The effect of 6 and 15 MV on intensity-modulated radiation therapy prostate cancer treatment: plan evaluation, tumour control probability and normal tissue complication probability analysis, and the theoretical risk of secondary induced malignancies

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Objective: The aim of this study was to investigate the effect of 6 and 15-MV photon energies on intensity-modulated radiation therapy (IMRT) prostate cancer treatment plan outcome and to compare the theoretical risks of secondary induced malignancies.

Methods: Separate prostate cancer IMRT plans were prepared for 6 and 15-MV beams. Organ-equivalent doses were obtained through thermoluminescent dosimeter measurements in an anthropomorphic Aldersen radiation therapy human phantom. The neutron dose contribution at 15 MV was measured using polyallyl-diglycol-carbonate neutron track etch detectors. Risk coefficients from the International Commission on Radiological Protection Report 103 were used to compare the risk of fatal secondary induced malignancies in out-of-field organs and tissues for 6 and 15 MV. For the bladder and the rectum, a comparative evaluation of the risk using three separate models was carried out. Dose–volume parameters for the rectum, bladder and prostate planning target volume were evaluated, as well as normal tissue complication probability (NTCP) and tumour control probability calculations.

Results: There is a small increased theoretical risk of developing a fatal cancer from 6 MV compared with 15 MV, taking into account all the organs. Dose–volume parameters for the rectum and bladder show that 15 MV results in better volume sparing in the regions below 70 Gy, but the volume exposed increases slightly beyond this in comparison with 6 MV, resulting in a higher NTCP for the rectum of 3.6% vs 3.0% ($p=0.166$).

Conclusion: The choice to treat using IMRT at 15 MV should not be excluded, but should be based on risk vs benefit while considering the age and life expectancy of the patient together with the relative risk of radiation-induced cancer and NTCPs.

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Three-dimensional conformal radiation therapy (3D-CRT) is most commonly delivered with high-energy photons, typically in the range of 6–18 MV. Intensity-modulated radiation therapy (IMRT) is known to improve target coverage and provide better organ-at-risk (OAR) sparing in comparison with 3D-CRT [1]. However, IMRT is associated with an increase in the number of monitor units (MUs) relative to 3D-CRT, which has led to concerns about a potential increased risk of radiation-induced malignancies [2]. This risk becomes more relevant at higher photon energies (>10 MV), where there is a possibility of greater leakage radiation, treatment head scatter, patient scatter and photoneutron contribution [3]. Subsequently, the majority of IMRT treatments being delivered in the UK today use 6-MV photons. The use of higher energies for deep-seated tumours, such as those in the prostate, have been favoured by some as providing better dose coverage to

the tumour target, while also improving normal tissue sparing [4].

It has been reported in the literature that IMRT may double the risk of fatal second cancers compared with 3D-CRT [5–9]. The risk of fatal cancer has been reported for 6-MV 3D-CRT and IMRT prostate treatments to vary by 0.6–1.5% and 1–3.0%, respectively [7, 8, 10]. For 15-MV photons, the risk has been reported to be 3.4% [10]. These values have been computed using data from the National Council on Radiation Protection and Measurements (NCRP) Report 116, assuming a linear lifetime risk value of 0.05 per Sievert for all fatal radiation-induced cancers for the general population [11].

There are as yet no epidemiological data for radiation-induced malignancy in patients with prostate cancer who received treatment with IMRT. A modest increase in second malignancies of 1 in 70 patients undergoing radiation and surviving for more than 10 years was reported for 3D-CRT, with the most common sites for secondary cancers being the bladder and rectum [12].

Currently, at our centre (St Luke's Cancer Centre, SLCC), 3D-CRT to the prostate is delivered mostly with

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15-MV photons, whereas IMRT is delivered with 6-MV photons. During the initial set-up of prostate IMRT at SLCC, all energy beams (6, 10 and 15 MV) were in clinical use. After 10 patients had been treated, it was decided by the clinical team to use only 6-MV photons until the use of higher energy beams was further evaluated, given that the potential advantages related to their use could be offset by a potential increase in the risk of second malignancy.

