_{D_i} \bullet \beta_{EAR} \bullet \mu(agex, agea)$$

where V_T is the total volume of a structure, RED_{Di} and V_D are as above, β_{EAR} is the initial slope for the dose-risk curve for radiation-induced second cancer and μ takes into account the age of the population examined, based on agex, the patient age at the time of irradiation and agea, the attained age of the patient (years). All EAR calculations in this study were calculated for patients irradiated at age 60 years (agex) and attaining age 80 years (agea) as representative of the localised prostate cancer population at risk. The factor, μ, was calculated according to Equation 6:

6) $$\mu\,(agex, agea) = \exp(\gamma_e(agex-30) + \gamma_a \times \ln(agea/70)$$

where γ_e and γ_a are age modifying factors (β_{EAR} was originally calculated for persons exposed at age 30 years and attaining age 70 years). The parameters used for EAR calculations are shown in Table 2.

The calculated OEDs for LDR and HDR brachytherapy were compared with those calculated in a previous study for 3D-conformal radiotherapy (3D-conformal) delivered as 78Gy in 39 fractions using the same three prostate datasets[4]. The relative risk of second cancer from brachytherapy was estimated compared to this 3D-CRT treatment schedule. OEDs for brachytherapy were also compared to those previously calculated for other additional external beam techniques using the mechanistic model: IMRT (78Gy in 39 fractions), volumetric modulated arc therapy (VMAT; 78Gy in 39 fractions using flattened and flattening filter free (FFF) beams), and stereotactic ablative radiotherapy (SABR; 42.7Gy in 7 fractions delivered using flattened and FFF beams)[4].

According to the models employed here, for single fraction brachytherapy, the risks of radiation-induced second rectal and bladder cancers peak around 9Gy and 2Gy respectively, before reducing steeply when using the bell-shaped model, and more gradually, when using the mechanistic model (as a degree of repair is permitted here). The shape of the dose-response relationship is illustrated graphically in Supplementary Material.

Results

According to the mechanistic model, LDR plans resulted in similar risks of second rectal cancer relative to HDR plans (average relative risk LDR_{mech}:HDR=0.97, range: 0.90-1.03). According to the bell-shaped model, the risk of second rectal cancer was lower with LDR than HDR brachytherapy with an average relative risk of 0.64 (range: 0.53-0.77). Similarly, according to both mechanistic and bell-shaped models, the risk of second bladder cancer was about 50% lower with LDR than HDR monotherapy (average relative risk LDR_{mech}:HDR=0.53 (range: 0.22-0.72), average relative risk LDR_{bell}:HDR=0.50 (range: 0.15-0.70). Regardless of whether mechanistic or bell-shaped models were used, the relative risk reduction with LDR monotherapy compared to HDR monotherapy was greater for second bladder cancers than rectal cancers (Fig. 1, where individual patient data is shown). In absolute terms, expressed in terms of the number of person-years, the risks of second rectal or bladder cancer were low for both LDR (irrespective of the model used for calculation) and HDR techniques (Fig. 2). For LDR, according to the mechanistic model, the average EARs for second rectal and bladder cancers were 0.71 per 10,000 person-years (PY; range: 0.68-0.78) and 0.84 per 10,000 PY (range: 0.37-1.12) respectively, and according to the bell-shaped model, were 0.47 and 0.78 per 10,000 PY (ranges: 0.40-0.51 and 0.26-1.08) respectively. For HDR, the average EARs for second rectal and bladder cancers were slightly higher at 0.74 and 1.62 per 10,000 PY (ranges: 0.66-0.80 and 1.42-1.72) respectively. As would be expected, including a degree of repair and repopulation in the LDR calculations resulted in increased OEDs and higher EARs, although in absolute terms these differences were small (differences between average EARs using mechanistic and bell-shaped models for second rectal and bladder cancers were 0.24 and 0.05 per 10,000 PY respectively, and, based on individual patient data, largest differences between EARs using mechanistic and bell-shaped models for second rectal and bladders cancers were 0.28 per 10,000 PY and 0.11 per 10,000 PY respectively). Similarly, the absolute differences in EARs between HDR and LDR techniques were also low (at most 0.27 per 10,000 PY for second rectal cancer and 0.83 per 10,000 PY for second bladder cancer based on averaged EARs, and, based on individual

patient data, at most 0.35 per 10,000 PY and 1.44 per 10,000 PY for second rectal and bladder cancers respectively).

