Radiation-induced second primary cancer risks from modern external beam radiotherapy for early prostate cancer: impact of stereotactic ablative radiotherapy (SABR), volumetric modulated arc therapy (VMAT) and flattening filter free (FFF) radiotherapy

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Radiation-induced second primary cancer risks from modern external beam radiotherapy for early prostate cancer: impact of stereotactic ablative radiotherapy (SABR), volumetric modulated arc therapy (VMAT) and flattening filter free (FFF) radiotherapy

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Abstract
Risks of radiation-induced second primary cancer following prostate radiotherapy using 3D-conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), flattening filter free (FFF) and stereotactic ablative radiotherapy (SABR) were evaluated. Prostate plans were created using 10 MV 3D-CRT (78 Gy in 39 fractions) and 6 MV 5-field IMRT (78 Gy in 39 fractions), VMAT (78 Gy in 39 fractions, with standard flattened and energy-matched FFF beams) and SABR (42.7 Gy in 7 fractions with standard flattened and energy-matched FFF beams). Dose-volume histograms from pelvic planning CT scans of three prostate patients, each planned using all 6 techniques, were used to calculate organ equivalent...
doses (OED) and excess absolute risks (EAR) of second rectal and bladder cancers, and pelvic bone and soft tissue sarcomas, using mechanistic, bell-shaped and plateau models. For organs distant to the treatment field, chamber measurements recorded in an anthropomorphic phantom were used to calculate OEDs and EARs using a linear model. Ratios of OED give relative radiation-induced second cancer risks.

SABR resulted in lower second cancer risks at all sites relative to 3D-CRT. FFF resulted in lower second cancer risks in out-of-field tissues relative to equivalent flattened techniques, with increasing impact in organs at greater distances from the field. For example, FFF reduced second cancer risk by up to 20% in the stomach and up to 56% in the brain, relative to the equivalent flattened technique. Relative to 10MV 3D-CRT, 6MV IMRT or VMAT with flattening filter increased second cancer risks in several out-of-field organs, by up to 26% and 55%, respectively. For all techniques, EARs were consistently low. The observed large relative differences between techniques, in absolute terms, were very low, highlighting the importance of considering absolute risks alongside the corresponding relative risks, since when absolute risks are very low, large relative risks become less meaningful.

A calculated relative radiation-induced second cancer risk benefit from SABR and FFF techniques was theoretically predicted, although absolute radiation-induced second cancer risks were low for all techniques, and absolute differences between techniques were small.

Keywords: prostate cancer, radiation-induced second primary cancer, stereotactic ablative radiotherapy (SABR), volumetric modulated arc therapy (VMAT), flattening filter free (FFF)

(Some figures may appear in colour only in the online journal)

1. Introduction

The development of a radiation-induced second primary cancer is an unwanted consequence of radiotherapy treatment. Theoretical concerns have been raised that modern techniques such as intensity-modulated radiotherapy (IMRT) may increase second cancer risk (Hall and Wu 2003). Owing to the relative newness of IMRT compared to the latency of second primary cancers, the clinical evidence regarding the impact of modern radiotherapy techniques on radiation-induced second cancer risk is too immature to determine if these concerns are warranted (Huang et al 2011, Zelefsky et al 2012a, 2012b). While radiation-induced second cancer risk from IMRT has been compared to that from 3D-conformal radiotherapy (3D-CRT) in prostate planning studies (Followill et al 1997, Kry et al 2005a, 2005b, Stathakis et al 2007, Ruben et al 2008, Bednarz et al 2010), far fewer comparisons with other techniques such as volumetric modulated arc therapy (VMAT) (Rechner et al 2012), stereotactic ablative radiotherapy (SABR) (Dasu et al 2011) and flattening filter free (FFF) techniques (Kry et al 2010, Halg et al 2012) have been performed.

This study aimed to compare radiation-induced second cancer risk from modern radiotherapy techniques used to treat early prostate cancer. Conventionally fractionated schedules using 3D-CRT, IMRT and VMAT with standard (flattened) and FFF beams were evaluated, together with SABR using VMAT with standard and FFF beams.
2. Methods

2.1. Contouring

Pelvic CT scans which were previously used for radiotherapy planning for three early stage prostate cancer patients were selected at random. On each of these, the CTV was defined as the prostate alone, expanded 6 mm to PTV (compatible with daily online imaging using fiducial markers (Adamson et al. 2011, Quon et al. 2012, Beltran et al. 2008). The rectum (recto-sigmoid junction to anus), bladder and femoral heads were contoured as organs-at-risk. A 5 mm shrink margin was created within the bladder and the subtraction of this from the whole bladder represented the bladder wall. Patients had empty rectums, thus the whole rectal volume represented rectal dose (since total rectal volume is considered a suitable surrogate for the rectal wall if the rectum is empty (Fiorino et al. 2009)). All pelvic bones were contoured.

2.2. Planning

Five plans were produced for each pelvic CT using Monaco v3.3 (Elekta, AB Sweden) with a Monte Carlo algorithm, 6 MV photons, a 2 mm grid and the Agility head (Elekta, AB Sweden). A 5-field step and shoot IMRT plan was produced, prescribed 78 Gy in 39 fractions, with beams at 180°, 252°, 324°, 36° and 108°. Two VMAT plans prescribed 78 Gy in 39 fractions were produced using one 240° arc (240° → 120°), one with a 6 MV beam and one with an energy-matched 6 MV FFF beam. Two SABR plans prescribing 42.7 Gy in 7 fractions were produced, using one 240° VMAT arc (240° → 120°), with 6 MV and energy-matched 6 MV FFF beams. ‘Energy-matched’ means the FFF beam energy was re-tuned to match the relative dose in water at 10 cm deep for a 10 × 10 cm standard 6 MV beam, 100 cm SSD (Paynter et al. 2014). Doses were prescribed so that ≥95% of the PTV received ≥95% of the prescription dose and median dose was within 1 Gy of the prescription dose. Organ-at-risk constraints are described in table 1. 3D-CRT plans cannot be produced using Monaco v3.3. A 10 MV 3D-CRT four-field (0°, 180°, 90°, 270°) 78 Gy in 39 fraction plan was therefore produced using Oncentra MasterPlan (Elekta, AB Sweden). Here, the prescription dose was normalized to the centre of the PTV and the 95% isodose covered the PTV (aiming for 100% coverage, accepting ≥95%).