This study has investigated whether high-energy IMRT offers better target coverage and normal tissue sparing for prostate cancer. This work has investigated the organ equivalent doses through thermoluminescent dosimeter (TLD) measurements in an anthropomorphic Alderson radiation therapy (ART) human phantom (RANDO; The Phantom Laboratory, Salem, NY) in order to assess the theoretical risk of secondary malignancies in organs and tissues distant from the tumour target. For the bladder and rectum, a comparative evaluation of calculating the risk using the linear non-threshold model [13–15], linear-plateau model [16] and initiation-inactivation model [17] was performed. The neutron dose contribution at 15 MV was estimated using polyallyl-diglycol-carbonate (PADC) neutron track etch detectors. Dosimetric plan evaluations were carried out for the planning target volume (PTV) and OARs, as well as an assessment of the total number of MUs for plans generated with different energies.

Methods and materials

Treatment planning

The planning scans of five patients who had completed a course of radical radiotherapy to the prostate were used. Patients were scanned according to departmental protocol using 2.5-mm slices from the sacro-iliac joints to the penile urethra. All patient details were anonymised. Prostate volumes were not outlined by the same oncologist. Outlining was carried out by the clinician treating each patient and was standardised by protocol. Outlining was tested against protocol in the form of outlining exercises. OARs included the bladder, rectum, femoral heads and bowel. IMRT plans at 6 and 15 MV for the five different planning scans were generated using the inverse-planning Helios optimisation tool in the Varian Eclipse treatment planning system (Varian Medical Systems Inc, Palo Alto, CA) and dose-volume calculations were performed using the pencil beam convolution algorithm. Target volume definition, plan objectives and constraints followed the protocol set out in the Conventional or High Dose Hypofractionated IMRT for Prostate Cancer (CHHiP) trial [18]. For this study, the conventional fractionation of 74 Gy in 2 Gy fraction⁻¹ was used in the IMRT treatment planning and measurements.

The prostate IMRT plans were generated adopting a 5-radiation-beam arrangement incorporating a left and right anterior oblique field, a left and right posterior oblique field and a posterior field. The same beam angles were used for 6- and 15-MV plans for each CT data set. In order to reduce uncertainty in the planning process, all plans were optimised at 6 MV and subsequently recalculated and optimised at 15 MV using a pre-defined optimisation template as a starting point. All plans

were normalised such that the median target dose was 100%.

Assessment of the dose-volume parameters for the prostate PTV, rectum and bladder were analysed for each plan at 6 and 15 MV. For the prostate PTV, the parameters that were compared were $D_{99\%}$ (minimum dose delivered to 99% of the volume), $D_{95\%}$, $D_{50\%}$, $D_{5\%}$ and the 95% conformity index ($CI_{95\%}$, i.e. the ratio of the irradiated volume receiving 95% of the prescribed dose and the volume of the PTV).

Although dose constraints for the bladder and rectum are usually specified in terms of percentage volume, it was only possible to compare the doses received in terms of absolute volume in cubic centimetres between different plans owing to the variability in the size of these organs between the five cases. Therefore, for the rectum and bladder, the dose parameters investigated were V_{30Gy} (volume receiving 30 Gy), V_{40Gy} , V_{50Gy} , V_{60Gy} , V_{70Gy} and V_{74Gy} . In all cases, the dose to the bowel and femoral heads were within CHHiP trial constraints and no further evaluation was performed.

Radiobiological evaluation

To determine whether there is a biological effect due to a potential difference in target volume dose heterogeneity between 6 and 15 MV, tumour control probability (TCP) calculations were performed in BIOPLAN (Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, UK) [19] using the mechanistic Poisson-based TCP model [20]. The following input parameters for the TCP models for prostate tumours were used: radiosensitivity parameter $\alpha=0.29 \text{ Gy}^{-1}$, interpatient variation in radiosensitivity parameter $\sigma_\alpha=0.07 \text{ Gy}^{-1}$, clonogenic cell density $\rho_c=10^7 \text{ cm}^{-3}$ and an α/β ratio of 10 [21]. These parameters have been fitted to clinical data from patients with intermediate risk disease. Although it has been suggested that an α/β ratio of 1.5 is more appropriate [22], use of this value in conjunction with the fitted parameters resulted in a TCP >99%, which means that these parameters put the prescribed dose in the insensitive part of the TCP curve (i.e. large changes in dose would be required to affect TCP), which is not consistent with clinical data. Using a value of 10 for α/β gave TCP in the region of 80%. For example, Zelefsky et al [23] reported 8-year actuarial prostate-specific antigen (PSA) relapse-free survival rates of 78% for intermediate-risk patients treated to 81 Gy in 1.8 Gy daily fractions using IMRT (using the Houston definition for biochemical relapse). There are some uncertainties in using TCP models to accurately predict outcome in prostate cancer [24], but for the purpose of our evaluation the parameters mentioned above were deemed suitable for estimating changes in TCP of between 6 and 15 MV.