Based on previously published work using the same three prostate datasets [4], OEDs for the brachytherapy techniques were compared to those calculated for 3D-CRT 78Gy in 39 fractions (Fig. 3, average and range for all three datasets shown for all techniques). Out of all the techniques examined, LDR and HDR brachytherapy resulted in the lowest risks of second rectal and bladder cancers relative to 3D-CRT. The excess absolute risks of second rectal and bladder cancers are illustrated for external beam techniques together with LDR and HDR techniques (Fig. 4, average and range for all three datasets shown for all techniques). The absolute risks of second rectal and bladder cancer were low for all external beam and brachytherapy techniques (highest average EARs for second rectal and bladder cancers: 2.7 per 10,000 PY (3D-CRT) and 2.4 per 10,000 PY (IMRT) respectively) but lowest for brachytherapy. Absolute differences between techniques were also low, at most 2.2 per 10,000 PY for rectal cancer (the difference between average EARs using 3D-CRT and LDR_{bell} brachytherapy), and 1.6 per 10,000 PY for bladder cancer (the difference between average EARs using IMRT and LDR_{bell} brachytherapy).

Discussion

Brachytherapy is one of several treatment options available to patients with localised prostate cancer. Patients may be treated with LDR or HDR brachytherapy. Clinical evidence suggests that both techniques result in high rates of PSA control [11-15]. As well as efficacy, the toxicity profiles of different techniques must also be considered, including the risk of second malignancy. Here we demonstrate that compared to external beam techniques, both LDR and HDR brachytherapy result in lower relative risks of second malignancy and very low absolute risks of second malignancy, although the absolute risks of second rectal and bladder cancer were low for all the techniques examined. LDR brachytherapy resulted in lower bladder cancer risks and lower or similar risks of rectal cancer relative to HDR brachytherapy according to the models used, but, in absolute terms, these differences were low. One might deduce that because of the very high (potentially cell sterilising) doses that are delivered to small volumes of normal tissues and because of the very rapid dose fall off

that occurs with brachytherapy, second malignancy risks would be lower compared to external beam techniques, and the findings of this study support this.

Clinical studies have evaluated second malignancy in patients treated with brachytherapy (predominantly LDR) in comparison to the general population or compared to non-irradiated prostate cancer patients. Few comparisons have been made between patients irradiated with brachytherapy compared to patients irradiated with other techniques. Compared to the general (i.e. non-prostate cancer) population, one SEER registry study[16] and three single institution studies[17-19] found that the risk of rectal cancer following brachytherapy monotherapy or combination brachytherapy and external beam radiotherapy (BT-EBRT) was no higher than that in the general population. The risk of bladder cancer after brachytherapy monotherapy was also found to be no different to that in the general population in one SEER registry study though there was an increased risk in patients who received combination BT-EBRT[16]. Two single institution studies, one examining brachytherapy monotherapy and one examining combination BT-EBRT and brachytherapy monotherapy found no significant difference in the risk of bladder cancer compared to the general population [18,19]. In contrast, two other single institution studies, one examining a mixed population of brachytherapy monotherapy and BT-EBRT patients, and one examining only brachytherapy monotherapy patients, found these patients to be at increased risk of bladder cancer compared to the general population [17,20].

Compared to non-irradiated prostate cancer patients, three SEER analyses[16,21,22] and two single institution studies[17,23] found no increase in the risk of rectal cancer in brachytherapy monotherapy patients. For patients treated with combination BT-EBRT, two of three SEER analysis found no difference in the risk of rectal cancer compared to non-irradiated patients[21,22], while the largest SEER analysis, observed an increase in the risk of rectal cancer but only after 10 years of follow-up[16]. Two single institution studies, one examining EBRT-BT patients specifically[23] and one examining a mixed population of brachytherapy monotherapy and combination BT-EBRT patients[24] observed no difference in the risk of rectal cancer compared to non-irradiated prostate cancer patients. In terms of bladder cancer, two SEER analyses [21,22] and three single institution studies[17,23,24] examining both brachytherapy monotherapy and combination BT-EBRT patients found no

difference in the risk of bladder cancer in comparison to non-irradiated patients. In contrast, a third and larger SEER analysis observed an increase in the risk of bladder cancer in both monotherapy and combination BT-EBRT patients compared to non-irradiated patients[16].