2.3. In-field and close-to-field second cancer risk assessment

Differential dose-volume histograms (DVHs) using 0.01 Gy bin widths for rectum, bladder wall, pelvic bones and pelvic soft tissue (total scanned volume minus bones and prostate) were exported and used to calculate organ equivalent dose (OED) and excess absolute risk (EAR) for second rectal and bladder cancers, as well as bone and soft tissue sarcomas within the scanned volume, for all three pelvic CT scans and all six techniques, as described below. Average values are presented.

2.4. Out-of-field second cancer risk assessment

All six techniques from one of the three pelvic CT scans were delivered to the RANDO® phantom (The Phantom Laboratory, USA) to assess out-of-field doses. Plans were delivered using a Synergy linac (Elekta, AB Sweden) with the Agility head (Elekta, AB Sweden) with and without FFF high dose rate mode. For conventionally fractionated treatments, three 2 Gy fractions were delivered. For each SABR plan, one 6.1 Gy fraction was delivered. Measurements were performed in the midline at increasing distances from the isocentre by substituting each
relevant phantom slice for a 2.5 cm tall Perspex block with an ionization chamber holder, such that measurements were performed at approximately midline depth (figure 1). Doses at specific distances from the isocentre were taken to represent doses received by organs located at approximately those positions (table 2).

Out-of-field measurements were performed using a semi-flex ionization chamber (PTW GmbH, Germany), calibrated for 6MV, 6MV FFF and 10MV beams. In other studies, thermoluminescent dosimeters (TLD) have often been used for out-of-field measurements given their relative energy independence. TLDs, however, can prove difficult in terms of accuracy and reproducibility, with uncertainties up to 10% quoted (Kragl et al 2011). The concern regarding chamber out-of-field measurements is the lower energy spectra in this region. It has been demonstrated, however, that the mean energy spectra out to 20 cm from the field edge are in the kilovoltage range (Kragl et al 2011), within the range of use of the chosen chamber. At 10–20 cm from the field edge, it appears the energy spectra are plateauing or at worst decreasing gradually (Kragl et al 2011), thus providing confidence in performing measurements at 20 cm and beyond. In keeping with out-of-field chamber measurements performed by others, we assumed 5% uncertainty to account for potential inaccuracies resulting from the MV calibrated ion chamber and positioning inaccuracies (Kragl et al 2011). Readings were corrected for temperature, pressure and leakage. To estimate the impact of drift on measurements, on the first full day of measurements, we positioned a second semi-flex chamber at 70 cm from the isocentre and doses were recorded here at the same time as recording measurements at points closer to the isocentre (figure 1). At 70 cm, where the impact of drift was assumed to be greatest, the average standard deviation was 2.57% of the mean reading at 70 cm. Drift was therefore not considered likely to have a major impact on measured dose for the majority of readings, and would therefore be adequately encompassed within the 5% error assigned.

Table 1. Organ-at-risk constraints.

<table>
<thead>
<tr>
<th>Organ</th>
<th>78 Gy in 39 fraction constraints</th>
<th>Source</th>
<th>SABR constraints</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>V70Gy(90%) &lt; 15%</td>
<td>HYPO-PR-RT trial (Franzen and Widmark 2011)</td>
<td>V41.4 Gy(97%) &lt; 3%</td>
<td>HYPO-PC RT trial (Franzen and Widmark 2011) plus biologically equivalent constraints to 74 Gy arm of CHHiP trial for high and low dose regions (Dearnaley 2010)</td>
</tr>
<tr>
<td></td>
<td>V59Gy(76%) &lt; 35%</td>
<td></td>
<td>V38.4 Gy(90%) &lt; 15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V51Gy(65%) &lt; 45%</td>
<td></td>
<td>V32.0 Gy(75%) ≤ 35%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V28.0 Gy(65%) ≤ 45%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V24.8 Gy(58%) &lt; 70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V19.6 Gy(46%) &lt; 80%</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>V80Gy(103%) &lt; 15%</td>
<td>RTOG 0126 (Radiation Oncology Group 2014)</td>
<td>V41.4 Gy(97%) &lt; 5%</td>
<td>Biologically equivalent constraints to 74 Gy arm of CHHiP trial (Dearnaley 2010)</td>
</tr>
<tr>
<td></td>
<td>V75Gy(96%) &lt; 25%</td>
<td></td>
<td>V34.7 Gy(81%) &lt; 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V70Gy(90%) &lt; 35%</td>
<td>Therapy</td>
<td>V29.9 Gy(70%) &lt; 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V65Gy(83%) &lt; 50%</td>
<td>Oncology Group 2014)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral heads</td>
<td>Dmax ≤ 55 Gy(70%)</td>
<td>HYPO-PR-RT trial (Franzen and Widmark 2011)</td>
<td>Dmax ≤ 29.9 Gy(70%)</td>
<td>HYPO-PC RT trial (Franzen and Widmark 2011)</td>
</tr>
</tbody>
</table>
2.5. Assessment of head leakage and scatter

To assess out-of-field dose due to head scatter and leakage, out-of-field chamber measurements were performed with the phantom pelvis (slices 30–35) removed, thus ensuring measured doses were predominantly from head scatter/leakage.