Normal tissue complication probability (NTCP) calculations were performed for the rectum using the Lyman-Kutcher-Burman model [25–27], generalised uniform dose concept [28] and Quantitative Analysis of Normal Tissue Effects in the Clinic [29] recommended best parameter estimates of $\alpha/\beta=3 \text{ Gy}$, volume effects parameter $n=0.09$, slope parameter $m=0.13$ and the dose for 50% complication probability (TD_{50})=76.9 Gy. For the bladder, there is limited NTCP parameter data owing to difficulties in fitting parameters to genito-urinary toxicity

[30, 31]. The general consensus is to use the Emami-Burman parameters of $n=0.5$, $m=0.11$ and $TD_{50}=80$ Gy, in conjunction with $\alpha/\beta=3$ Gy [28, 32].

Thermoluminescent dosimeter measurement

TLD measurements were performed in an anthropomorphic ART phantom known as RANDO at both 6 and 15 MV for the five different treatment plans delivered to the RANDO phantom using a Varian Clinac iX (Varian Medical Systems Inc). The RANDO phantom available for this study was version ARTF 1025, which represents a human who is 1.55 m tall and weighs 50 kg. The phantom is transected horizontally, and each 2.5 cm slice has holes that are plugged with soft tissue-equivalent and lung-tissue equivalent 5-mm-diameter pins that can be replaced by TLD holders [33]. The phantom was CT scanned without TLDs, according to the IMRT protocol at SLCC, using 2.5-mm slices. Once the treatment plan for a particular planning scan was complete, it was possible to copy the plan from a patient onto the RANDO phantom image set with the same beam geometry, actual fluences and MUs. It was then possible to deliver a plan on the phantom with TLDs in place.

The TLDs used were the Harshaw TLD-700 lithium fluoride doped with traces of magnesium and titanium (LiF:Ti,Mg) square $3.2 \times 3.2 \times 0.89$ -mm chips (Thermo Fisher Scientific Inc, Waltham, MA). The chips were all calibrated separately at 6 and 15 MV against a Farmer-type ionisation chamber, with each single chip given its own sensitivity. Their dose response was determined by irradiating sets of 10 TLDs with doses ranging from 0 to 400 cGy. The TLDs were read out using a QADOS Harshaw 5500 reader with pre-heat at 145°C for 10 s and a temperature ramp of 17°C per second up to a maximum temperature of 300°C for 10 s. The TLDs were annealed after each use in a dedicated oven at 400°C for 1 h, followed directly by 100°C for 2 h.

Around 130 TLDs were available for use and these were distributed uniformly throughout the phantom. Where possible, three TLDs were placed at a particular position in order to reduce uncertainties in dose measurement. Skin measurements were performed by placing 20 TLDs on the surface.

The most radiosensitive organs [according to the recommendations in International Commission on Radiological Protection (ICRP) Report 103 [34]] were outlined on the phantom with reference to bony landmarks. The small and large intestines were not outlined; however, an estimate of the volume was made. One could then estimate the average absorbed dose to each organ based on the TLD positions and measurements and thus estimate an equivalent dose to each organ.

The red bone marrow, which is important in order to assess the risk of a fatal incidence of leukaemia, was not outlined. In order to be able to estimate the dose to the red bone marrow, the work by Ellis [35] that described the distribution of the active red bone marrow in a normal 40-year-old male was employed. Therefore, the average red bone marrow dose, D_{RBM} , was calculated using Equation (1), derived from the data of Ellis [35]:

$$D_{\text{RBM}} = 0.13D_{\text{Brain}} + 0.08D_{\text{Thyroid}} + 0.11D_{\text{Heart}} + 0.03D_{\text{C-spine}} + 0.14D_{\text{T-spine}} + 0.11D_{\text{L-spine}} + 0.14D_{\text{Sacrum}} + 0.26D_{\text{F-H}} \quad (1)$$

where D_{Brain} is the average dose to the brain, D_{Thyroid} is the average dose to the thyroid, D_{Heart} is the average dose to the heart, $D_{\text{C-spine}}$ is the average dose to the cervical spine, $D_{\text{T-spine}}$ is the average dose to the thoracic spine, $D_{\text{L-spine}}$ is the average dose to the lumbar spine, D_{Sacrum} is the average dose to the sacrum and $D_{\text{F-H}}$ is the average dose to the femoral heads.

