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Intensity Modulated Radiotherapy:

Effect on Dose Distribution and Scattered Dose and Implications for Carcinogenesis

Acknowledgements

To Sid Davis who brought me over as a fellow, and told me to "Find a project in IMRT and get a higher degree." Then later, after I commented in passing that IMRT increases integral dose replied, "Does it?" which made me stop and think.
And which led to the course of academic pursuit presented in this thesis.

To the physicists among my co-authors who spent weekends and nights carrying out the experiments herein, and daytimes avoiding my badgering to get on with those same experiments.

To my overseas collaborators who me gave advice, expertise and goodwill from afar.

And to my wife Vanessa and daughters Ariel, Eliyah and Oriah who give me love, laughter and home.

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Declarations

PART A: General Declaration

Monash University

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals and no unpublished publications. The core theme of the thesis is the effect of Intensity Modulated Radiotherapy on dose distribution inside and outside the beam portals and consequent effects on carcinogenic risk. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Surgery.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.
In the case of chapters two, three, four and five my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
Two	The Effect of Intensity-Modulated Radiotherapy on Radiation-Induced Second Malignancies	published	Concept, design, data analysis and interpretation
Three	A Comparison of Out-of-Field Dose and Its Constituent Components for IMRT versus Conformal Radiation Therapy: Implications for Carcinogenesis	published	Concept, design, data analysis and interpretation
Four	Constituent Components of Out-of-Field Scatter Dose for 18MV IMRT vs. 3D CRT: a Comparison with 6MV and Implications for Carcinogenesis	published	Concept, design, data analysis and interpretation
Five	Effect of Intensity-Modulated Pelvic Radiotherapy on Second Cancer Risk in the Postoperative Treatment of Endometrial and Cervical Cancer	published	Concept, design, data analysis and interpretation

I have / have not (circle that which applies) renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

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PART B: Declaration for Thesis Chapter Two

[This declaration to be completed for each conjointly authored publication and to be placed at the start of the thesis chapter in which the publication appears.]

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Declaration for Thesis Chapter Two

Declaration by candidate

In the case of Chapter two, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Concept and design	90%
data collection	25%
data interpretation	90%
manuscript writing	90%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Signed and dated	%contribution if Monash students
Alistair Hunter	Advice and assistance with radiobiological calculations. Manuscript review.		

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 12.8.14
Head of Department's Signature	[redacted]	**Date** 12-8-14

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Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Concept and design	90%
data collection	25%
data interpretation	90%
manuscript writing	90%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	%contribution for student co-authors only
Sidney Davis	Manuscript review	
Cherie Evans	Radiotherapy plan generation. Manuscript review	
Phillip Jones	Radiotherapy plan generation. Manuscript review	
Matthew Haynes	Execution of experiment and measurements. Manuscript review	
Frank Gagliardi	Execution of experiment and measurements. Manuscript review	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

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Head of Department's Signature	[redacted]	**Date** 12·8·14

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In the case of Chapter Three, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Concept and design	90%
data collection	10%
data analysis	85%
data interpretation	80%
manuscript writing	95%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	%contribution for student co-authors only
Craig Lancaster	Execution of experiment and measurements. Manuscript review	
Phillip Jones	Radiotherapy plan generation. Manuscript review	
Ryan Smith	Execution of experiment and measurements. Manuscript review	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

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Declaration for Thesis Chapter four

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In the case of Chapter Four, the nature and extent of my contribution to the work was the following:

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Concept	95%
Design	80%
data collection	5%
data interpretation	85%
manuscript writing	90%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	% contribution student co-authors
Ryan Smith	Design and execution of experiment and measurements. Manuscript review	
Craig Lancaster	Design and execution of experiment and measurements. Manuscript review	
Matthew Haynes	Design and execution of experiment and measurements. Manuscript review	
Phillip Jones	Radiotherapy plan generation. Manuscript review	
Vanessa Panettieri	Design and execution of experiment and measurements. Manuscript review	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

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Head of Department's Signature	[redacted]	Date 12.8.14

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Declaration for Thesis Chapter Five

Declaration by candidate

In the case of Chapter Five, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Concept	50%
Design	60%
data collection	30%
data interpretation	60%
manuscript writing	65%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	% contribution for student co-authors only
Phillip Jones	Radiotherapy plan generation. Manuscript review	
Frank Gagliardi	Execution of experiment and measurements. Manuscript review	
Jeremy Millar	Manuscript review	
Daniel Zwahlen	Declaration on next page	
Uwe Scneider		

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 12.8.14
Head of Department's Signature	[redacted]	**Date** 12.8.14

PART B: Declaration for Thesis Chapter 5

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Declaration for Thesis Chapter 5

Declaration by candidate

In the case of Chapter 5 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Signed and dated	%contribution if Monash students
Uwe Schneider	Radiobiological calculations. Manuscript review.	[redacted]	
Daniel Zwahlen	Oversight of radiotherapy plan generation. Data collection. Initial data interpretation. First draft of manuscript		
[name 3] *			

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	Date 12/8/14
Main Supervisor's Signature	[redacted]	Date 12-8-14

List of publications

Ruben, Jeremy D, Sidney Davis, Cherie Evans, Phillip Jones, Frank Gagliardi, Matthew Haynes and Alistair Hunter. 2008. "The Effect of Intensity-Modulated Radiotherapy on Radiation-Induced Second Malignancies." International Journal of Radiation Oncology, Biology, Physics 70 (5): 1530–36. doi:10.1016/j.ijrobp.2007.08.046.

Ruben, Jeremy D, Craig M Lancaster, Phillip Jones and Ryan L Smith. 2011. "A Comparison of Out-of-Field Dose and Its Constituent Components for Intensity-Modulated Radiation Therapy Versus Conformal Radiation Therapy: Implications for Carcinogenesis." International Journal of Radiation Oncology, Biology, Physics, 81 (5): 1458–64. doi:10.1016/j.ijrobp.2010.08.008.

Ruben, Jeremy D, Ryan Smith, Craig M Lancaster, Matthew Haynes, Phillip Jones and Vanessa Panettieri. 2014. "Constituent Components of Out-of-Field Scatter Dose for 18-MV Intensity Modulated Radiation Therapy Versus 3-Dimensional Conformal Radiation Therapy: a Comparison with 6-MV and Implications for Carcinogenesis." International Journal of Radiation Oncology, Biology, Physics, In Press. doi:10.1016/j.ijrobp.2014.05.052.

Zwahlen, Daniel R*, Ruben, Jeremy D *, Phillip Jones, Frank Gagliardi, Jeremy L Millar and Uwe Schneider. 2009. "Effect of Intensity-Modulated Pelvic Radiotherapy on Second Cancer Risk in the Postoperative Treatment of Endometrial and Cervical Cancer." International Journal of Radiation Oncology, Biology, Physics, 74 (2): 539–45. doi:10.1016/j.ijrobp.2009.01.051.
*Co-First Authors

Abstract

Background

Intensity modulated radiotherapy (IMRT) produces highly complex and conformal radiation dose distribution at the cost of exposing more normal tissue to low isodoses and greater monitor unit (MU) requirements. Hence concerns have been raised regarding its increased carcinogenic potential.

Aims

Over four experiments, this thesis examines the effect of IMRT on radio-carcinogenic risk through its alteration of radiation dose distribution within the treatment portals as well as its effect on scattered dose to tissues beyond the beam edge. The thesis examines the implications of such altered dose distribution for carcinogenic risk using a range of credible dose-response relationships. Dose distribution from IMRT and resultant carcinogenic risks are compared to those of three-dimensional conformal radiotherapy (3DCRT) for beam energies and disease sites relevant to clinical radiotherapy. The thesis also investigates the influence of beam energy on individual components of out-of-field scatter for both modalities.

Methods

The first experiment analyses in-field dose distribution through dose volume histogram (DVH) analysis and measures out-of-field scatter in an anthropomorphic phantom using thermo-luminescent dosimeters, for various clinical scenarios. Carcinogenic risks are calculated using several credible dose-response relationships by dividing normal tissues into smaller volumes of homogenous dose and summating their proportional carcinogenic contributions. Its findings questioned previous assertions about IMRT's effect on out-of-field scatter and prompted two further experiments investigating out-of-field scatter in detail. These experiments were performed for both IMRT and 3DCRT in a specially constructed water phantom using both low- and high-energy photon beams. They provide detailed information on the individual contributions of the constituent components of out-of-field dose, namely head leakage,

collimator scatter and internally scattered radiation. They analyse the implications for carcinogenesis including the influence of photoneutrons. The fourth experiment described in the thesis is an extension of the first, and examines the effect of high energy pelvic IMRT on in-field dose distribution together with previously measured peripheral doses, so as to generate carcinogenic estimates for the entire body. This experiment also provides information regarding the clinically relevant area of gynaecologic IMRT which was not covered in the first experiment.