2.6. Second cancer risk evaluation

A variety of models exist for radiation-induced second cancer risk assessment, and the optimal is widely debated. Schneider’s concept of OED (Schneider et al 2005, 2011), which incorporates the impact of fractionation, was adopted. This concept states that two different dose distributions which result in the same second cancer risk have the same OED. For higher dose in-field and close-to-field regions, where the dose–response is not considered linear, the OED concept was used to calculate risks of rectal and bladder cancer using:

(a) Schneider’s mechanistic model (Schneider 2009), which includes tissue specific repair/repopulation constants,

(b) a bell-shaped model (which suggests that risk increases in a linear fashion with dose up to a threshold before decreasing due to cell sterilization at higher doses without normal tissue repair (Schneider et al 2011), and

(c) a plateau model (which suggests that risk increases initially in a linear fashion as dose increases up to a threshold at which risk levels off due to cell sterilization at higher doses with full normal tissue repair (Schneider et al 2011).

The risks of radiation-induced pelvic bone and soft tissue second malignancies were calculated using a specific mechanistic sarcoma model (Schneider 2009).
Table 2. Parameters for RED and EAR calculations (Schneider et al 2011) and source of dosimetric data.

<table>
<thead>
<tr>
<th>Site</th>
<th>Mechanistic model</th>
<th>Bell shaped model</th>
<th>Plateau model</th>
<th>$\beta$</th>
<th>$\gamma_e$ (years)</th>
<th>$\gamma_a$ (years)</th>
<th>Source of dose</th>
<th>Position of chamber from isocentre (cm) $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>0.033</td>
<td>0.56</td>
<td>0.013</td>
<td>0.065</td>
<td>0.73</td>
<td>−0.056</td>
<td>DVH</td>
<td>——</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.219</td>
<td>0.06</td>
<td>0.213</td>
<td>0.633</td>
<td>3.8</td>
<td>−0.024</td>
<td>DVH</td>
<td>——</td>
</tr>
<tr>
<td>Pelvic bone sarcoma</td>
<td>Separate sarcoma model: $\alpha = 0.067$ based on intermediate repopulation ($R = 0.5$), $\beta = 0.20$</td>
<td>——</td>
<td>——</td>
<td>——</td>
<td>−0.013</td>
<td>−0.56</td>
<td>DVH</td>
<td>——</td>
</tr>
<tr>
<td>Pelvic soft tissue sarcoma</td>
<td>Separate sarcoma model: $\alpha = 0.060$, based on intermediate repopulation ($R = 0.5$), $\beta = 0.60$</td>
<td>——</td>
<td>——</td>
<td>——</td>
<td>−0.013</td>
<td>−0.56</td>
<td>DVH</td>
<td>——</td>
</tr>
<tr>
<td>Colorectum</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>7.4</td>
<td>−0.056</td>
<td>Chamber 20</td>
<td>——</td>
</tr>
<tr>
<td>Liver</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.4</td>
<td>−0.021</td>
<td>Chamber 25</td>
<td>——</td>
</tr>
<tr>
<td>Stomach</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5.2</td>
<td>−0.002</td>
<td>Chamber 30</td>
<td>——</td>
</tr>
<tr>
<td>Lung</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8.0</td>
<td>0.002</td>
<td>Chamber Average of readings at 40 and 50</td>
<td>——</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3.2</td>
<td>−0.002</td>
<td>Chamber Average of readings at 40, 50 and 60</td>
<td>——</td>
</tr>
<tr>
<td>Thyroid</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.40</td>
<td>−0.046</td>
<td>Chamber 60</td>
<td>——</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.73</td>
<td>−0.024</td>
<td>Chamber 60</td>
<td>——</td>
</tr>
<tr>
<td>Mouth</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.73</td>
<td>−0.024</td>
<td>Chamber 65</td>
<td>——</td>
</tr>
<tr>
<td>Brain and CNS</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.70</td>
<td>−0.024</td>
<td>Chamber 70</td>
<td>——</td>
</tr>
</tbody>
</table>

$^a$ $\beta$: excess cases per 10 000 person-years gray, based on A-bomb survivors exposed at 30 years and surviving to 70 years, and modified for a UK population (see Schneider et al (2011) for further detail). Note this $\beta$ is used for EAR calculation only. $\beta$ within the $\alpha/\beta$ ratio is calculated from $\alpha$ based on $\alpha/\beta = 3$ Gy for all tissues.

$^b$ Positions of liver, stomach, thyroid and salivary glands based on work of Blais et al (2012).

$^c$ Point considered representative of dose received by transverse colon; DVH: dose–volume histogram.

Note: See text for explanation regarding $\alpha$, $R$, $\beta$, $\gamma_e$ and $\gamma_a$. 

For low dose out-of-field regions, where dose–response is considered linear, the OED concept was used with a linear model.