Polyallyl-diglycol-carbonate detector neutron track etch detector measurement

PADCs were provided and processed by the Computational Dosimetry Group from the Radiation Protection Division of the Health Protection Agency (HPA-RPD; formerly the National Radiological Protection Board). The PADCs themselves were encased in a plastic holder, which induces secondary protons from the neutron interaction. The ionisation caused by the protons in PADC dosimeters forms small weaknesses in its polymeric structure. These weaknesses become vulnerable to attack by an etchant (in this case sodium hydroxide). This may then be blown up into a larger hole using electrochemical etching. In this procedure, the PADC dosimeters were chemically etched for 8 h and then electrochemically etched for 11.5 h at about 1200 volts. The dosimeters were then scanned and the number of holes present counted by computer software. The PADCs were calibrated at the HPA-RPD using a $^{241}\text{Am-Be}$ source. The PADCs were positioned 35 cm from the source and exposed for 2 h, giving them a dose of 2 mSv.

A total of 35 PADC detectors were placed on the surface of the Rando phantom. The phantom was then irradiated three times using the 15-MV IMRT treatment for the plan with the largest irradiated volume. It has been reported that the neutron dose rate at the isocentre is $0.002\text{ Sv (neutron) Gy (photon)}^{-1}$, and that the average energy of neutrons produced at the isocentre for 15 MV photons is approximately 0.4 MeV [36]. The neutron equivalent doses were reported in the operation quantity personal dose equivalent at 10-mm depth in tissue, $H_p(10)$. The response of the PADC was determined by folding the fluence response characteristics of the PADC with the fluence-energy photoneutron distribution for a linear accelerator using a program developed at HPA-RPD [37]. The folding program uses an algorithm to determine the ratio of the reading of the PADC detector to the true dose equivalent. The photoneutron energy spectra used in order to fold the response of the PADC detectors were measured by Thomas et al [38]. The average calculated response for the PADCs, after calibration, was determined to be $175\text{ tracks mSv}^{-1}$.

Out-of-field organ risk of secondary induced cancer estimation

Organ absorbed doses were converted to organ equivalent doses in terms of sieverts using the radiation weighting factor [34]; for photons this weighting factor is unity, and therefore the two quantities were equal. The risk of secondary induced malignancy in specific organs was then calculated using risk coefficients taken from ICRP 103 [34], which are given as percentages per sievert.

The TLD photon data of this study were compared with data by Howell et al [39] and Kry et al [40], who performed measurements at 6, 15 and 18 MV for dynamic multi-leaf collimation (MLC) delivery and step-and-shoot IMRT, respectively. The organs compared were the thyroid, stomach, liver and lung. Both studies reported the out-of-field doses in microsieverts per MU; therefore, the same was done to compare the data.

Assessing the risk of secondary cancer in irradiated volume using three different models

Models based on atomic bomb survivors are valid for low doses but cannot be easily related to the higher doses received by OARs [16]. The effect of beam energy on the risk of inducing secondary cancer of the bladder or rectum, or leukaemia was assessed using three different models. The first was to use the linear non-threshold (LNT) model, which assumes a proportional increase of the risk of cancer with radiation dose [13–15]. The second model used was the linear-plateau model, which assumes that the risk saturates at 4 Gy and above [16]. The third model was the non-linear competition model, which takes into account the induction of carcinogenic mutations and cellular survival using Equations (2) and (3):

$$\text{Risk} = \frac{\sum_i v_i \times \text{Risk}(D_i)}{\sum_i v_i} \quad (2)$$

where v_i is the volume of tissue receiving dose D_i given in n individual fractions and $\text{Risk}(D_i)$ is given by the non-linear dose–response relationship of the competition model. ICRP 103 risk coefficients were used. The effect can be calculated using the modified UNSCEAR equation [17], taking into account fractionation, n :

$$\text{Risk}(D_i) = \left(aD_i + \frac{bD_i^2}{n} \right) \exp \left[- \left(\alpha D_i + \frac{\beta D_i^2}{n} \right) \right] \quad (3)$$

where a and b are coefficients for the linear and quadratic terms for stochastic effects, respectively, and α and β are the coefficients for the linear and quadratic terms for cell killing, respectively. For each of the three models, differential dose–volume histograms (DVHs) for the bladder and rectum were used to calculate the risk in every dose interval of the DVH, and then one integrates over the total intervals to give the result [16]. For leukaemia, Equation (1) was used in conjunction with Equations (2) and (3) to calculate the theoretical risk, taking into account distribution of red bone marrow in the human body.