More relevant for this study, are the three clinical studies (one SEER analysis[22] and two single institution studies[24,25]) that have compared second cancers in brachytherapy patients with prostate patients treated with external beam radiotherapy. The one SEER analysis observed no difference in the risk of second rectal and bladder cancer in patients treated with brachytherapy monotherapy or combination BT-EBRT compared to patients irradiated using external beam radiotherapy alone[22]. Similarly, neither of the single institution studies has observed any difference in the risk of rectal or bladder cancer, between patients irradiated using external beam radiotherapy and brachytherapy monotherapy patients and a mixed population of brachytherapy monotherapy and combination BT-EBRT patients [24,25]. This is partly in contrast to this current work, which has suggested the risk of second rectal and bladder cancers may be lower than other external beam techniques. In all of the above clinical studies, however, the follow-up in brachytherapy patients is generally shorter than in studies examining second cancer risks in patients treated with external beam techniques. In addition, patient numbers in brachytherapy cohorts are generally lower than those examined in studies of second cancers in external beam patients. As such, an accurate picture regarding the second cancer risks following brachytherapy in comparison to the general population, non-irradiated prostate cancer patients and patients irradiated with external beam techniques cannot yet be formed. Furthermore, where combination BT-EBRT is examined, both the external beam and brachytherapy components will contribute to second cancer risk and the proportion of risk attributable to brachytherapy cannot be determined, adding to the difficulties in drawing a definitive conclusion about second cancer risk from brachytherapy.

In the absence of adequate clinical evidence, planning studies can be used to give an estimation of second cancer risk. Few studies, however, have examined the risks of second cancer from prostate brachytherapy. In fact only one study was identified which estimated

second cancer risks from brachytherapy[26]. Both LDR and HDR brachytherapy monotherapy were examined in addition to combination external beam radiotherapy with an HDR brachytherapy boost. This study estimated risks using the Competition model, a model which predicts maximal cancer inductions at doses of around 4Gy[27]. To allow comparisons between these different techniques, doses were normalised to the same biological end-point by calculating the biologically effective doses for the DVH bins by multiplying the physical dose by the relative effectiveness of each technique [26]. It was found that the risk of rectal cancer was low with all techniques but lowest for brachytherapy monotherapy. Here the average lifetime risk of rectal cancer was $2.0X10^{-4}$% for LDR monotherapy, $1.0x10^{-4}$% for HDR monotherapy and 0.06% for combination external beam and HDR treatment [26]. On average, therefore, HDR monotherapy resulted in lower rectal cancer risks than LDR monotherapy, although in absolute terms the difference was minimal and clinically insignificant. Despite the differences in modelling technique and the calculation of a lifetime risk rather than a risk per 10,000 PY, as used in this current piece of work, it can be concluded that both studies demonstrate that the estimated risks of radiation-induced rectal cancer are low and that the differences in second cancer risks between LDR and HDR brachytherapy are clinically insignificant.

There is much debate as to the most appropriate means of estimating second malignancy risks and a variety of models exist, none of which have been shown to be a perfect fit to the clinical data[28]. In addition, the error associated with such models can be very large with EAR estimates resulting in errors of up to 100% (Equation 5), although relative risk calculations using OED are associated with lower errors at 5-10% (Equation 1)[29,30]. The complexity of the situation increases further when trying to use models that were designed for the analysis of external beam techniques, and which likely did not consider the impact of treatment with different dose rates or even the impact of high dose per fraction treatments. This may at least partly explain the paucity of planning studies that try to estimate second cancer risks form prostate brachytherapy. We examined single fraction HDR monotherapy. The dose rate here is similar to external beam treatments, upon which the OED concept was originally based. We used the bell-shaped model for these calculations, and assumed the effect of fractionation and repair/ repopulation is so small it can be neglected. For LDR brachytherapy monotherapy the situation is more difficult. Although treatment is delivered