The OED concept is discussed in detail elsewhere (Schneider et al. 2005, 2011), but in summary:

\[
\text{OED} = \frac{1}{V_T} \sum_i V_{D_i} \text{RED}_{D_i}
\]

where \( V_T \) is the total volume of the structure under consideration, \( V_{D_i} \) is the volume of the dose bin \( i \) which receives dose \( D_i \) and the \( \text{RED}_{D_i} \) is the risk equivalent dose for the dose bin receiving dose \( D_i \). RED is calculated according to

(i) \( \text{RED}_{D_i} = D \)

when a linear model is applied (Schneider et al. 2011), as is appropriate for low dose out-of-field regions

and

(ii) \( \text{RED}_{D_i} = \frac{e^{-\alpha D_i}}{R} \left( 1 - 2R + R^2 e^{\alpha D_i} - (1 - R)^2 e^{-\frac{\alpha R}{1-R} D_i} \right) \)

according to Schneider’s mechanistic model which incorporates \( R \), a tissue specific repair/repopulation parameter (Schneider et al. 2011). The impact of fractionation here and in subsequent models is considered according to \( \alpha' \) (Schneider et al. 2011):

\[
\alpha' = \alpha + \beta d = \alpha + \beta \frac{D}{D_T} \]

where \( d \) is the dose per fraction, \( D_T \) is the dose prescribed to the target and \( D_T \) is the prescribed dose per fraction. Schneider et al. fitted the parameters \( \alpha \) and \( R \) for carcinoma induction using data from Atomic bomb survivors and patients treated with radiotherapy for Hodgkin disease (Schneider et al. 2011). \( \beta \) is such that \( \alpha/\beta = 3 \text{ Gy} \).

To illustrate the possible OED in the extreme scenarios of no repair/repopulation, and full repair/repopulation, RED and thus OED can also be calculated according to

(iii) \( \text{RED}_{D_i} = D \exp(-\alpha D) \),

a bell-shaped model (\( R = 0 \)) (Schneider et al. 2011) and

(iv) \( \text{RED}_{D_i} = \frac{1 - \exp(-\alpha D)}{\alpha} \),

a plateau model (\( R = 1 \)) (Schneider et al. 2011).

All of the above models approach a linear model at low doses (Schneider et al. 2011). When considering radiation-induced sarcoma, RED is calculated as (Schneider et al. 2011)

\[
\text{RED} = \frac{e^{-\alpha D}}{R} \left( 1 - 2R + R^2 e^{\alpha D} - (1 - R)^2 e^{-\frac{\alpha R}{1-R} D} - \alpha' RD \right).
\]

RED was also used to calculate the EAR of developing a radiation-induced second cancer in an organ with volume \( V_T \) after exposure to dose RED at one age (\( \text{age}_x \)) and after attaining a greater age (\( \text{age}_a \)), according to (Schneider et al. 2011)

\[
\text{EAR}_{\text{org}} = \frac{1}{V_T} \sum_i V_{D_i} \cdot \text{RED}_{D_i} \cdot \beta \cdot \mu(\text{age}_x, \text{age}_a)
\]
where $\beta$ is the initial slope for the dose–response curve for radiation-induced second cancers, $V_D$ is the volume of the DVH bin receiving dose $D_i$, $\text{RED}_D$ is the RED for that bin and $\mu$ is a modifying factor which adjusts for age at exposure (agex) and attained age (agea), calculated according to (Schneider et al 2011)

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

where $\gamma_e$ and $\gamma_a$ are age modifying factors and where $\beta$ was originally defined for persons exposed at age 30 years and attaining age 70 years.

All EAR calculations in this study were performed for patients irradiated at age 60 years and attaining age 80 years. All parameters for second cancer risk calculation were taken from (Schneider et al 2011) and are shown in table 2.

Doses and risks presented are those for the whole treatment course.

### 3. Results

#### 3.1. Plans

The number of monitor units (MU) required for all fractions in the delivered plans are shown in table 3.

#### 3.2. In-field or close-to-field second cancer risks

Ratios of OED, thus relative risks of second rectal and bladder cancers and pelvic bone and soft tissue sarcoma for each technique relative to 3D-CRT, and averaged over the three evaluated pelvic CT scans, are shown in figure 2.

SABR techniques, both FFF and flattened, resulted in the lowest OEDs for in-field and close-to-field tissues, and thus resulted in the greatest risk reductions relative to 3D-CRT, regardless of the model used.

Considering all alternative 78 Gy techniques relative to 3D-CRT, and all models, relative risks of rectal cancer, bladder cancer or soft tissue sarcoma were within 9%, 8% and 2% of that for 3D-CRT respectively. Risk of bone sarcoma was lower using all alternative techniques compared to 3D-CRT.

When comparing FFF with the equivalent flattened technique, for in-field and close-to-field tissues, there was minimal difference in risk (average relative risks for FFF consistently within 2% of flattened techniques).

The EAR for in-field or close-to-field radiation-induced second cancer was low for all techniques and models (figure 3). Rectal and bladder cancer EARs ranged from 1.44–2.69

<table>
<thead>
<tr>
<th>Technique</th>
<th>Number of MUs for whole treatment course</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABR FFF</td>
<td>13446</td>
</tr>
<tr>
<td>SABR</td>
<td>13010</td>
</tr>
<tr>
<td>VMAT 78 Gy FFF</td>
<td>25775</td>
</tr>
<tr>
<td>VMAT 78 Gy</td>
<td>24040</td>
</tr>
<tr>
<td>IMRT 78 Gy</td>
<td>13623</td>
</tr>
<tr>
<td>3D-CRT 78 Gy</td>
<td>10429</td>
</tr>
</tbody>
</table>

Table 3. MUs required for delivery of whole treatment course for the six radiation techniques delivered to the RANDO phantom (all from one patient).
and 1.70–2.42 per 10,000 persons per year (PY) respectively using the mechanistic model. Within each model, absolute differences between techniques were low, at most 1.25 and 0.96 per 10,000 PY for rectal and bladder cancer respectively. For each in-field or close-to-field site, absolute differences between models were also low, at most 1.09 per 10,000 PY for the rectum, and 0.66 per 10,000 PY for the bladder.