Estimating the total lifetime and 40-year post-exposure risk

The probability of any fatal cancer is calculated using the out-of-field and in-field organs using Equation (4):

$$\text{Total risk} = R_{\text{Thyroid}} \cup R_{\text{Lungs}} \cup R_{\text{Oesoph}} \cup R_{\text{Stomach}} \cup R_{\text{Liver}} \cup R_{\text{Colon}} \cup R_{\text{Skin}} \cup R_{\text{Gonads}} \cup R_{\text{Leukaemia}} \cup R_{\text{Rectum}} \cup R_{\text{Bladder}} \quad (4)$$

The risk of fatal cancer up to 40 years after exposure and the lifetime risk for different age ranges were calculated using age-dependent risk coefficients from Muirhead et al [41]. The majority of the total risk is estimated by the out-of-field calculated risks. These used population-averaged risk coefficients from ICRP 103 (age range 0–80 years). A median of 40 years at age of exposure was therefore assumed. To this end, the age-dependent risk coefficients given by Muirhead et al were normalised at 40 years at age of exposure to deduce correction factors for the 40-year and lifetime risk to apply to the calculation in Equation (4).

Statistical and uncertainty analysis

Statistical analysis comparing 6 and 15-MV second cancer risk, TCP and NTCP, and dose–volume parameters was carried out using the paired two-sample two-tailed t -test for the means, where statistical significance was $p < 0.05$. TLD uncertainty was calculated as the standard error of the mean for each set of TLDs placed in a certain location and was also a combination of the uncertainty in the individual chip response (1%) and calibration (3%). The estimated uncertainty in the PADC dose was $\pm 10\%$ and was a combination of the uncertainty in the PADC measurement ($\pm 2.5\%$) as well as the uncertainty in the photoneutron energy spectra used to fold the response of the PADC ($\pm 13\%$) [38]. It is difficult to predict the accuracy of the risks calculated because the coefficients were based on an entire population. For this reason, the risk factors presented in this study should be regarded as relative rather than absolute.

Results

Prostate PTV volumes varied between 57 and 148 cm³, with a standard deviation of 34 cm³. The dose–volume parameters for the prostate PTV at 6 and 15 MV are summarised for all plans in Table 1. Table 2 shows the dose–volume parameters for the rectum and bladder at both energies. In all plans, no rectal volume received a 100% dose. In terms of sparing, it was found for both the rectum and bladder that 15 MV was better at sparing in the lower doses, but at doses above 70 Gy there

Table 1. Average prostate planning target volume dose parameters for all plans

Volume (%)	Minimum dose delivered (%)				p -value
	6 MV	SD	15 MV	SD	
99	97.4	0.8	97.9	0.5	0.373
95	98.4	0.4	98.7	0.2	0.423
5	101.3	0.2	101.2	0.3	1.000
CI _{95%}	1.57	0.09	1.65	0.10	0.001
TCP	80.4	1.3	80.1	1.4	0.049

CI_{95%}, 95% conformity index; SD, standard deviation; TCP, tumor control probability.

Table 2. Average dose–volume parameters for rectum and bladder for all plans

Dose (Gy)	Volume receiving dose (cm ³)									
	Rectum					Bladder				
	6 MV		15 MV			6 MV		15 MV		
	Average	SD	Average	SD	p-value	Average	SD	Average	SD	p-value
30	45.4	12.7	42.2	12.4	0.063	131.3	25.2	121.4	21.8	0.012
40	33.5	9.2	29.7	8.5	0.011	94.4	15.6	88.3	14.6	0.007
50	23.7	6.3	22.0	6.4	0.060	71.5	9.9	67.8	11.8	0.053
60	15.1	3.7	14.6	4.2	0.519	52.2	7.8	50.8	8.1	0.292
70	3.4	1.5	4.0	1.0	0.662	25.5	7.9	27.8	9.6	0.107
74	–	–	–	–	–	6.3	3.0	7.2	4.8	0.730

SD, standard deviation.

was a small increase in the volumes irradiated. In all plans the bowel and femoral head tolerances were within the CHHiP constraints [18]. Rectal NTCP was found to be $3.0 \pm 0.9\%$ for 6 MV and $3.4 \pm 1.1\%$ for 15 MV ($p=0.166$). Bladder NTCP was calculated to be 0% for both 6 and 15 MV; however, this is unlikely to be clinically meaningful and is a reflection of the scarcity of data, as well as the difficulties in fitting parameters to genito-urinary toxicity.