Outcomes

IMRT is demonstrated to constrict high isodoses while spreading out lower ones. Thus the effect of IMRT on in-field risk is variably advantageous or disadvantageous depending on dose-response model used. IMRT is consistently demonstrated to increase overall out-of-field scatter because of excess collimator scatter, despite a reduction in internally scattered radiation. Head leakage contributes very little. IMRT thus invariably increases out-of-field carcinogenic risks but these increases are small in absolute terms. High-energy beams increase machine scatter, for both modalities but reduce internal scatter; the net effect on out-of-field photon dose approximates zero. Photoneutron production however is significant - especially for high-energy IMRT which produces roughly twice as many photoneutrons as 3DCRT. These carry a high radio-carcinogenic risk.

Carcinogenic risks are almost always increased by IMRT although relative risks appear lower than initially feared, and small in absolute terms. The increase in risk varies with dose-response model used, MU demand relative to 3DCRT, anatomical site, beam arrangement and beam energy. Dose-response models reflecting ever-increasing risk with increasing dose (no plateau); and less inter-modality MU disparity favour IMRT. High-energy IMRT carries the highest carcinogenic risk.

Chapter 1

1. Introduction

Theme, background and structure of the thesis

1.1 Theme of the thesis

This thesis examines the effect of Intensity Modulated Radiotherapy (IMRT) on radio-carcinogenic risk through analysing the technology's effect on radiation dose distribution within the beam portals as well as its effect on scattered dose to tissues beyond the beam edge. It examines the implications of such altered dose distribution for carcinogenic risk using several calculation methods and credible dose-response relationships. The radiation dose distribution from IMRT and resultant carcinogenic risks are compared to those from conventional three-dimensional conformal radiotherapy (3DCRT) for varying beam energies and disease sites relevant to clinical radiotherapy.

1.2 Background

3DCRT vs. IMRT

In contrast to 3DCRT which employs beams of homogenous x-ray fluence, shaped to the target volume in the beam's eye view, IMRT is a radiotherapy technique whereby the x-ray fluence of each shaped beam is modulated so as to be inhomogeneous. The fluence pattern is usually generated through a process of inverse planning driven by computer algorithm guided by a radiotherapy planner. In modern linear accelerator-based radiotherapy the desired fluence pattern is achieved either through the use of sub-fields/ segments (step and shoot), or through the continuous and independent movement of individual multi leaf collimator (MLC) leaves across the field at varying and inconstant

speeds (sliding window). Other techniques like the use of compensators have been used too but are time consuming and require bespoke hardware for each patient.

The inhomogeneous fluence of the treatment beam facilitates complex, curved isodose distributions rather than the conventional geometric patterns with straight lines more usually achieved with 3DCRT. High isodose lines are more conformal with IMRT. The price to pay for greater complexity and conformality is an increased number of treatment fields as well as longer beam-on time to produce an equivalent isocentre dose. IMRT is thus monitor unit (MU) inefficient. This is a direct consequence of the intensity modulation of each beam and perhaps the smaller effective field sizes of IMRT [1].The longer beam-on time results in greater head leakage and collimator scatter to the patient. In addition, IMRT usually employs more beams than the equivalent 3DCRT techniques for the same anatomical site so larger volumes of normal tissue are directly exposed to the treatment beams. Together with the intensity modulation this results in the spreading out of low isodoses but conversely, in a reduction to the volumes of tissue receiving high doses.

The resultant increase in head leakage and collimator scatter with IMRT and the increased volumes of tissue directly exposed to treatment beams raised concerns about consequentially higher carcinogenic risk [2-5]. In addition, when beam energies greater than 10MV are used, the prolonged beam on times with IMRT also lead to excess photoneutron production compared to 3DCRT which further increases relative second tumour risk [3] .

These concepts are discussed further in the subsequent thesis chapters.

Radio-carcinogenesis

While x-rays have the power to cure cancer, they may also induce cancer formation. This fact has been appreciated for almost as long as x-rays have been known: in 1902, just a year after Roëntgen accepted the Nobel Prize for his discovery, a skin cancer was reported in an area of radiation damaged skin [6].

The precise mechanism(s) whereby radiation initiates or promotes carcinogenesis is not fully understood and many theoretical models exist [6,7]. While radiotherapy causes cell death through producing double chromosome breaks (and possibly also double-stranded DNA breaks), either directly or indirectly, it is probably non-lethal, single strand breaks affecting genes controlling cellular replication, apoptosis, senescence, DNA damage prevention or DNA repair which are the radiation lesions responsible for radio-carcinogenesis [6]. It is important to note that cancer biologists do not yet completely understand the process of neoplastic transformation in tissue, let alone how radiation interplays with the process. Most cancer biologists accept that carcinogenesis is a multi-step process [7] with carcinogens interacting as initiators and promoters of the process. Although radiation has classically been regarded as an initiator of carcinogenesis, there is

some data demonstrating that it can also act as a promoter, causing increased clonal expansion (promotion) of already initiated cells in response to radiation [8-10]. Since the precise molecular pathways of radio-carcinogenesis are neither central to the theme of the present thesis nor relevant to the scientific hypotheses tested herein, they are not considered further.

A vexing problem in the area of radio-carcinogenesis is the dose-response relationship for this dreaded effect. Prospective studies in human subjects are not feasible so we rely on in-vitro data, animal data, atomic bomb survivor data and retrospective studies. All suffer from significant limitations. The most useful data is naturally from human studies. The atomic bomb survivor data from the Life Span Study (LSS) is probably the gold standard and presents data for a range of ages at exposure and radiation doses between 50mSv-2Sv single fraction equivalent [5,11]. It is never the less beset by uncertainties including the accuracy of the calculated gamma and neutron doses received by subjects (especially in the very low dose range), the neutron energy spectra involved and their influence [12-15], and very importantly for radiotherapy (although not generally for diagnostic radiology), the influence of fractionation on radio-carcinogenesis, since subjects in the LSS received a single exposure of radiation unlike most radiotherapy patients[14]. Although multiple studies have been done on radiotherapy patients, they invariably have a retrospective component or are limited in the accuracy of their clinical and/or dosimetric data regarding the precise location that later manifested a radiogenic tumour and in the availability of matched controls [16-19].

The shape of the dose response curve is generally accepted as linear between 50msv-2Sv acute exposure based on LSS data, but above and below these limits there is considerable uncertainty and the true relationship is unresolved [2,5,11,19,20]. Below 50mSv the International Commission for Radiation Protection (ICRP) and Committee on the Biological Effects of Ionizing Radiations (BEIR) VII reports recommend adopting the "linear no threshold" (LNT) model which is in essence an extrapolation of the observed data at higher doses and proposes that second cancer risk reduces linearly with reducing dose even below 50mSv [14,21]. Others support the same conclusion, including a recent, large Australian study of 680,000 subjects [20,22,23]. Although widely adopted, the linear no threshold model may however be an oversimplification since there are data suggesting that cells do not remain inert during low dose irradiation, but demonstrate adaptive responses to this evolutionary stressor such as the up regulation of DNA repair enzymes and antioxidant molecules, as well as senescence or apoptosis [24]. Thus the French Academy of Sciences, for example, does not support the LNT relationship for radiation carcinogenesis, favouring instead a hormetic response at very low radiation doses which implies a relative insensitivity to radiation carcinogenesis in this dose range [25]. Conversely, the dose response curve might reflect hypersensitivity to radiation-induced second cancers at very low doses due to factors like bystander cell effects [20,26,27]. Hence the cancer induction risk curve might trend upwards as well as downwards in this dose range [5,19]. This is illustrated in *Figure 1* overleaf.