in a single fraction, supporting the use of a bell-shaped model, the lower dose rate delivery is thought to permit a degree of normal tissue repair[10], suggesting that the bell-shaped curve may underestimate the risk of second cancer and that a mechanistic model which includes an element of repair/ repopulation may be more appropriate. A degree of repair and repopulation will result in a proportion of normal cells becoming at risk of malignant transformation (instead of being completely sterilised), thus resulting in an increase in OED and second malignancy risk. In order to demonstrate both possibilities we opted to calculate risk for LDR monotherapy using both the bell-shaped and mechanistic models. We did not adopt a plateau model, which assumes full repair/ repopulation between fractions, as there would be no break in radiation dose delivery with LDR to permit full repair/ repopulation. According to the mechanistic model, the risk of rectal cancer was broadly similar between HDR and LDR treatments and the risk of bladder cancer lower with LDR. According to the bell-shaped model the risks of rectal and bladder cancers were lower with LDR compared to HDR monotherapy. Even if the relative differences between HDR and LDR brachytherapy were as large as the calculation according to the bell-shaped model suggests, in absolute terms the differences between LDR and HDR monotherapy treatments are small and clinically irrelevant. The authors accept that using the mechanistic model for a single fraction LDR treatment is not using the model in the manner in which it was originally designed, and so there are greater uncertainties associated with the risks estimated for LDR treatments than the other evaluated treatments. The use of the mechanistic model, however, does allow a degree of repair and repopulation to be included in the calculation, which intuitively seems appropriate given the low dose rate nature of treatment delivery.

This study has limitations. As mentioned above, there is uncertainty in all models of second cancer risk estimation, and this uncertainty is increased when applying these models to the setting of brachytherapy, particularly LDR brachytherapy. The optimal way to account for LDR irradiation (e.g. biologically effective dose transformation, OED calculation using a mechanistic model) in this setting is unknown. In addition, we did not look at pulsed dose rate Brachytherapy (PDR) brachytherapy as this is infrequently used for prostate cancer and is more complex given its fractionation (incorporation of repair effects).

Only three prostate datasets were examined in this study, potentially limiting the generalisability of our findings. For prostate cancer, the positions of the rectum and bladder in relation of the prostate are relatively constant in comparison to other tumours such as lung cancers where the proximity to organs at risk can be very variable. As such, inter-patient variation in second rectal and bladder cancer risks may be less than the inter-patient variation in the risk of other second cancers in patients with other, more anatomically variable, primary sites, although this will be influenced by the models used and radiotherapy delivery technique. Combination BT-EBRT treatments were not included as this would introduce further uncertainties into the risk estimations.

Other limitations of this work include that the brachytherapy DVHs used to estimate second malignancy risk would not be fully representative of the actual doses received by the normal tissues. For HDR treatments, the imaging modality used for plan calculation may be different to what we used (can be CT or US) and this could result in some small differences in the DVHs produced. Furthermore, in the case of LDR brachytherapy, the DVH is based on a pre-plan, and so is not the same as the delivered plan, generally assessed on CT +/- MRI, nor are the effects of seed migration or oedema incorporated into the DVH. For HDR treatments, dose may be delivered with the probe in place, which results in part of the rectum receiving lower doses than the doses represented by the DVHs used for risk calculations here (where the probe was not included during plan calculation). The use of the TG-43 formalisation for dose calculation in brachytherapy treatments has limitations as no account for tissue composition and inter-source absorption is made. Future planning systems may provide more accurate dosimetry with the use of Monte Carlo based methods[31,32]. We anticipate, however that the impact of these inaccuracies, in terms of the calculation of the risk of second malignancy, would be small, and indeed the uncertainties introduced as a result of these inaccuracies are much smaller than the uncertainties associated with the second malignancy risk estimation process itself.