The average number of MUs delivered per prescribed Gy of photon for the different energies was lower for the 15-MV plans at 294 ± 12 MU Gy⁻¹ than for the 6-MV plans at 351 ± 17 MU Gy⁻¹.

TLD doses were averaged in each slice and doses were plotted starting 5 cm from the PTV target. The average TLD doses at 6 and 15 MV averaged over the five patients are shown in Figure 1. The results show an almost exponential decrease in the dose with increased distance from the PTV and towards the head of the phantom.

The neutron equivalent doses recorded ranged between 0.5 and 3.6 mSv per photon Gy (*i.e.* for a 74-Gy treatment, the neutron equivalent dose range was 37–263 mSv). PADC doses have also been plotted on Figure 1, and this shows that the neutron dose drops only slightly with increasing distance from the isocentre. The highest dose was not received by the PADC placed on the central axis, but by those either side. The reason is

that the PADCs either side of the central axis were in the most collimated part of the beam, where photoneutron production is expected to be greatest. For the PADC placed in the centre of the irradiated field, the overall dose recorded was equivalent to a dose of 2.0 ± 0.3 mSv photon Gy⁻¹, which agrees well with reported neutron dose rates at the isocentre of 0.002 Sv (neutron) Gy (photon)⁻¹ for 15 MV [36]. The composite of neutron and photon dose appeared to be almost double that of the photon-only dose for the out-of-field organs. The neutron dose measured in the in-field region appeared to be negligible against the higher photon dose (approximately 0.2% contribution). However, this neutron dose is estimated as an entrance surface dose, and is indeed an overestimate of the dose at depth. More detailed organ dosimetry, using Monte Carlo calculations, was planned using voxel-based anthropomorphic phantoms.

Average organ photon equivalent doses for all five patients are summarised in Figure 2, per Gy photon. The organs to receive the highest out-of-field doses were the gonads and colon. In all cases, the doses due to 15-MV photons were lower than those due to 6 MV. Photon organ equivalent doses per MU in the current study agree reasonably well with published data for both energies (Table 3).

The estimated secondary induced cancer risk for out-of-field organs is shown in Table 4. Table 5 shows the

Figure 1. Average thermoluminescent dosimeters doses in each phantom slice as a function of distance away from the isocentre. PTV, planning target volume.

Figure 2. Average photon organ equivalent doses per prescribed photon Gy given for various out-of-field organs.

calculated risk of developing a fatal secondary cancer for the bladder and rectum using the three different risk models.

The probability of any secondary cancer calculated using Equation (4) was found to be 2.8% for 6 MV and 1.6% for 15 MV ($p < 0.001$). Age-corrected calculations are shown in Figure 3 for the 40-year risk and in Figure 4 for the lifetime risk of fatal cancer. Using the combined photon and neutron dose at 15 MV for the single measurement, it was found that the calculated total risk was 1.3 times that of the photon-only risk (*i.e.* if this factor is applied to all patients then the average total risk at 15 MV would become around 2.0%).

The results show an increased risk of developing a fatal cancer from 6 MV compared with 15 MV. As one would expect, the peak age range where the risk is highest is 40–59 years old, the lowest age range which is considered in this study. The risk decreases above 70 years of age, significantly so above 80 years of age. This is mainly because of different life expectancy.

Discussion

Several authors have investigated the out-of-field doses to organs distant from the tumour volume. Most studies have concentrated on prostate cancer, as this is the most common site for IMRT, as well as having a good treatment prognosis. TLD measurements have been performed by various investigators at IMRT energies ranging from 6 to 18 MV for step-and-shoot IMRT [40] and dynamic MLC delivery [36, 42]. Howell et al [39]

compared 3D-CRT with IMRT and deduced an effective dose to the out-of-field organs of $0.0543 \text{ Sv Gy}^{-1}$ and $0.0554 \text{ Sv Gy}^{-1}$ for 6 and 18 MV, respectively. It has been reported that the photon equivalent dose decreases exponentially with distance [40]. Our study is in agreement with these findings. Recently, Ruben et al [43] compared scatter, leakage, relative contributions of internal patient scatter, collimator and head leakage for 6-MV 3D-CRT *vs* IMRT using a customised water bath. They found that linear accelerator scatter and leakage was the dominant source of secondary dose; this was reported to be 65% of the total secondary dose, whereas for 3D-CRT the dominant source was internal patient scatter (70%).