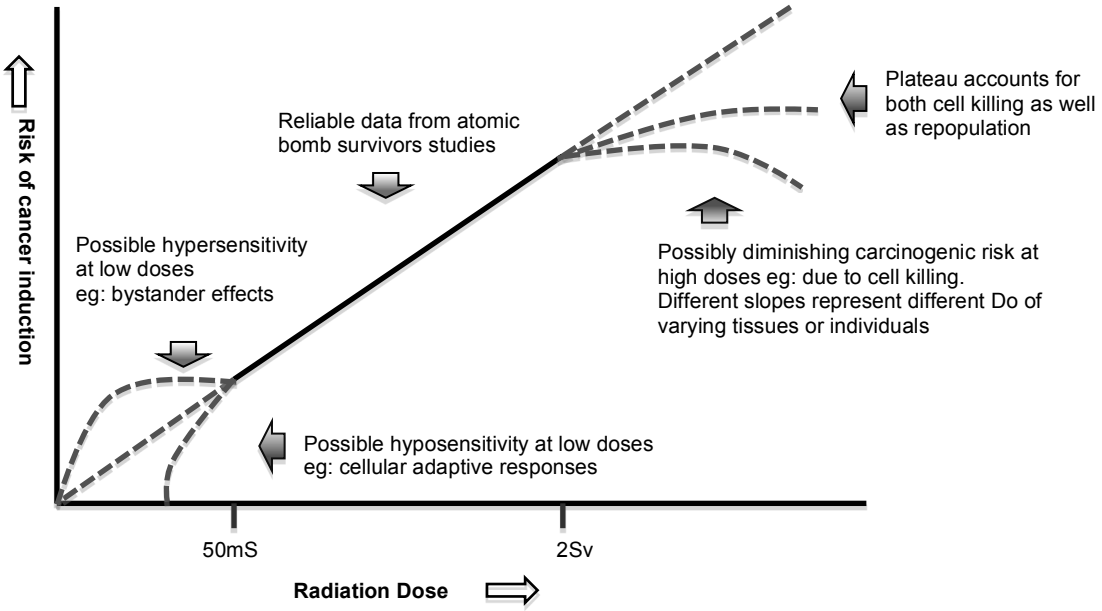
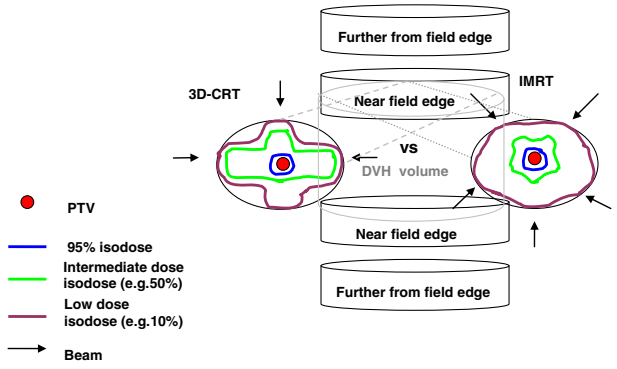


Figure 1. Uncertainties around the dose-response relationship for radiation-induced cancer. *Adapted from Hall, EJ. 2004* [5]

Above 2Sv, most models predict a flattening in the radio-carcinogenesis curve as some cells are killed outright by the higher radiation doses rather than mutated [28]. Such models vary in their complexity and in their inclusion of variables such as repair, repopulation, and stem cell repopulation [29]. As illustrated in *Figure 1*, they may result in a response curve which plateaus above a certain dose (plateau dose-response) or even decrease at a certain point (linear with a negative exponential term). Although a continued linear increase in risk with increasing dose is theoretically possible, there is not much human data supporting this and it is not generally accepted as likely [2]. Thus controversy and uncertainty also prevails regarding the precise dose-response relationship at high doses, due to the lack of reliable data. To further complicate matters, different organs appear to have different radio-carcinogenic response curves at doses between 15-60Gy [19]. Attributing a dose-risk relationship for the body would depend therefore on which organs are included in calculations [19] and could possibly account for some differences between studies. Stomach, pancreas, lung and breast show increased risks with increasing dose, while bladder and rectal curves remain flat [19,29]. Colon appears to show an

inverse radiation carcinogenic dose response relationship at high doses [19]. It is becoming clear though that cancer risk does increase in some contexts with increasing doses, even those as high as are experienced in clinical radiotherapy [18,19,29-33]. The true dose response curve is likely to lie somewhere between a linear-exponential and a linear model. It is worth noting that radiation induced sarcoma's develop almost exclusively in areas of higher radiation dose – thus the incidence of radiation induced sarcoma's in atomic bomb survivors is no higher than the general population

The shape of the dose response curve for radio-carcinogenesis used for second cancer calculations has a major impact on the resultant risk estimates, especially at doses <0.5Sv and >2Gy which are applicable to the majority of tissues in an irradiated patient and which is precisely where much of the uncertainty lies. A model predicting linearly (or otherwise) increasing risk predicts lower risks from IMRT compared to 3DCRT in the higher dose regions due to its improved conformity. However, the spreading out of lower dose regions over greater volume of tissue would increase risk – it is this effect that is likely to dominate. Similarly, a model predicting decreasing risk with increasing dose at high radiation doses predicts higher risks from IMRT for the same reasons – improved conformity of high isodose lines and spreading out of lower ones conferring increasing risk. A model predicting plateauing of risk probably also favours 3DCRT due to the larger volumes of tissue receiving a low dose from IMRT, but this does depend on the dose level at which the risk plateaus. The true situation is more complex though since most cancers develop in organs within the field that receive high doses such as bladder and rectum in the case of prostatic carcinoma treatment. IMRT decreases their dose significantly so could ultimately reduce the in-field risk as has been demonstrated [34-38]. Out-of-field doses are low more than a few centimetres from beam edge and carcinogenic risk will generally increase with dose in the dose range encountered, hence IMRT is likely to pose greater carcinogenic risk to out-of-field tissues irrespective of risk model used. *Figure 2* overleaf, provides a graphical representation of the above concepts.



Region:	Result of IMRT:	Possible impact on risk of RISPC:	
PTV	Similar dose distribution in high dose region	? No change in RISPC risk	
DVH volume	Increased volume of tissue irradiated to low doses BUT Integral dose remains similar[42]	? Increased risk RISPC ? Similar risk RISPC (depends on model used- actual effect size may be small[42, 59])	
Near field edge (~0-10cm from field edge)	Improved conformity→ less within patient scatter[52]	? Reduced risk RISPC	Overall increased out-of-field dose from IMRT but in absolute terms, increase in dose very small, and so potentially very small impact on RISPC risk[52].
Near field edge (~10-20cm from field edge)	Increased beam on time →increased collimator scatter[52]	? Increased risk RISPC	
Further from field edge (~>20cm from field edge)	Increased MU requirement→ increased leakage[52]	? Increased risk RISPC	

RISPC: Radiation induced second primary cancer; IMRT: intensity modulated radiotherapy; 3D-CRT: three dimensional conformal radiotherapy; DVH: dose volume histogram; MU: monitor units; RISPC: radiation induced second primary cancer

Figure 2 Illustration of factors which may impact on the risk of radiation induced second primary cancers when using IMRT instead of 3D-conformal radiotherapy.

Figure 2. Factors which may impact on radio-carcinogenic risk from IMRT vs. 3DCRT.
Reprinted with permission from Murray et al. [39].
References 42 and 52 in the figure refer to chapters two and three of the thesis respectively.

The effect of fractionation on radio-carcinogenic risk is also unclear. Although much data supports the protective effect of fractionation and lower dose rates on second cancer risk, this is not entirely consistent since some data shows a counterintuitive increased risk [40,41]. Never the less the Dose and Dose Rate Effectiveness Factor (DDREF) of 2 recommended by the ICRP is widely accepted to account for the generally accepted protective effect of fractionation employed in modern radiotherapy [14].

These controversies are further discussed in chapters two and three, and to a lesser degree in other chapters.

1.3. Rationale, and structure of the thesis

The thesis is placed in its historical context along with the reasoning behind its undertaking. Each chapter is then framed within the logical progression of the thesis as questions and gaps in knowledge raised by preceding chapters are explored in subsequent ones.

The possibility of greater carcinogenic risk from IMRT compared to 3DCRT is indeed an important consideration since the clinical benefits of IMRT over 3DCRT have still not been demonstrated in terms of improved survival or local control. However, randomised evidence does support IMRT's superiority at sparing organs at risk [42-44]. This randomised evidence was not mature at the time the research in this thesis was begun, but even now, in the absence of demonstrated survival advantage, dosimetric and functional advantages of IMRT still need to be weighed against potentially higher rates of second cancer induction. Thus establishing whether its postulated excess carcinogenic risks are valid and accurately quantifying them, was and still is, an important area in clinical radiation oncology and worthy of study. This is evidenced by the commissioning of a European Society of Therapeutic Radiation Oncology (ESTRO) review of the data in this area [39].