When comparing only 78 Gy techniques, absolute differences between techniques were small, at most 0.25 and 0.19 per 10,000 PY for rectal and bladder cancer respectively.

3.3. Out-of-field second cancer risks

Figure 4 shows radiation-induced second cancer risks relative to 3D-CRT (linear model). As for in-field or close-to-field tissues, SABR resulted in reduced relative radiation-induced second cancer risks in out-of-field organs.

In contrast to in-field or close-to-field tissues, FFF in comparison to the equivalent flattened technique, resulted in relative radiation-induced second cancer risk reductions in out-of-field organs. The impact of FFF increased at greater distances from the treatment field. For example, in the region of the stomach, SABR FFF resulted in a 20% risk reduction relative to SABR, and VMAT 78 Gy FFF resulted in a 19% risk reduction relative to VMAT 78 Gy. In the region of the brain, both SABR FFF and VMAT 78 Gy FFF resulted in 56% risk reductions relative to equivalent flattened techniques.

In all out-of-field organs, IMRT resulted in increased radiation-induced second cancer risks relative to 3D-CRT, although increases were frequently small. At most, 26% risk increases were observed in the salivary gland and thyroid region using IMRT relative to 3D-CRT. Similarly, VMAT 78 Gy resulted in increased second cancer risks in most out-of-field organs of up to 55% relative to 3D-CRT. In contrast, VMAT 78 Gy FFF resulted in reduced second cancer risks relative to 3D-CRT of up to 32%.

EARs for second cancers in out-of-field organs were low for all sites and techniques (figure 5). At greater distances from the field, where the relative impact of FFF was greatest, in absolute terms, risks were very small. For example, in the region of the brain, the 56% risk reduction observed for FFF relative to the equivalent flattened technique, corresponded
to absolute reductions from 0.0041 to 0.0018 per 10,000 PY for VMAT 78 Gy versus VMAT 78 Gy FFF and 0.0024 to 0.0011 per 10,000 PY for SABR versus SABR FFF, thus highlighting the fact that when absolute risks are very low, large relative risks become less relevant.

In absolute terms, the increased risk from IMRT relative to 3D-CRT was also small: the 26% relative risk increase corresponded to an EAR increase from 0.0041 to 0.0051 per 10,000 PY for 3D-CRT versus IMRT for salivary gland cancer, and from 0.0009 to 0.0011 per 10,000 PY for thyroid cancer. Similarly the 55% risk increase from VMAT 78 Gy relative to 3D-CRT, amounted to absolute increases from 0.0027 to 0.0041 per 10,000 PY for cancers of the brain respectively. The 32% risk reduction observed with VMAT 78 Gy FFF relative to 3D-CRT was also small in absolute terms (0.0027 to 0.0018 per 10,000 PY for second brain cancers). Thus this data also illustrate that large relative risks become unhelpful when absolute risks are very low.

Combining all the out-of-field EARs, plus EARs for pelvic bone and soft tissue sarcoma, as well as the highest average EAR from each of the three models used for second rectal and

Figure 3. EARs of second malignancy in in-field or close-to-field tissues for whole treatment course based on patients being irradiated aged 60 and attaining 80 years. Error bars display the range of relative risks for the three pelvic CT scans used for planning.

Figure 4. Relative risks of second malignancy in out-of-field tissues relative to 3D-CRT for whole treatment course. 5% error bars are shown to account for dosimetric and positioning uncertainty.
Thus SABR FFF resulted in the lowest ‘total’ second cancer risk (4.24 per 10,000 PY), and IMRT resulted in the highest ‘total’ second cancer risk (7.44 per 10,000 PY), thus the largest difference between techniques was low at 3.2 per 10,000 PY. The absolute differences between VMAT 78 Gy FFF, VMAT 78 Gy, IMRT 78 Gy and 3D-CRT were very low, at most 0.62 per 10,000 PY.

3.4. Dose from head scatter and leakage

Out-of-field measurements performed following removal of the phantom pelvis demonstrated that FFF resulted in reduced out-of-field doses due to head scatter/leakage compared to equivalent flattened techniques. The proportion of dose resulting from head leakage/scatter is shown in figure 7.

3.5. Components of dose and distance

Changes in total dose, head leakage/scatter and within patient scatter (total dose minus head leakage/scatter) with distance are shown in figure 8. A slight increase in dose from within patient scatter was observed with FFF compared to the equivalent flattened beam at 10 and 15 cm from the isocentre, but this was outweighed by the reduction in dose due to reduced head leakage/scatter with FFF, resulting in lower total doses with FFF compared to the equivalent flattened technique. Beyond 15 cm from the isocentre, within patient scatter was similar between FFF and the equivalent flattened techniques.

4. Discussion

We aimed to assess radiation-induced second cancer risk following modern, clinically relevant prostate radiotherapy techniques. For all techniques, EARs were low. SABR conferred a consistently lower second cancer risk in all organs, while FFF conferred lower second cancer risk.
risks in out-of-field organs, with the greatest relative impact at increasing distances from the field, where absolute benefits were small. The very low calculated absolute risks highlight the importance of not considering relative risks in isolation but also considering the associated absolute risks, as where absolute risks are very small, relative risks become far less important.

Prostate SABR delivers lower physical doses compared to conventionally fractionated treatments. Both lower physical doses and hypofractionation contributed to the observed second cancer risk reductions. The rationale for hypofractionation resulting in reduced second cancer risk has been discussed elsewhere (Schneider et al 2010).