Epidemiological studies investigating the incidence of second cancer following conventional radiotherapy have reported that most secondary sarcomas and a high proportion of carcinomas occur within 5 cm of the field edge [44]. In this study, it was found that within this region the 6-MV dose was higher than that at 15 MV. This can be explained by greater scatter at 6 MV than at 15 MV. Further away from the target, the dose is still lower at 15 MV than at 6 MV. Higher energies result in greater leakage; however, in this case this is balanced by the lower amount of MUs needed in the IMRT plans compared with 6 MV (this being around 16% lower at 15 MV). The combination of lower scatter and lower MUs at higher energies would explain the photon dose difference seen in Figure 1.

The neutron equivalent doses measured in our study were $0.5\text{--}3.6 \text{ mSv } 15 \text{ MV photon Gy}^{-1}$ compared with Reft et al [45], who calculated neutron equivalent doses at 18 MV using Cr-39 track etch detectors at $2\text{--}6 \text{ mSv photon Gy}^{-1}$

Table 3. Comparison of photon organ equivalent doses per monitor unit (MU) of the current data and published data

Organ	Organ equivalent dose in μSv per MU					
	This study		Kry et al [40]		Howell et al [39]	
	6 MV	15 MV	6 MV	15 MV	6 MV	15 MV
Thyroid	2.7	1.0	2.6	1.8	2.3	1.7
Stomach	9.1	5.7	8.2	8.0	3.3	3.1
Lung	3.2	1.9	3.7	3.8	2.4	2.0
Liver	11.2	6.7	8.2	7.9	3.7	3.7

Table 4. Calculated risk of developing a lifetime fatal secondary malignancy by organ site, given both as a percentage and as a fraction

Organ	6 MV			15 MV (photon)			p-value	15 MV (corrected for neutron dose)
	Calculated risk (%)	SD	Risk of 1 in	Calculated risk (%)	SD	Risk of 1 in		Calculated risk (%)
Thyroid	0.01	0.002	10 134	0.003	0.0003	34 393	0.020	0.01
Lungs	0.14	0.019	701	0.07	0.01	1422	0.029	0.13
Oesophagus	0.05	0.008	2049	0.02	0.004	4305	0.035	0.06
Stomach	0.53	0.071	188	0.27	0.04	365	0.076	0.40
Liver	0.09	0.009	1131	0.04	0.01	2296	0.039	0.06
Colon	1.25	0.097	80	0.54	0.06	187	0.006	0.63
Skin	0.004	0.003	24 651	0.003	0.01	36 862	<0.001	0.10
Gonads	0.08	0.004	1253	0.03	0.003	3546	0.001	0.10
Leukaemia	0.25	0.06	394	0.18	0.10	566	0.151	0.18

SD, standard deviation.

In our study, the neutron equivalent doses translated to an effective dose of 1 mSv, which contributed to 2% of the photon effective dose at 15 MV. Other studies have reported a neutron dose equivalent of 33 mSv in the target volume and OARs at 15 MV for a dose delivery of 81 Gy [46], and that neutron equivalent doses were independent of distance, decreased with increasing depth in a patient and were a significant contributor to out-of-field doses [47]. Furthermore, Kry et al [47] have carried out Monte Carlo calculations for out-of-field photon and neutron doses in a Rando phantom for 6 and 18 MV photons, and have reported that there was a small difference in the risk of secondary cancer between the two energies.

We found that for all out-of-field organs there was at least a doubling of the risk of developing a fatal cancer due to photons only at 6 MV relative to 15 MV ($p < 0.05$ for all organs, except for the stomach, where $p = 0.076$). There was a moderate increased risk at 6 MV for leukaemia ($p = 0.151$). After correcting for neutron dose, it was found that the risks were comparable. For rectum and bladder risk, the DNA competition model shows a slightly higher risk at 15 MV ($p = 0.018$), which may be attributed to the better sparing of IMRT (*i.e.* a larger volume of the rectum or bladder receiving lower doses). Comparison between the risk using the DNA competition, linear-plateau and LNT models shows that the LNT model would provide unrealistic risk estimates for these organs. The estimates provided by the linear-plateau model are more consistent with clinical evidence. A modest increase in second malignancies of 1 in 70 patients undergoing radiation and surviving for >10 years has previously been reported for 3D-CRT, with the most common sites for secondary cancers being the bladder and rectum [12].