At the time this research was begun, IMRT was just beginning to enjoy wider and accelerating uptake into general clinical practice. Its attractiveness lay in its ability to produce highly conformal dose distributions offering superior target coverage while simultaneously providing superior sparing of organs at risk [42,44-48]. As noted above, despite the increasing enthusiasm for IMRT, several authors had raised concerns about potentially increased second cancer risk over 3DCRT, suggesting that these risks might be increased as much as eight-fold using the newer technology [2-4,49,50].

However, these studies were flawed in that their conclusions were based on incomplete assessments of the alterations in dose deposition brought about by IMRT. Some only considered IMRT's effects on the tissues within the DVH, ignoring tissues in the rest of body [2]; while others considered only tissues distant from the primary beam portals, ignoring the effects of altered dose distribution within the beam portals [3,4,50]. Since carcinogenic risk is body-wide, all body tissues – both within and beyond the beam portals – must be included in risk calculations to obtain the true second cancer risk. Just a

single study had considered risks to both tissues inside and outside the DVH, but did not actually measure or calculate the dose to tissues beyond the DVH. Instead it assumed a homogenous dose for all out-of-field tissue, irrespective of distance from field edge, based on a single measurement 50cm away from field edge. In addition, it was performed in 1995 using a linac which is likely to vary in terms of head architecture and construction from those a decade later [51].

The second chapter of the thesis thus describes the experiment performed to obtain the first complete and accurate assessment of second cancer risk from IMRT compared to 3DCRT. This study differs from the four published before it [2,35,52,53] because it accurately measures and calculates dose distribution from IMRT for the body in its entirety, not just a limited portion thereof. Alterations in dose distribution within the portals, scattered dose close to beam edge as well as to distant tissue, and consequential complete carcinogenic risks for the patient were assessed using current radiotherapy techniques for both 3DCRT and IMRT applied to multiple clinical sites. The results were unexpected based on the previously published limited data; although risks differed depending on site and radiotherapy technique, in some situations risks were comparable or even marginally lower with IMRT (prostatic and two-field breast radiotherapy). Perhaps most surprising was that in situations where MU discrepancy was not great between modalities, the scattered radiation dose to distant tissues from IMRT was slightly reduced compared to 3DCRT. Since MU demand was higher, leakage from the treatment head would unavoidably have been higher and therefore IMRT appeared to be reducing either collimator scatter or internal patient scatter (phantom scatter) or both. Hypotheses were generated to explain this phenomenon and a subsequent experiment was designed to test those hypotheses. That experiment is described in the third chapter of the thesis.

The third chapter of the thesis describes the experiment performed to separate out the three constituent components of scattered radiation dose to peripheral tissue for 6-megavolt (MV) IMRT and to compare them to 3DCRT. Six MV beam energy was chosen as it is the most commonly used energy for IMRT. The hypothesis that internally scattered radiation might be reduced by IMRT was shown to be correct and explains the phenomenon observed in the first chapter whereby out-of-field scatter may be reduced with IMRT if MU demands are modest relative to 3DCRT. In that scenario, reduced internal scatter may counterbalance the modest increase in machine scatter. The second experiment thus answers the question that prompted its undertaking. In addition the experiment provides insight into the relative contributions of different scatter components to out-of-field dose at varying distances from field edge. The chapter also discusses the implications of its results for second cancer induction in distant tissues.

Because the experiment was limited to 6MV beam energy, neither the effects of beam energy on peripheral scatter nor the effect of intensity modulation on high-energy beams are examined in this chapter. Furthermore, the low photon energies investigated do not require consideration of photoneutrons, which are potent carcinogens, since these are only produced by beams of 10MV or more. Since chapters two and three do not

investigate the effects of high energy beams on scattered dose from IMRT compared to 3DCRT and the implications for carcinogenesis, a third experiment was designed to investigate these issues and is discussed in the next chapter.

The fourth chapter of the thesis describes the experiment performed to measure the components of out-of-field dose for 18MV IMRT compared to 18MV 3DCRT and discusses the findings. The implications of high beam energy for second cancer induction are also considered for both IMRT and 3DCRT. The design of the experiment allows comparison with the measurements for 6MV beams reported in chapter two for most of the components of peripheral scatter. Thus chapter four also examines the differences in out-of-field scatter for 6- vs. 18MV IMRT and for 6- vs. 18MV 3DCRT respectively.

Chapters two to four thus provide a comprehensive investigation into the effect of intensity modulation on scattered dose to out-field-tissue as well as the effect of 6MV IMRT on dose distribution inside the beam portals. They also examine the likely implications of IMRT for second cancer induction using a variety of calculation methods and plausible dose response relationships. Since high energy IMRT is seldom used clinically, chapters two to four provide an almost complete investigation of this topic from a clinically relevant point of view.

However, while the effect of high energy IMRT on out-of-field dose is examined, its effect on dose distribution in-field is not. Furthermore, because chapter two focuses on scenarios applicable to real life clinical practice, 6MV pelvic IMRT is analysed compared to 18MV 3DCRT (in the prostatic setting). From an academic point of view, and also to provide data to those centres that do use high energy IMRT – although in the minority – an experiment comparing pelvic 18MV IMRT to 18MV 3DCRT in terms of both in-field and out-of-field dose is desirable. It is also desirable to provide data for IMRT performed for gynaecological malignancy that is not examined in the second chapter. Such an experiment would essentially render an examination of the topic of the present thesis complete from all clinically relevant angles and is presented in the next chapter.

The fifth chapter of the thesis describes the study of second cancer risk from both 6- and 18MV IMRT compared to 18MV 3DCRT for the adjuvant radiotherapy of the female pelvis. In addition to providing information on the effect of high energy IMRT on dose distribution within the portals which has not yet been considered in the thesis, it also provides second cancer risk estimates for a clinically relevant scenario, regularly encountered, which is not covered in the second chapter. Furthermore, the method used to calculate second cancer risk is a refinement of that used in the first chapter, although conceptually identical. Since the main thrust of the experiment is the radio-carcinogenic effect of 18MV IMRT on in-field tissues - the source of the majority of the risk - the scattered out-of-field dose was not measured but assumed to be homogenous and was based on previous measurement. Detailed measurements of peripheral scatter from 18MV IMRT compared to 3DCRT have however, already been comprehensively covered in chapter four of the thesis.

Clinically, the context of adjuvant pelvic radiotherapy for gynaecological cancers was selected for this chapter, as it was an area of increasing clinical interest where IMRT could be expected to deliver significant toxicity reduction over 3DCRT. The Radiation Therapy Oncology Group (RTOG) 0418 trial had recently been activated to explore this issue further. Presently, the conclusions presented in the chapter are more relevant than ever because of the positive results of that trial which confirmed reduced toxicity and favourable tumour control outcomes leading to ever wider uptake of IMRT in this setting [54,55].

Chapter 2

The effect of intensity modulated radiotherapy on radiation-induced second malignancies

A comparison with 3DCRT of various energies using beam arrangements that reflect current clinical practice at several anatomical sites commonly encountered in clinical radiotherapy.

The chapter is framed in terms of its background context and its relationship to subsequent thesis chapters on page twelve of chapter one.

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THE EFFECT OF INTENSITY-MODULATED RADIOTHERAPY ON RADIATION-INDUCED SECOND MALIGNANCIES

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Purpose: To compare intensity-modulated radiotherapy (IMRT) with three-dimensional conformal radiotherapy (3D-CRT) in terms of carcinogenic risk for actual clinical scenarios.
Method and Materials: Clinically equivalent IMRT plans were generated for prostate, breast, and head-and-neck cases treated with 3D-CRT. Two possible dose–response models for radiocarcinogenesis were generated based on A-bomb survivor data corrected for fractionation. Dose–volume histogram analysis was used to determine dose and its distribution to nontargeted tissues within the planning CT scan volume and thermoluminescent dosimetry for the rest of the body. Carcinogenic estimates were calculated with and without a correction factor accounting for cancer patients' advanced age and reduced longevity.
Results: For the model assuming a plateau in risk above 2-Gy single-fraction-equivalent (SFE), IMRT and 3D-CRT produced risks of 1.7% and 2.1%, respectively, for prostate; 1.9% and 1.8%, respectively, for nasopharynx; 1% each for tonsil; and 1.4–2.2% and 1.5–1.6%, respectively, depending on technique, for breast. Assuming a reduction in risk above 2-Gy SFE, risks for IMRT and 3D-CRT were 1.1% and 1.5%, respectively, for prostate; 1.4% and 1.2%, respectively, for nasopharynx; 1% each for tonsil; and 1.3–1.8% vs. 1.3–1.6%, respectively, for breast. Applying a correction factor of 0.5 for cancer patients halved these risks and their relative differences.
Conclusions: Carcinogenic risks were comparable in absolute terms between modalities. Risks are dependant on technique used. Risks with IMRT are influenced by monitor unit demand and are therefore software/hardware dependant. The dose–response model accounting for cell killing at higher doses fitted best with actual observed risks. © **2008 Elsevier Inc.**

IMRT, Carcinogenesis, Late effects, 3D conformal radiotherapy, Second malignancy.