Conclusions

Despite the limitations and uncertainties in the estimation, the modelled risk of second rectal and bladder cancer from brachytherapy monotherapy appears low. The relative risk of radiation-induced bladder cancer was lower from LDR brachytherapy compared to HDR brachytherapy. Depending on the model used, the relative risk of rectal cancer was similar or lower with LDR brachytherapy compared to HDR. In absolute terms, however, the differences were very small. Brachytherapy second rectal and bladder cancer risks are lower than the risks associated with external beam treatments. The clinical evidence regarding second cancer risk from brachytherapy is encouraging but immature, and so this study provides reassurance regarding the long-term safety of brachytherapy with regard to second malignancy risk.

Conflict of Interest Statement: None declared

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Figure 1. Risks of second rectal or bladder cancer from LDR brachytherapy monotherapy relative to HDR brachytherapy monotherapy. Two different models have been used to estimate the risk of second rectal and bladder cancer for LDR brachytherapy.

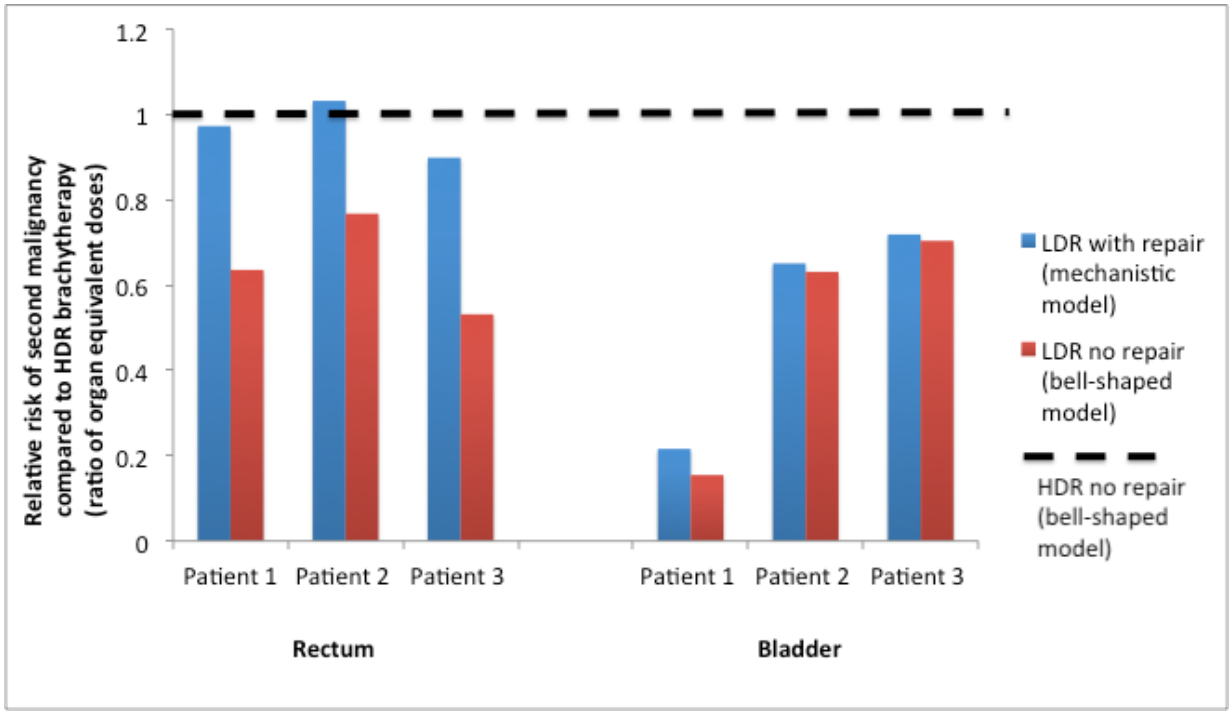


Figure 2. Excess absolute risk of second rectal or bladder cancer from LDR brachytherapy monotherapy and HDR brachytherapy monotherapy. Two different models have been used to estimate the risk of second rectal and bladder cancer for LDR brachytherapy.