While other groups have also observed the relative impact of FFF on out-of-field doses in prostate cancer (Kry et al 2010, Halg et al 2012), we are unaware that others have quantified the size of the benefit or assessed risk in the setting of energy-matched FFF and standard (flattened) beams. As above, it is clinically relevant to consider relative risks alongside
corresponding absolute risks, although it is acknowledged that calculation of EAR, as an extension of OED calculation, introduces additional uncertainties (i.e. the steepness of the initial portion of the dose–response curve and adjustment for the age of the population in question). Despite this, calculated absolute benefits from FFF at large distances from the isocentre, were very small for this population. Irradiation of younger patients would result in greater absolute benefits from FFF. Most prostate cancer patients are, however, in the age range we considered, making calculated EARs relevant for the majority.

Kry et al (2010) evaluated non-energy matched FFF beams. An increase in total out-of-field dose was observed 3–15 cm from the field edge which was attributed to lower energy FFF photons resulting in increased within patient scatter, potentially increasing second cancer risks (Kry et al 2010). Using energy-matched FFF beams, we observed no such increase in total out-of-field dose, and the slight increase in within patient scatter was outweighed by the substantial reduction in head leakage/scatter.

Few groups have evaluated radiation-induced second cancer risk in prostate cancer from SABR (Dasu et al 2011) and VMAT (Rechner et al 2012). Comparisons with data from other groups are difficult because of the different methods employed. In addition, whole body risk is often calculated rather than individual organ risks. The impact of linac based SABR techniques on second malignancy risk has not been widely examined and we are aware of only one other group which has investigated this (Dasu et al 2011). Dasu et al quantified risks of second rectal and bladder cancer following 42.7 Gy in 7 fractions and 78 Gy in 39 fractions, both delivered using 3D-CRT (Dasu et al 2011). Exported DVHs were used to calculate risks using the competition model. Overall predicted risks were low, and CTV-PTV margin size had a larger impact on risk than fractionation schedule. The group concluded that the risks of second rectal and bladder cancers were similar between conventionally fractionated and ultra-hypofractionated regimens (Dasu et al 2011). Thus the potential in-field benefits of SABR that we observed in this study were not observed in Dasu et al’s work. This likely reflects the differences in the modelling processes used: the competition model used predicts a maximum second cancer effect at around 4 Gy, while according to the OED model and accompanying parameters, risks may become maximal at higher doses (see below). In addition, while both models incorporate fractionation, fractionation is incorporated into each model differently.
Recalculating the risk of second bladder and rectal cancers for the three prostate patients using the competition model, and the same parameters as used by Dasu et al, we also observed broadly similar risks of second cancers between hypofractionated and all conventionally fractionated techniques (table 4). Reaching a definitive conclusion about which of the two models is more accurate is difficult, if not impossible.

There is epidemiological evidence which suggests that following irradiation for prostate cancer most second cancers arise in regions which receive doses greater than 5 Gy, thus including the rectum and bladder, and so adding support to Schneider’s model (Berrington de Gonzalez et al 2011). Similarly, data from patients irradiated for cervical cancer has suggested that there is an increasing dose–risk relationship for second rectal and bladder cancer for doses up to 60 Gy and greater (Boice et al 1988). In contrast, however, it has been demonstrated that the dose–risk relationship for second rectal and bladder cancers following irradiation for a variety of primary tumour sites is essentially flat from doses of 1 to 60 Gy (Suit et al 2007), and other work, also following irradiation of a variety of primary tumour sites, has demonstrated that most second tumours arise at the edge of the PTV (Epstein et al 1997, Dorr and Herrmann 2002), which, in one of these studies, corresponded with regions receiving 6 Gy or less (Dorr and Herrmann 2002). No one model of radiation-induced carcinogenesis has ever been shown to be a perfect match for the epidemiological data, and epidemiological data, at times, appears conflicting. It is perhaps best, therefore, to view the differing results from the OED concept and competition model as illustrations of the uncertainties associated with the radiation-induced second cancer risk calculation process.

Few groups have evaluated radiation-induced second cancer risk in prostate cancer following VMAT compared to other external beam photon techniques. Rechner et al (2012) however, principally compared risks of bladder and rectal second cancers risks from VMAT with proton arc therapy. Excess relative risks were calculated and ratios of excess relative risks were used for comparisons (another modelling process which incorporates the effects of fractionation and reports risk relative to that in an non-irradiated population (Sachs and Brenner 2005, Shuryak et al 2009a, 2009b)). DVH data provided details of the therapeutic dose for VMAT and were also used to estimate secondary radiation doses (i.e. dose resulting from head leakage and scatter and additional within patient scatter). Monte Carlo simulations and previously published data were used to estimate secondary radiation doses resulting from proton arc therapy. Proton arc therapy predicted significantly lower risks of second bladder or rectal cancer according to linear-exponential and linear-plateau models compared to VMAT, while there was no significant difference in second rectal or bladder cancer risk when using the linear model. The group also compared calculated excess relative risks of second bladder and rectal from VMAT with that previously estimated for IMRT by

<table>
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<tr>
<th>Rectum</th>
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<th>Range</th>
<th>Bladder</th>
<th>Average</th>
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<td>VMAT 78 Gy FFF</td>
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<td>0.54–0.64</td>
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<tr>
<td>VMAT 78 Gy</td>
<td>0.58</td>
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<td>0.25</td>
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<td>IMRT 78 Gy</td>
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<td>0.25</td>
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another group (Fontenot et al 2009). Numerically, VMAT resulted in lower risks of second bladder and rectal cancer compared to IMRT (excess relative risk for bladder cancer: 5.25 with VMAT and 8.88 with IMRT, excess relative risk for rectal cancer: 2.09 with VMAT and 3.32 for IMRT) (Rechner et al 2012). These risks, however, were calculated using a linear model, which is often considered inappropriate in higher dose regions (Hall and Wuu 2003, Ruben et al 2008). The use of a different model may also explain why greater differences were observed between IMRT and VMAT by Rechner et al and were greater than what was observed in this current piece of work.