INTRODUCTION

Radiation-induced cancers are an uncommon but feared late complication of radiation therapy. Carcinogenic risk seems to be highest for tissues receiving low doses (≤6 Gy) (1, 2). However, there seems to be a tissue-specific dose–response effect for radiocarcinogenesis, with radiation-induced sarcomas developing in tissues receiving higher doses (30–60Gy) and carcinomas developing in tissues receiving much lower doses (3, 4). Both the integral dose to normal tissue and its dose distribution therefore influence this risk.

Dosimetric studies have established intensity-modulated radiotherapy (IMRT) as superior to three-dimensional conformal radiotherapy (3D-CRT) in terms of target coverage, conformity, and sparing of normal tissues. In addition, IMRT is superior in terms of functional sparing of critical organs and offers control and survival outcomes equivalent to those with 3D-CRT (5–7). However, concern has been raised regarding its carcinogenic potential (3, 8, 9). Conventional wisdom holds that IMRT increases integral dose to normal tissues. In addition, IMRT spreads out radiation dose so that a larger volume of tissue receives lower, more carcinogenic radiation doses (10, 11). Intensity-modulated RT might therefore be expected to pose a greater carcinogenic risk than 3D-CRT. It has been estimated that IMRT may increase the risk of a second fatal cancer by a factor of 1.2–8 (3, 9, 12).

Previous studies examining the carcinogenic implications of IMRT have either considered only dose to tissues within the planning CT volume using dose–volume histogram (DVH) analysis (3) or dose to distant tissues through thermoluminescent dosimeter (TLD) measurements (9, 12). In the

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Table 1. Radiotherapy techniques

Primary site	IMRT	3D-CRT
Prostate (3 cases)	5-, 7-, and 9-field plans for each (6 MV)	3-, 4-, and 6-field plans for each (18 MV)
Breast (2 cases)	1) Forward planned, 2 tangential fields with 3 additional segments per field	1) 2 tangential fields with 1 additional segment per field. Virtual wedge in lateral beam only.
	2) Inverse planned, 4 fields, angles chosen to provide optimal target coverage	2) 2 tangential fields with 1 additional segment per field. Physical wedges in both beams.
Tonsil (1 case)	7 equispaced beams	3 phases incorporating spinal shielding, matching electron fields, and conformal boosts to tumor bed.
Nasopharynx (1 case)	7 equispaced beams plus conventional lower anterior neck field	5-field conformal plan with boosts to nodal masses in neck and conventional lower anterior neck field

Abbreviations: IMRT = intensity-modulated radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy.

present study we compared the carcinogenic risk of IMRT with that of 3D-CRT considering the body in totality, including both tissues represented in the DVH as well those outside this volume through TLD measurements. We aimed to compare the two modalities for real clinical situations using actual patient plans and commonly used treatment techniques.

METHODS AND MATERIALS

Treatment planning

Existing 3D-CRT plans were de-archived for prostate, breast, tonsillar, and nasopharyngeal cancers, and clinically equivalent IMRT plans were generated using Plato RTS v1.8 and Plato-ITP v2.5, respectively (Nucletron, Veenendaal, The Netherlands). The clinically equivalent IMRT plans provided at least equivalent target coverage and conformed to the same critical organ tolerances or better as those set out for 3D-CRT. Additional 3D-CRT and IMRT plans with varying beam arrangements were produced for prostatic cases as enumerated in Table 1. 18 MV photons were used for prostatic 3D-CRT. Although many departments use 18 MV for IMRT too, the majority use 6 MV (3). We intended to compare the two modalities for real-life situations and therefore chose 6 MV for our prostatic IMRT. In any case, work from Pirzkall *et al.* (13) suggests that integral dose (on DVH analysis) is unaffected by IMRT beam energy.

Dosimetric analysis and treatment delivery

Normal tissue was defined as all tissue outside the planning target volume (PTV). Dose–volume histogram analysis provided dosimetric data for normal tissue within the planning CT volume. Normal tissue lying beyond the planning CT volume, and therefore not included in the DVH, was defined as "distant normal tissue." For distant normal tissue, dosimetric data was obtained from TLD measurements (TLD-100; Bicron, Solon, OH). Each treatment plan was delivered to a RANDO phantom with 22-26 TLDs evenly distributed throughout the distant normal tissue (Fig. 1). Beginning 5 cm from the edge of the CT volume, TLDs were symmetrically placed in the mid-coronal plane, 5 cm either side of the midline, every 5 cm in the craniocaudal direction. Each plan was delivered as a single fraction to minimize the possible insensitivity of TLDs to tiny radiation doses. TLD's were annealed (TLD Ofen Typ 1321, PTW, Freiberg) for 3 hours before analysis (Auto TLD reader QS 5500, Harshaw, Solon, OH). Thermoluminescent dosimeters underwent regular calibration as part of our departmental quality assurance protocol.

The volume of tissue represented in the DVH was obtained from the planning software. The volume of distant normal tissue was calculated by subtracting the DVH volume from the total volume of the phantom. Dose to limbs was ignored because these tissues are less radiogenic than others and are not represented in the RANDO phantom (3).

Calculation of carcinogenic risk

The process of radiocarcinogenesis is not yet fully understood, and an accurate risk model does not exist. The best data for carcinogenic risk from radiation is from A-bomb survivor studies, although this is subject to important limitations.

First, because these data relate to a general population they overestimate the risk in cancer patients, who are usually older than average and have a reduced life expectancy anyway because of their disease. A correction factor may therefore be required when applying such data to the radiotherapeutic setting. On the basis of A-bomb data, a correction factor of 0.85 would account for the advanced average age of cancer patients (>50 years) (14). However, this factor requires further attenuation to account for the reduced longevity of cancer patients compared with an average population. A correction factor of 0.5 was thus ultimately employed.

Second, A-bomb survivors received a single exposure of radiation, whereas radiotherapy patients receive fractionated therapy over an extended period, allowing for some repair of DNA damage. A dose rate effectiveness factor (DREF) of 2, as recommended by

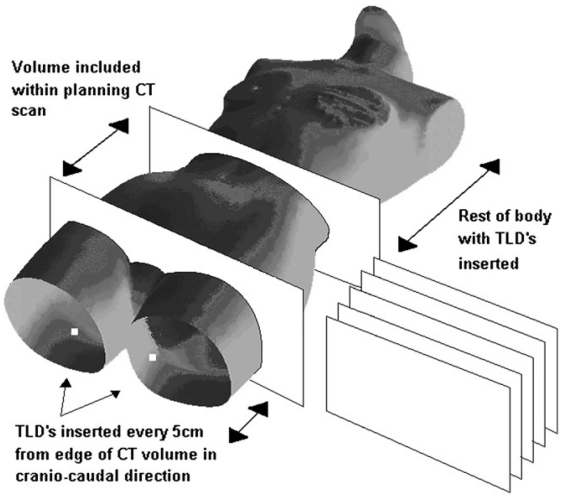

Fig. 1. Schematic illustrating computed tomography (CT) scanned volume for prostate radiotherapy planning and thermoluminescent dosimeter (TLD) placement in the rest of the body.