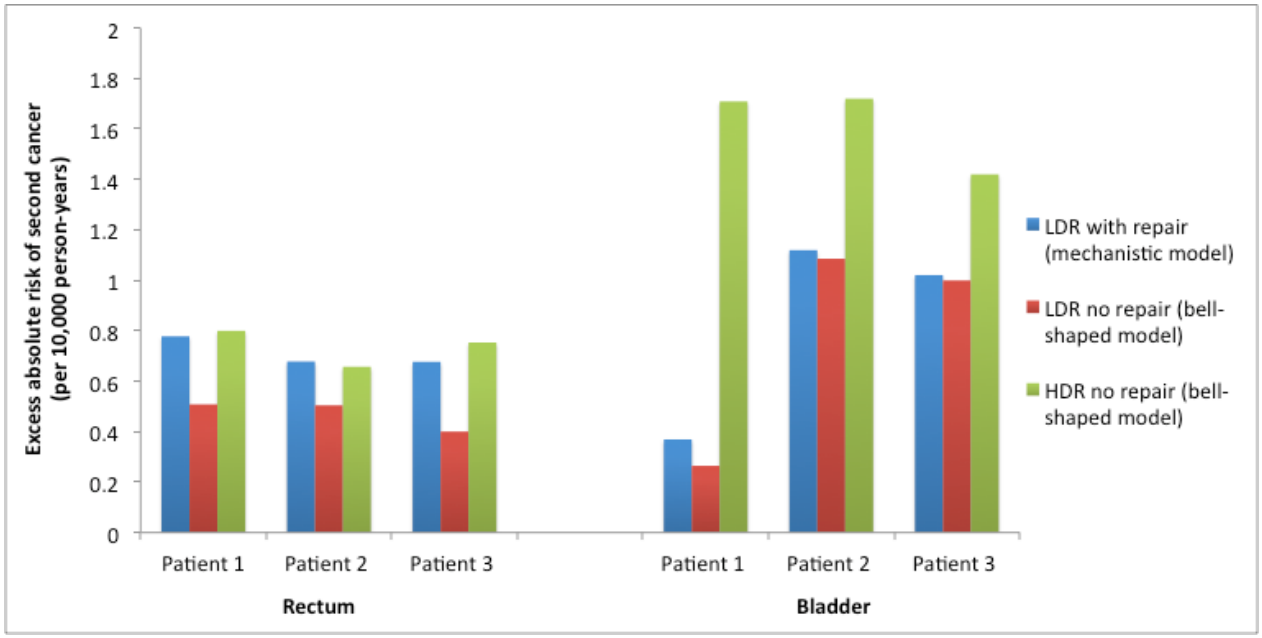
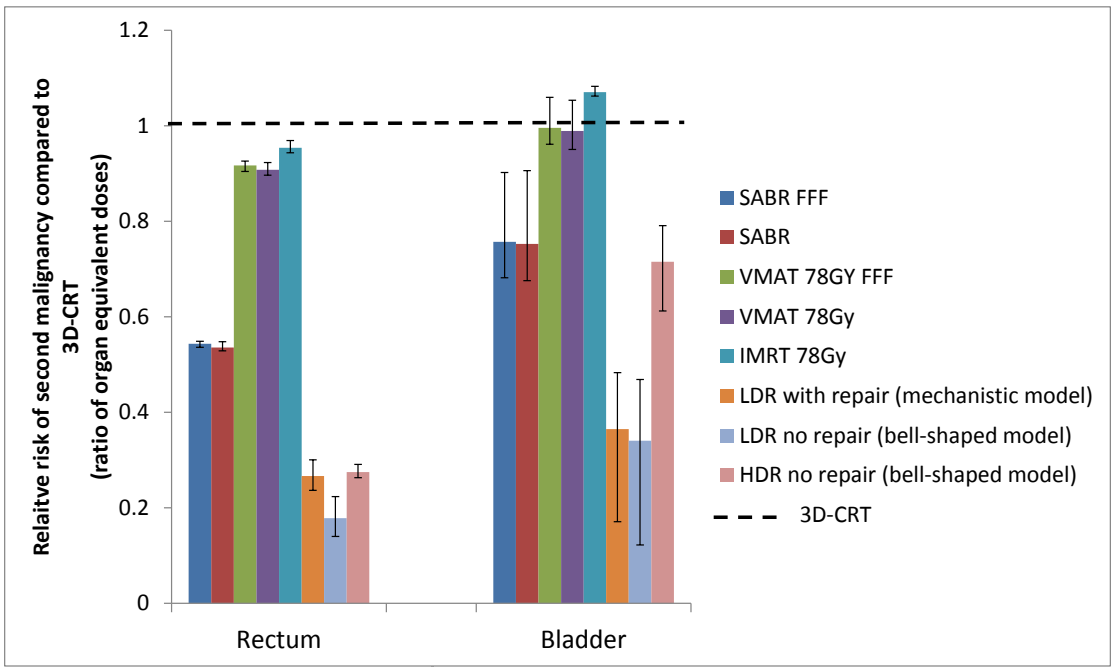