Theoretical concerns have been raised regarding a potential large increase in second cancer risk using IMRT compared to 3D-CRT (Followill et al 1997, Hall and Wuu 2003, Kry et al 2005a, 2007, Stathakis et al 2007). Recent papers have suggested that any increased risk from 6MV IMRT would be very small, particularly when compared to higher energy 3D-CRT (as often employed clinically) (Ruben et al 2008, 2011, Bednarz et al 2010, Ardenfors et al 2014). The theoretical risk increase is often attributed to two things: increased MU requirements for IMRT, resulting in increased head leakage, thus contributing to out-of-field dose, and the change in dose distribution, resulting in an increased volume of normal tissue receiving low doses. We observed increased risks from 6MV IMRT and VMAT 78 Gy relative to 10 MV 3D-CRT in out-of-field organs of up to 26% and 55% respectively, likely because of increased MU. In absolute terms, however, where the greatest relative risk increases occurred, absolute increases were very small. VMAT 78 Gy FFF, however, resulted in reduced risks relative to 3D-CRT, although, again, absolute differences in risk were low. When considering individual in-field or close-to-field tissues, the impact of a change in dose distribution when moving from 3D-CRT to IMRT did not translate into clinically relevant increases in second cancer risk according to the models employed here. This can be explained through inspection of the DVHs for in-field and close-to-field organs. DVHs for all 78 Gy treatments for one pelvic CT are plotted in figures 9(a)–(d). The relationship between dose and risk equivalent dose (RED) according to Schneider’s models has also been superimposed onto the DVH curves (Schneider et al 2011). Note that the values for RED are not shown, but the dose–RED curves are plotted purely to illustrate the shape of the dose–risk relationship.

Visual inspection of differential DVHs for the rectum for all 78 Gy treatments (figure 8(a)) are not suggestive that the rectum receives a greater proportion of low dose irradiation with IMRT, and dose distributions are largely similar between 3D-CRT and IMRT until around 40 Gy where there is a peak in the 3D-CRT DVH. For IMRT a smaller peak is seen around 48 Gy. In Schneider’s model for rectal cancer induction, and based on the fractionation used here (i.e. 39 fractions), the risk peaks at about 23 Gy according to the bell-shaped model, and at about 35 Gy according to the mechanistic and plateau models. The 40–50 Gy region is therefore in the region of decreasing risk and the 48 Gy peak in the IMRT DVH falls in a lower risk portion of the curve compared to the 40 Gy peak for the 3D-CRT curve, and this may contribute to the slightly reduced risk observed in the risk of rectal cancer using IMRT relative to 3D-CRT (although in absolute terms the difference in risk is very small). Considering the VMAT treatments, a higher proportion of rectal tissue receives doses in the 15 to 25 Gy range compared to IMRT and 3D-CRT. This dose region falls in the highest risk portion of the bell-shaped model, thus resulting in the slightly increased risk of rectal cancer using VMAT relative to 3D-CRT and IMRT using this model. Considering the competition model, which predicts maximum effect at around 4 Gy, IMRT and VMAT treatments display a slightly higher volume of tissue receiving doses in the 3–4 Gy region, resulting in the slightly higher risks seen with IMRT and VMAT according to this model (table 4).

In the case of the bladder DVHs (figure 8(b)), IMRT appears to result in a slight increase in the volume of tissue receiving 2–5 Gy, which encompasses the area of maximal effect.
Figure 9. (a) Differential DVHs comparing 78 Gy techniques: rectum; RED: risk equivalent dose. (b) Differential DVHs comparing 75 Gy techniques: bladder (only first 10.5 Gy shown to allow differences to be more clearly observed); RED: risk equivalent dose. (c) Differential DVHs comparing 78 Gy techniques: pelvic bones; RED: risk equivalent dose. (d) Differential DVHs comparing 78 Gy techniques: pelvic soft tissues; RED: risk equivalent dose.
according to Schneider’s bladders models, thus resulting in the slightly higher relative risk of second bladder cancers from IMRT compared to 3D-CRT. For both VMAT treatments, a smaller volume of tissue receives doses in the region of 1–2 Gy compared to 3D-CRT, and similar volumes of tissues receive doses of 3–5 Gy compared to 3D-CRT, thus resulting in only very slight second bladder cancer risk reductions using VMAT. These differences in dose distributions between techniques also explain the slight increase in second bladder cancer risk observed using IMRT compared to 3D-CRT, and similarities in risk between VMAT and 3D-CRT, according to the competition model.

Considering the pelvic bone DVHs (figure 8(c)), VMAT results in a larger volume of tissue receiving very low doses (<1 Gy) and IMRT results in a slightly increased volume of tissue receiving doses around 2 Gy and around 6–10 Gy compared to 3D-CRT. Schneider’s model, however, predicts a peak in bone sarcoma risk at around 54 Gy. A peak in dose is seen for the 3D-CRT plan at just above 40 Gy, thus falling in the higher risk region of the dose–RED curve, and contributing to the increased relative risk of second bone sarcoma observed for 3D-CRT compared to all other techniques, while the increased volume of bone receiving lower doses from IMRT and VMAT fall on a much lower risk part of the dose–risk curve, and thus have little impact on the calculated risk.