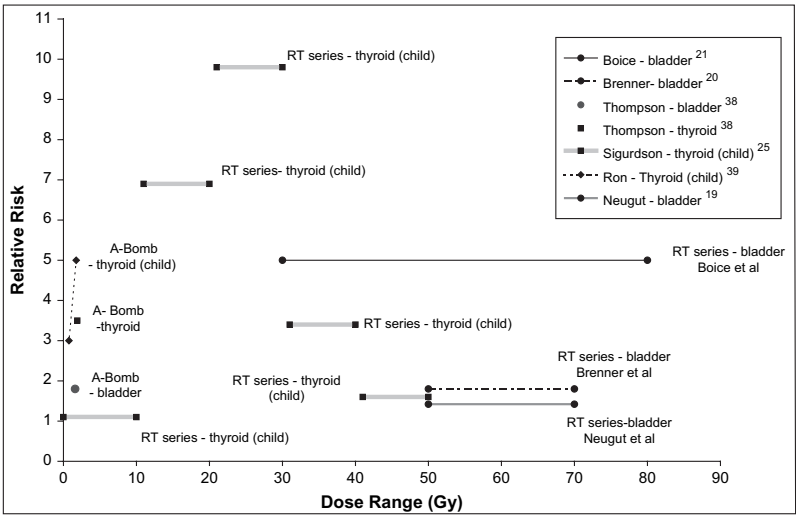

Fig. 2. Clinical studies using adequate patient numbers, follow-up periods, and control groups show an increased risk of cancer induction by radiotherapy. Studies by Brenner *et al.* (20), Boice *et al.* (21), and Neugut *et al.* (19) suggest a risk in therapy patients similar to that for A-bomb survivors (38, 39) who received low doses only. They therefore support a plateauing of risk above 2 to 3-Gy single fraction whole-body exposure. Data from Boice *et al.* (21) regarding leukemic risk and from Sigurdson *et al.* (25) regarding thyroid cancer induction in children exposed to radiotherapy suggest a reduction in carcinogenesis at higher doses.

the International Commission on Radiological Protection and the National Council on Radiation Protection and Measurements (15, 16), was used to account for this. Thus, in terms of carcinogenic potential, for a DREF of 2, an exposure of 2 Sv of atomic bomb radiation equates to 4 Sv of fractionated radiotherapy.

Third, A-bomb data are most reliable for single exposures up to approximately 3 Gy. The data show that risk is linear up to 2 Gy (4 Gy of fractionated radiotherapy) reaching 8%, after which the curve begins to bend downward (3, 17, 18). Above this level the dose–response curve is not known with certainty, but three plausible dose–response relationships could be postulated:

(1) Risk continues to rise linearly with increasing dose (linear-no-threshold model). There are no reliable human data to support this, and it must therefore be considered an unlikely possibility.
(2) Risk levels off and plateaus. Some studies of radiotherapy patients exposed to high doses of therapeutic irradiation show rates of solid cancer induction comparable to those of A-bomb survivors who received only small doses (19–21), suggesting a plateauing of risk at high doses. Models accounting for cell killing but also considering either repair (22) or repopulation (23) also support such a relationship.
(3) Risk decreases with increasing dose. Carcinogenic risk may decrease with increasing dose because of cell killing at higher doses (24). Clinical evidence supporting such a dose–response relationship in humans includes data for leukemic risk in adult radiotherapy patients, as well as for thyroid cancer induction in the Childhood Cancer Survivor Study cohort (2, 25). Other observations that support this theory are the higher relative risk in A-bomb survivors compared with therapeutically irradiated patients (26) and a study by Dorr and Herrmann (1) showing that cancer induction is less likely in tissues receiving higher doses.

Figure 2 illustrates the clinical evidence for dose–response relationships 2 and 3.

Because of the uncertainty regarding the dose–response relationship for carcinogenesis at radiotherapy doses ≥4 Gy, we constructed two different dose–response curves to account for scenarios 2 and 3 above. Both model an initial linear increase in risk with dose, but one saturates at 8% risk at 4 Gy of fractionated radiotherapy (assuming a plateauing of risk), whereas the other decays after this maximum is reached with a slope defined by a $D_0 = 10$ (assuming a decreasing risk with increasing dose above 4 Gy due to the effects of cell killing at higher doses). This value of 10 for Do approximates that observed for leukemia induction at doses >4 Gy in cervical cancer patients who received radiotherapy (2, 3). The two curves are represented in Fig. 3.

For tissue represented in the DVH, carcinogenic risk was calculated as follows. Normal tissue DVHs were divided into dose bins of 0–4 Gy, 4–8 Gy, and then every 8 Gy. The volume in each bin was calculated, as well as its proportional contribution to the total normal tissue volume in the DVH. The risk associated with each bin was calculated by averaging the risk for each 1-Gy increment within the bin according to the dose–response curves in Fig. 3. The overall risk for normal tissue within the DVH was calculated by summing the risks for each bin in proportion to each one's contribution to the total volume of normal tissue within the DVH. For distant tissue the average dose was obtained from TLD readings. These doses covered a very narrow range, and all but the closest TLDs to the field edge for the four-field breast IMRT plan received <1 Gy. Their average value is thus likely to be representative of the carcinogenic risk.

Photoneutrons are produced in the collimator and treatment head when photons of 10 MV or more are used. They were thus included in carcinogenesis calculations for 18-MV prostatic 3D-CRT but are not relevant for other scenarios in which only 6-MV photons were used. Measured data for effective neutron dose with 18-MV radiotherapy using 10 × 10-cm fields were obtained from D'Errico *et al.* (27) and Vanhavere *et al.* (28). Effective neutron dose at 40 cm from the central axis at 5-cm depth was used to represent dose to distant

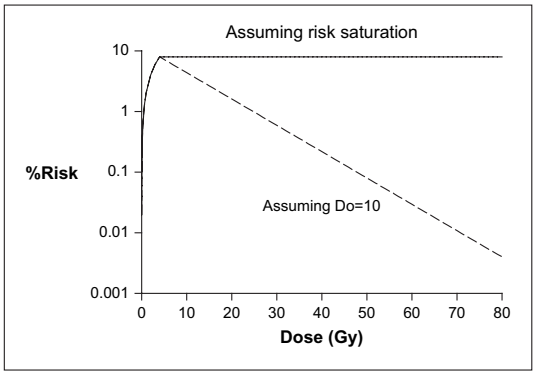

Fig. 3. Dose–response models for radiocarcinogenesis.

tissue, and effective dose at 7.5 cm from central axis at 5-cm depth was used for tissues within the planning CT volume.

After calculating the risk associated with the tissue represented in the planning CT volume and that associated with the remainder of the body, an overall carcinogenic risk was then calculated for each tumour site and modality by averaging the two figures according to their proportional contribution to the total body volume of the phantom.

RESULTS

Carcinogenic risks assuming no reduction above 4 Gy of fractionated radiotherapy

The carcinogenic risks of IMRT were comparable to those for 3D-CRT at all sites.

For prostate radiotherapy IMRT carried a 0.8% risk and 3D-CRT a 1.0% risk. However, most prostate cancer patients enjoy long-term survival, and our proposed correction factor is inappropriate for these patients. In this scenario, omitting the correction factor produced estimates of 1.7% and 2.1% for IMRT and 3D-CRT, respectively.

For head-and-neck radiotherapy, both modalities produced equivalent risk estimates of 0.5% and 0.9% at the tonsil and nasopharynx, respectively. If we omitted the correction factor that is inappropriate for long-term survivors, risk estimates were 1% for both modalities for tonsillar carcinoma and 1.9% and 1.8% for IMRT and 3D-CRT, respectively, for nasopharyngeal carcinoma.

In the setting of breast cancer, forward-planned tangential-field IMRT was associated with 0.7% risk, compared with 0.8% for 3D-CRT using a virtual wedge. The risk was higher for four-field IMRT at 1.1% compared with 0.8% for 3D-CRT with physical wedges. Because most patients who undergo breast-conservation therapy will be long-term survivors, it may be most appropriate to use uncorrected risk estimates of 1.4%, 1.5%, 1.6%, and 2.2% for two-field IMRT, 3D-CRT (virtual wedge), 3D-CRT (physical wedges), and four-field IMRT respectively.

Carcinogenic risks assuming a reduction in risk above 4 Gy with a slope of $D_0 = 10$

Again, carcinogenic risks were comparable between the two modalities. In the prostatic setting, the risk estimates were 0.6% and 0.8% for IMRT and 3D-CRT, respectively. In long-term survivors for whom the correction factor was omitted, the risks increased to 1.1% and 1.5%, respectively. For tonsillar radiotherapy both modalities produced risks of 0.5% (1% in long-term survivors). Nasopharyngeal IMRT resulted in 0.7% risk compared with 0.6% for 3D-CRT (1.4% and 1.2%, respectively, if not corrected for age and cancer mortality risk). Breast IMRT using tangential fields and 3D-CRT using a virtual wedge both resulted in 0.7% risk (1.3% risk in long-term survivors). Four-field breast, IMRT, however produced an estimate of 0.9%, and 3D-CRT with physical wedges, 0.8% (1.8% and 1.6%, respectively, in long-term survivors).