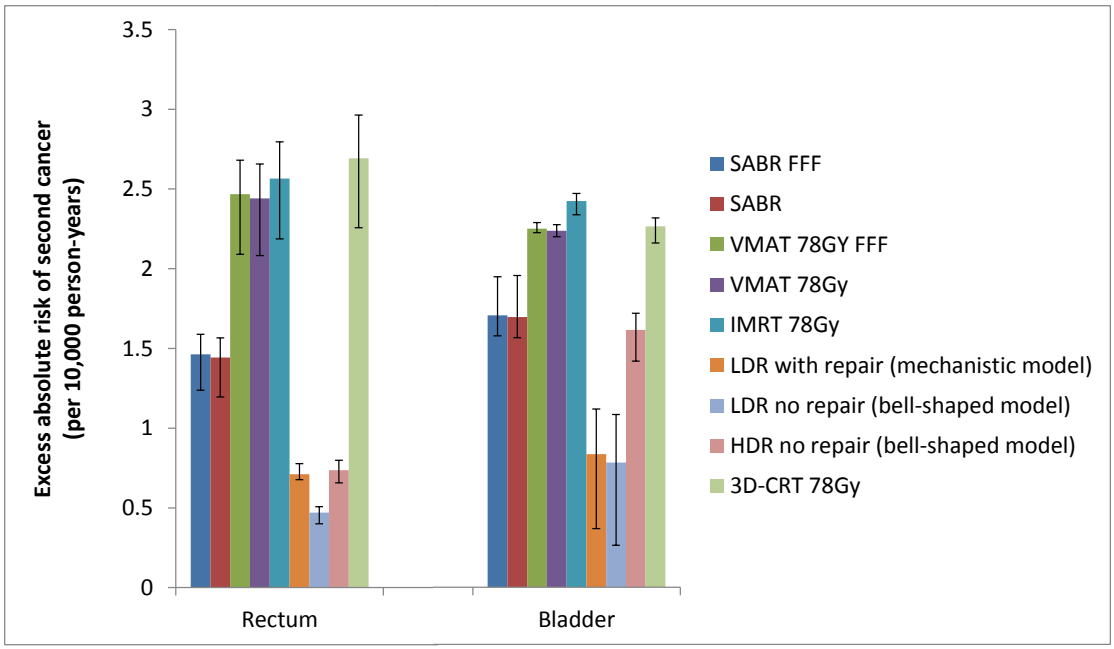