An interesting finding was the slightly raised rectal NTCP at 15 MV compared with 6 MV (3.6% and 3.0%, respectively). This is due to the fact that, while 15 MV performs better at sparing the rectum at doses below 70 Gy, an extra volume of around 1 cc received doses of >70 Gy compared with 6 MV. Also, if the competition model is true, then the risk of secondary rectal cancer is also slightly increased at 15 MV because a greater volume received <30 Gy. It was also observed that the $CI_{95\%}$ was slightly better at 6 MV, indicating better target homogeneity. There also appears to be a reduction in TCP of around 0.3% at 15 MV compared with 6 MV ($p = 0.049$); however, it is unlikely that this would have clinical significance.

It has been noted by Sachs and Brenner [48] that the competition model may underestimate the risk at high doses, and those authors have reported a biologically based and minimally parameterised model that incorporates carcinogenic effects, cell killing and proliferation/repopulation effects that were consistent with clinical data for high-dose second cancer incidence in Hodgkin's lymphoma and breast cancer patients. This model was later extended by Shuryak et al [49] for radiation-induced leukaemia to include long-range migration through the bloodstream of haematopoietic stem cells from distant locations. Future evaluations of the risks using these models are planned.

There are other limitations to this method of experimentally deducing cancer risk. Different patients have different anatomy, and it is difficult to make an accurate assessment of different organ risks specific to an individual patient. However, it should be noted that through the verification of the IMRT plan, the same output conditions could be reconstructed within the

Table 5. Calculated risk of developing a lifetime fatal secondary malignancy for the rectum and bladder

Risk model	Bladder			Rectum		
	6 MV	15 MV	p-value	6 MV	15 MV	p-value
LNT (%)	9.24	8.84	<0.001	20.7	19.9	0.003
LP (%)	0.876	0.860	0.233	2.50	2.49	0.213
Competition (%)	0.15	0.17	0.010	0.14	0.17	0.018

LNT, linear non-threshold; LP, linear-plateau.

Figure 3. 40-year post-exposure secondary cancer risk due to IMRT treatment for 6 and 15 MV. Error bars indicate the spread of risk estimates across the five patients. IMRT, intensity-modulated radiation therapy.

phantom to give a similar radiation distribution. Organ risks were therefore specific to the RANDO phantom and were satisfactory in making a comparison between the energies. It should also be noted that all solid organs except bone and lung were represented by the same tissue-equivalent material. There are also large uncertainties in determining the absolute risk of second cancer using current models, as discussed by Kry et al [50]. In this work, the risks calculated were not absolute but were compared relatively between the two energies.

In agreement with other authors [4, 45, 47, 51], our results indicate that the use of higher energies is dosimetrically comparable with 6-MV IMRT in prostate cancer patients, and is therefore a reasonable energy to be used. It was also observed that the time taken to produce a plan with 15 MV was less and used a lower number of MUs. There are currently (and there will be for years to come) a lack of epidemiological data on radiation-induced cancers due to IMRT, but our results indicate that 15 MV in prostate cancer patients may be associated with a lower out-of-field secondary cancer risk.

Conclusions

It has been shown that there is a small increased overall theoretical risk of developing a fatal cancer from 6-MV prostate IMRT compared with 15-MV prostate IMRT, taking into account all the organs. The theoretical risk of secondary induced malignancy in specific organs was also calculated, and it was found that for all out-of-field organs there is a moderate increased risk of developing a fatal cancer at 6 MV. The risk of developing fatal leukaemia was slightly raised at 6 MV compared with 15 MV, and risks of bladder or rectal cancer were similar at both energies. Conversely, there is a slightly raised rectal NTCP at 15 MV compared with 6 MV (3.6% compared with 3.0%, respectively). There also appears to be a reduction in TCP of around 0.3% at 15 MV compared with 6 MV ($p=0.049$); however, it is unlikely that this would have clinical significance. The weight of evidence suggests that photon energies above 10 MV should not be excluded in IMRT treatment. However, considering the lack of epidemiological data on radiation-induced cancer due to IMRT, it is recommended that the choice to treat at 15 MV is taken as a risk *vs* benefit

Figure 4. Lifetime risk of secondary induced cancer due to the IMRT treatment for 6 and 15 MV. Error bars indicate the spread of risk estimates across the five patients. IMRT, intensity-modulated radiation therapy.

decision, considering the age and life expectancy of the patient together with the relative risk of radiation-induced cancer and NTCPs.

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