DISCUSSION

Although it has been widely held that IMRT increases carcinogenic risk compared with 3D-CRT, our results show that this is not necessarily true. Indeed, this was not generally the case for the software and hardware combination used in our study. Compared with 3D-CRT, IMRT tends to spread out low, carcinogenic doses to tissues within the DVH volume, but the integral dose to these tissues actually remains relatively constant (29–32). Consequently, only a small increase in risk for these tissues was observed (Table 2).This risk to these nearby tissues would be influenced by the shape of the dose–response curve above 4 Gy. However, the overall risk of cancer induction is body-wide. Thus the dose to distant tissues that make up the bulk of the body is also important. This dose comprises three main components: internal patient scatter, collimator scatter, and head leakage. The former two factors might actually be lower with IMRT than with 3D-CRT because of smaller field sizes and the <100% intensity of IMRT beams. These two factors dominate the picture for tissues 15–30 cm from the field edge (33, 34). For more distant tissue, however, head leakage predominates and is unavoidably higher with IMRT because of an increase in monitor units (MU). Because the dose of scattered and leakage radiation to distant tissues is very low, so is the associated risk. Nevertheless, if the discrepancy in MU demand is too great between IMRT and 3D-CRT, excessive head leakage with IMRT could overwhelm any possible gains in scattered radiation dose. This coupled with IMRT's higher carcinogenic risk for tissue in-field and nearby (within the DVH volume) would ultimately result in a higher risk of second cancers with IMRT. In the setting of our study, however, MU demand with IMRT was only 2 to 4 times higher, and hence its associated risks were very comparable to those of 3D-CRT. Such may not be the case for other software/hardware combinations: Kry *et al.* (9) found a 5 times greater MU requirement for IMRT, which translated into a substantially increased risk of cancer induction in distant tissue. That study, however, did not consider tissues within the DVH. Hall and Wuu (3) explored the effect of IMRT on carcinogenesis using DVH analysis of a prostatic radiotherapy plan. Their risk estimates were similar to our own if considering DVH analysis alone

Table 2. Carcinogenic risk related to the DVH volume compared to the rest of the body, together with monitor units for cases studied

		Tumor site	Risk in DVH volume (%)	Risk in rest of body (%)	Monitor units
Risk peaks 8% at 4 Gy and saturates thereafter	3D-CRT	Prostate	1.50	0.59	9,494
	IMRT		1.45	0.21	17,812
	3D-CRT	Breast (virtual wedge)	1.38	0.12	5,430
	IMRT	2-field IMRT	1.38	0.07	5,280
	3D-CRT	Breast (physical wedges)	1.32	0.25	14,030
	IMRT	4-field IMRT	1.98	0.26	72,175
	3D-CRT	Nasopharynx	1.60	0.20	116,829
	IMRT		1.59	0.30	406,141
	3D-CRT	Tonsil	0.86	0.16	14,018
	IMRT		0.86	0.17	19,985
Risk peaks 8% at 4 Gy and declines thereafter	3D-CRT	Prostate	0.96	0.59	9,494
	IMRT		0.91	0.21	17,812
	3D-CRT	Breast (virtual wedge)	1.17	0.14	5,430
	IMRT	2-field IMRT	1.16	0.14	5,280
	3D-CRT	Breast (physical wedges)	1.15	0.50	14,030
	IMRT	4-field IMRT	1.26	0.52	72,175
	3D-CRT	Nasopharynx	0.81	0.39	116,829
	IMRT		0.79	0.60	406,141
	3D-CRT	Tonsil	0.67	0.33	14,018
	IMRT		0.64	0.34	19,985

Abbreviations: DVH = dose-volume histogram; IMRT = intensity-modulated radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy.

(3.8%/3.1% for IMRT/3D-CRT, respectively, vs. 3.6%/3.3% for D_0 = 10 in the present study), but once we factored in dose to the rest of the body, risk estimates dropped considerably. Although we expected the risks to distant tissue to be much greater for IMRT than for 3D-CRT, this was not actually the case. In the prostatic setting these risks were more than halved (Table 2). Although MU demand was double for IMRT, smaller field size and reduced average field intensity seem to have reduced scatter sufficiently to more than compensate for any increase in head leakage. For four-field breast and nasopharyngeal IMRT, risks to distant tissue were increased, but only marginally in absolute terms. Because the MU demand of nasopharyngeal IMRT was 4 times higher than with 3D-CRT the resultant carcinogenic risk to distant tissue was 1.5 times higher; but because the associated absolute risk is so small, the real effect of IMRT was minimal. It seems therefore that our concerns about the carcinogenic potential of IMRT based on increased scatter and leakage may have been excessive.

Breast radiotherapy using physical wedges increases wedge scatter and also head leakage compared with virtual wedges (35) (because of higher MU demand). This is reflected in the doubling of carcinogenic risk to distant tissue observed in our study (Table 2). However, because the absolute risks involved are so minute there is little effect on overall risk of cancer induction. The dose distribution to tissues around the target is similar in both cases, and so too is the associated risk. Ultimately therefore, there is little difference in absolute terms between virtual and dynamic wedges. IMRT and 3D-CRT likewise produced similar risk estimates in absolute terms.

Although it is recognized that organs vary in carcinogenicity (36), the different radiogenic potentials of different organs are accounted for in our calculations because we have used A-bomb survivor data, which reflect whole-body exposure. Thus we did not attempt to estimate the positions of viscera not physically replicated within the phantom. In addition, we believe that the accuracy of such a process is limited.

Although uncertainty about the carcinogenic dose–response at >4 Gy is less relevant for the majority of normal tissues, which lie at some distance from the field edge and mostly received <0.5 Gy (data not shown), the major component of carcinogenic risk was tissue within the DVH volume, which received >4 Gy (Table 2). Our results are based on dose–response modeling for doses above 4 Gy and are also dependant on correction factors like the DREF. We acknowledge therefore that they may imperfectly reflect the actual

risks. Our calculated value for long-term survivors of prostatic 3D-CRT of 1.5% using $D_0 = 10$ is encouraging however, being almost identical to the 1.4% actual risk observed for patients surviving ≥10 years according to SEER data reported by Brenner *et al*. (20). Similarly, our findings of only 0.7–1.6% risk for breast 3D-CRT are in keeping with those of Obedian *et al*. (37), who performed a study of more than 1000 patients with adequate follow-up and a surgical control group. Even if the absolute risk values in the present study may ultimately be inaccurate, the risk ratios of IMRT vs. 3D-CRT should remain valid.

CONCLUSION

Integral dose to nontargeted tissues within the DVH volume is relatively unchanged by IMRT and may even be reduced (29–31). The spreading of low doses by IMRT could increase the carcinogenic risk in these tissues if the dose–response curve does in fact curve downward at higher doses because of cell killing; this effect was small, however, in the cases we examined. Although IMRT has been reported to increase integral dose to distant normal tissue and hence carcinogenic risk (9), this seems critically dependant on MU demand and was not observed using our software/hardware except for nasopharyngeal IMRT.

Absolute risks for cancer induction were similar for IMRT and 3D-CRT when the body was considered in totality. These risks may vary with planning algorithms and hardware combinations. Our calculated results fitted best with observed risks when a model assuming cell killing at higher doses was used rather than one assuming a plateauing of risk.

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Chapter 3

Comparison of Out-of-Field Dose and Its Constituent Components for IMRT Versus 3DCRT: Implications for Carcinogenesis

To test the hypothesis generated in chapter one that IMRT may reduce some components of out-of-field scatter rather than increase them as previously held, and to characterise and compare the contribution of individual components of scatter to out-of-field dose for both modalities.

The chapter is framed in terms of its background context and its relationship to other thesis chapters on page twelve of chapter one.