Figure 3. Risks of second rectal or bladder cancer from several radiotherapy techniques relative to 3D-confromal radiotherapy. Two different models have been used to estimate the risk of second rectal and bladder cancer for LDR brachytherapy.



Average values for three plans displayed. Error bars display the range of values for all three evaluated plans. All external beam risks estimated using a mechanistic model.

Figure 4. Excess absolute risk of second rectal or bladder cancer from several prostate radiotherapy techniques. Two different models have been used to estimate the risk of second rectal and bladder cancer for LDR brachytherapy.



Average values for three plans displayed. Error bars display the range of values for all three evaluated plans. All external beam risks estimated using a mechanistic model.

Supplementary Material

Figure 1. Does-response relationship for rectum (Figure 1a) and bladder (Figure 1b) for single fraction brachytherapy according to Schneider's mechanistic model (repair permitted) and bell-shaped model (no repair) [1]. The vertical axis is intentionally left blank but reflects the Risk Equivalent Dose as described in the main manuscript.

Figure 1a) Rectum

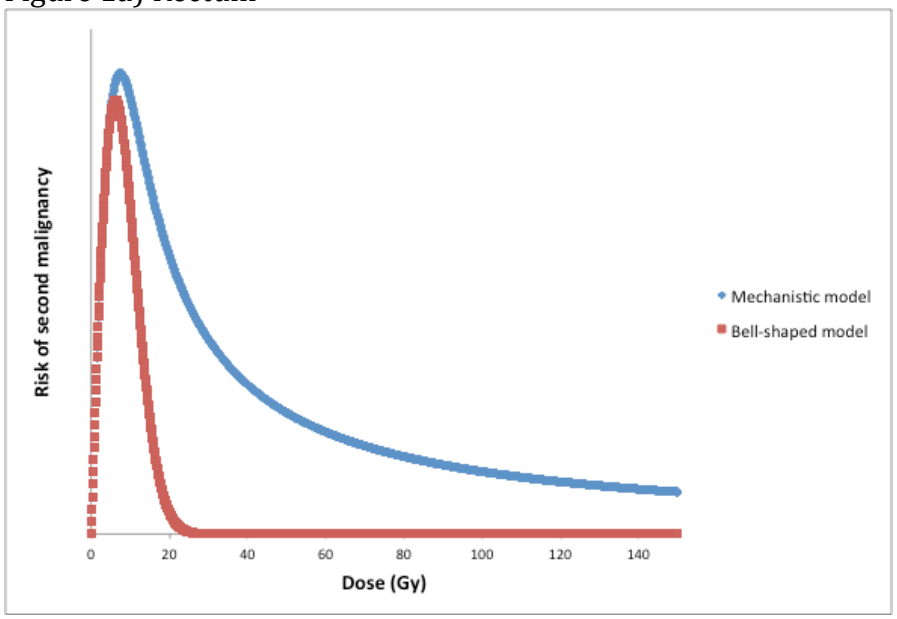
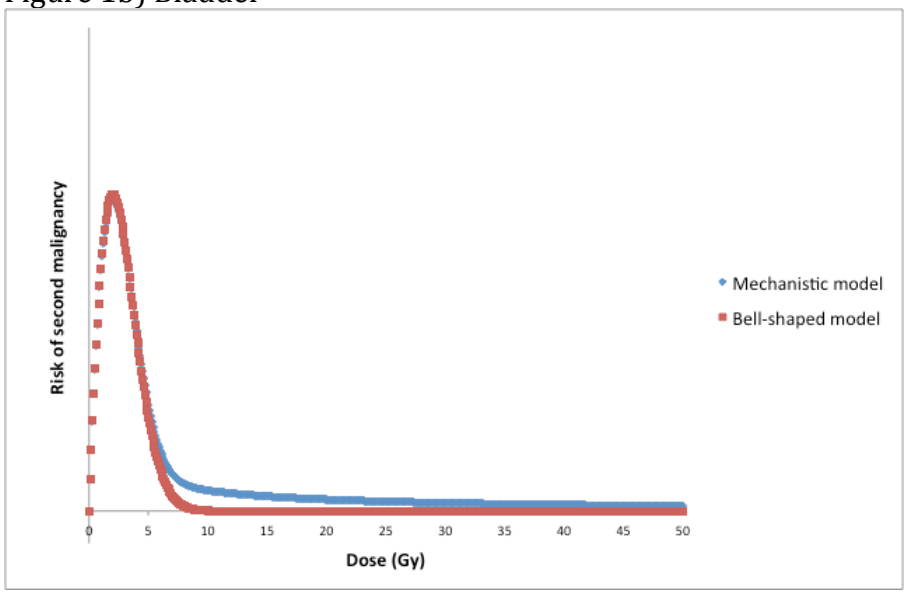


Figure 1b) Bladder



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