In terms of the soft tissue DVHs (figure 8(d)), where perhaps one might expect to see the biggest impact of an increased volume of tissue receiving a lower dose of radiation with IMRT or VMAT techniques, it can be seen that VMAT, as with the pelvic bone DVHs, results in a higher volume of tissues receiving very low doses (i.e. <1 Gy), while 3D-CRT results in a slightly larger volume of tissue receiving 2–3 Gy. Schneider’s model predicts maximum effect at around 58 Gy and so it is doses in this region which will have the largest impact on risk. In the 50–60 Gy region, the DVH is largely similar for all techniques, and there is only a very slight peak at about 42 Gy for 3D-CRT. Overall, therefore, calculated risks for pelvic soft tissue sarcoma are similar for all four techniques, and the traditional concern that IMRT/VMAT techniques result in a larger volume of normal tissue receiving lower (and thus more cancer inducing) doses appears to contribute little to the overall calculated risk, according to the model used here.

The rectal, bladder, pelvic bone and pelvic soft tissue DVHs for the SABR FFF and standard (flattened) plans were very similar (data not shown), thus explaining the similar second cancer risks estimations for these two techniques, regardless of whether the OED concept or competition model was used.

There are a number of limitations in our work. Firstly, as alluded to above, there are uncertainties in radiation-induced second cancer models and parameters. Schneider’s concept of OED was employed as this incorporates fractionation and, with the mechanistic model, includes repair and repopulation (Schneider et al 2011). Models based on full and no repair/repopulation, were also adopted to illustrate a range of possibilities. All models suggested benefit from SABR in in-field or close-to-field tissues, which is where the majority of radiation-induced second cancers arise (Epstein et al 1997, Dorr and Herrmann 2002, Berrington de Gonzalez et al 2011). Similarly, all models predicted broadly comparable second rectal and bladder cancer risks from 3D-CRT, 5-field IMRT and VMAT 78 Gy (FFF or standard).

Secondly, the appropriateness of these linear-quadratic (LQ) based models for high dose per fraction treatments could be questioned (Brenner 2008, Kirkpatrick et al 2008). Our SABR prescription dose was 6.1 Gy per fraction, and, most normal tissues received doses far below the prescription dose. Where concern about high dose per fraction treatments and the LQ model have been raised, this is usually in the setting of radiosurgical doses (e.g. >10 Gy per fraction) (Kirkpatrick et al 2008). Thus the doses considered in this current study were within the range in which the LQ model is considered reliable.
Thirdly, we did not assess the impact of neutron contamination on second cancer risks for the 10 MV plan. It has previously been demonstrated, however, that at 10 MV this effect is very small (Kry et al. 2005a). Fourthly, only three patients’ pelvic CT scans were evaluated for in-field and close-to-field second cancer risks, and only one was evaluated for out-of-field risks. Similar to this study, the majority of prostate cancer planning studies which evaluate radiation-induced second cancer risks in a series of adult patients, all planned using the same variety of techniques, do so in one to three patients. The reason for the small sample size is that the primary interest is differences between techniques rather than inter-patient variability (Kry et al. 2005b, 2010, Schneider 2006, Stathakis et al. 2007, Ruben et al. 2008, Fontenot et al. 2009, Bednarz et al. 2010, Kragl et al. 2011, Blais et al. 2012, Rechner et al. 2012) A few studies have, however, compared up to 10 patients, each planned using the same variety of techniques (Fontenot et al. 2010, Patil et al. 2010, Yoon et al. 2010). Dasu et al. (2011), however, aimed to evaluate inter-patient variability in second cancer risk and so included 100 patients, each planned using SABR and conventionally fractionated radiotherapy, although this analysis was restricted to rectal and bladder DVH analysis, and did not include out-of-field dose measurements. Given the relative anatomical constancy of the prostate in relation to organs-at-risk, however, any variability in second cancer risk is likely to be less than what might be expected for tumours with greater variability in location, suggesting that a low number of patients may be acceptable. This is reinforced by the consistency in results for the three evaluated patients, thus adding confidence to our use of a small patient sample. For out-of-field organs, minimal variation in dose between patients would be expected, and so the use of one patient, planned in several different ways, is adequate for comparison of different techniques.

We did not include the impact of image-guided radiotherapy (IGRT) on second cancer risk as this will vary with the IGRT technique employed. The CTV–PTV margin was intended for daily online IGRT with fiducial markers. Thus conventionally fractionated regimens will require at least 39 images while SABR will require at least 7 images. If automatic couch adjustments are used, and treatment is sufficiently rapid, then further imaging following shifts or post-treatment would be unnecessary. The need for fewer images with ultra-hypofractionated regimens potentially adds additional second cancer benefit to SABR techniques.

Different hardware and software combinations as well as treatment margins may all contribute to differences in second cancer risk (Ruben et al. 2008, Dasu et al. 2011). We attempted to minimize these as far as possible by delivering all plans on the same machine, by creating plans using the same planning system as far as possible, and by using the same CTV–PTV margin. Differences in risks observed in this study should therefore largely be due to the doses, fractionations and planning techniques under evaluation. Our findings are, however, specific for the planning and delivery systems adopted here.

5. Conclusion

In summary, we compared radiation-induced second cancer risks following contemporary clinically relevant radiotherapy techniques for early prostate cancer. SABR resulted in reduced relative second cancer risks in all organs, while FFF resulted in reduced second cancer risks in out-of-field organs relative to equivalent flattened techniques, particularly at greater distances from the treatment field. Although large differences in relative risk were sometimes observed, in absolute terms, second cancer risks were low, emphasizing the importance of considering absolute risks in addition to the comparison of relative risks. Until clinical data regarding
radiation-induced second cancers in irradiated prostate patients treated with contemporary techniques matures, data from this and other planning studies should be considered when selecting appropriate radiation techniques for individual patients.

Conflicts of interest

Elekta have a research agreement with St James’s Institute of Oncology which provides funding for PhD work and provides support for travel to meetings

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