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CLINICAL INVESTIGATION **Normal Tissue**

A COMPARISON OF OUT-OF-FIELD DOSE AND ITS CONSTITUENT COMPONENTS FOR INTENSITY-MODULATED RADIATION THERAPY VERSUS CONFORMAL RADIATION THERAPY: IMPLICATIONS FOR CARCINOGENESIS

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Purpose: To investigate differences in scatter and leakage between 6-MV intensity-modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3DCRT); to describe the relative contributions of internal patient scatter, collimator scatter, and head leakage; and to discuss implications for second cancer induction.
Methods and Materials: Dose was measured at increasing distances from the field edge in a water bath with a sloping wall (*1*) under full scatter conditions, (*2*) with the field edge abutting but outside the bath to prevent internal (water) scatter, and (*3*) with the beam aperture plugged to reflect leakage only.
Results: Internal patient scatter from IMRT is 11% lower than 3DCRT, but collimator scatter and head leakage are five and three times higher, respectively. Ultimately, total scattered dose is 80% higher with IMRT; however this difference is small in absolute terms, being 0.14% of prescribed dose. Secondary dose from 3DCRT is mostly due to internal patient scatter, which contributes 70% of the total and predominates until 25 cm from the field edge. For IMRT, however, machine scatter/leakage is the dominant source, contributing 65% of the secondary dose. Internal scatter predominates for just the first 10 cm from field edge, collimator scatter for the next 10 cm, and head leakage thereafter.
Conclusions: Out-of-field dose is 80% higher with IMRT, but differences are tiny in absolute terms. Reductions in internal patient scatter with IMRT are outweighed by increased machine scatter and leakage, at least for small fields. Reductions from IMRT in dose to tissues within the portals and in internal scatter, which predominates close to the field edge, means that calculations based solely on dose to distant tissues may overestimate carcinogenic risks. © 2011 Elsevier Inc.

IMRT, scatter, leakage, second cancer risk, 3D conformal radiation therapy.

INTRODUCTION

The use of intensity-modulated radiation therapy (IMRT) in clinical practice is becoming more widespread. IMRT uses multiple, conformally shaped radiation beams with heterogeneous fluence profiles to produce complex isodose distributions. It thus improves target coverage while simultaneously avoiding organs at risk (1–3). Using a multileaf collimator (MLC), the fluence pattern of an IMRT beam is modulated through the use of multiple smaller segments, or by use of a sliding window whereby the MLC leaves move across the portal in an ever-changing sequence, irradiating only a portion of the field at any moment in time. Beam-on time and monitor unit requirements of IMRT are therefore higher than for three-dimensional conformal radiation therapy (3DCRT). This results in an increase in collimator scatter and leakage radiation from the treatment head that in turn, has led to concern about the increased potential for second cancers after IMRT (4, 5). There is, however, a third component of scatter, which is internal or patient scatter produced through radiation interactions with the patient's body tissues. For 3DCRT, internal scatter has been reported as the dominant source of radiation dose outside the field for approximately 18 to 30 cm (6, 7). This component is likely to be reduced by IMRT for two reasons. First, because appropriately optimized IMRT requires narrower lateral beam margins than 3DCRT (8), IMRT field sizes may be smaller; and second, because an ever-changing portion of the portal that may include the PTV is always shielded, the intensity of each IMRT field is less than 100% that of an unmodulated beam.

The components of scatter have been investigated for 3DCRT (6); however we are unaware of similar data for

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conventional MLC-based IMRT, although head leakage from the largely defunct NOMOS-Peacock system has been described (9). The contributions of each component to total patient dose and its distribution are relevant for radiation carcinogenesis. The increase in collimator scatter and head leakage with IMRT has been estimated to double carcinogenic risk (5, 10). Such estimates, however, are based on dose to distant tissues only, and neglect the effect of IMRT on tissue within and surrounding the radiation portals. Studies that have included both dose to distant tissues (from scatter and leakage radiation) as well as to tissues within and close to the beam portals (from the primary beams and internal patient scatter) have found little increase in second cancer risk with IMRT, and even a decrease in risk in some cases (11–13). This might be explained by a reduction in integral dose within the beam portals, a reduction in internal patient scatter and possibly a difference in the dose distribution through IMRT, although the effect of the latter depends on the dose–response relationship for second cancer induction.

In the present work, we examine differences in scatter and leakage from IMRT compared to 3DCRT, characterize the relative contributions of leakage and the two components of scatter as well as their spatial distributions, and attempt to explain discrepancies in the literature about the effect of IMRT on second cancer induction.

METHODS

For the purposes of this study, 6-MV 3DCRT and IMRT plans were produced for the same tonsillar target volume. Both plans used five fields with identical gantry angles. Both provided 95% to 107% target coverage with acceptable spinal cord dose. The IMRT plan delivered 3.7 times more monitor units (MU) than its 3DCRT counterpart, in good agreement with previous studies (5, 12). The average field size was 6.5 × 6.5 cm for IMRT and 7 × 7 cm for 3DCRT.

A 75 × 30 × 35-cm water tank was constructed from Perspex, with one end angled to match the divergent beam of a Varian 21EX Linac (Varian Medical Systems Inc, Palo Alto, CA) fitted with a Millennium multileaf collimator (MLC). The water tank was filled to a depth of 30 cm. A sliding Perspex clasp holding a Farmer-type FC65-P ionisation chamber (IBA Dosimetry GmbH, Schwarzenbruck, Germany) was fitted along the length of the side wall to achieve reproducible position measurements. The chamber was positioned at 10 cm depth, and source to surface distance (SSD) was set at 90 cm.

The IMRT plan and the 3DCRT plan were then delivered in turn. The first measurement was performed 10 cm away from the central axis (~6 cm from the field edge), and the chamber was moved in 5-cm increments away from the field edge before each subsequent dose measurement. All five fields were delivered for each measurement position for each plan. All fields were delivered at gantry angle of 0° to coincide with the tank's divergent edge. The process was performed using three different set-up arrangements to separate out the individual dose contributions from head leakage, collimator scatter, and internal patient scatter, as described below (Fig. 1).

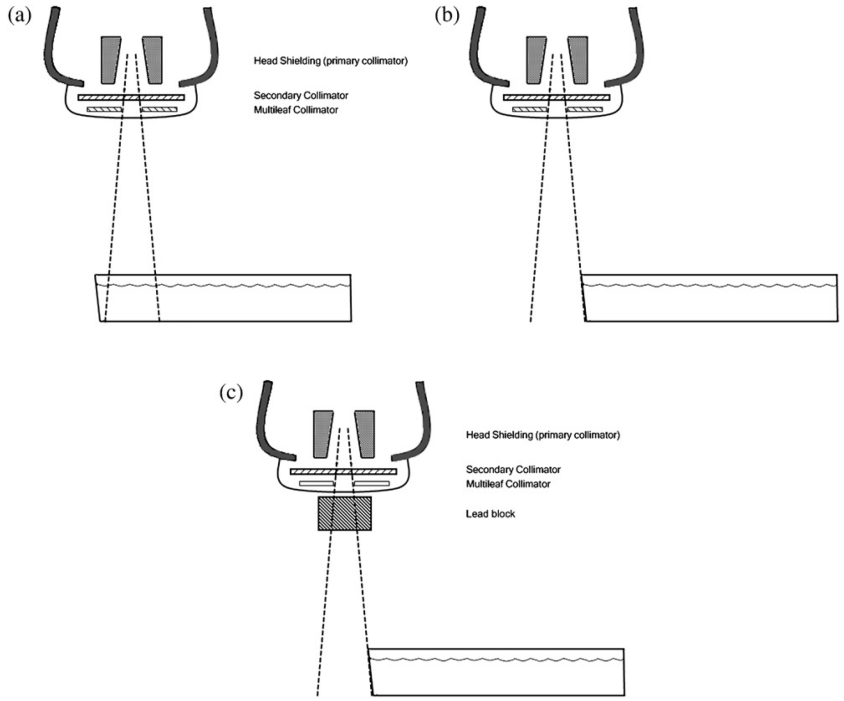

Fig. 1. (a) To measure water scatter + collimator scatter + head leakage. (b) To measure collimator scatter + head leakage. (c) To measure head leakage.

To measure the total dose of scattered radiation from head leakage, collimator scatter, and internal patient scatter, the water tank was positioned so that the treatment beam passed through the water in the tank (Fig. 1a). For the second experiment, the water tank was moved relative to the isocenter so that the angled edge of the tank aligned with the divergent edge of the primary beam. The beam thus did not pass through or interact with the water in the tank, and so eliminated the contribution of internal scatter. The resultant dose thus reflected only head leakage and collimator scatter (Fig. 1b). By subtracting the doses obtained in Experiment 1b from those of Experiment 1a, the contribution of internal patient scatter was calculated (6). The water tank was left in the same position for the third experiment, but the Y-jaws of the secondary collimator that move parallel to the long axis of the tank were now closed, and the beam aperture was plugged with a lead block (Fig. 1c). This reduced the measured primary beam transmission at the isocenter by 99.9%. The position of the open X-jaws was left unaltered to maintain treatment head geometry in the measurement axis relative to the previous measurements. The doses for IMRT and the conformal field were again delivered in turn. The measured dose at each out-of-field position was thus a result of leakage radiation through the treatment head only. By subtracting the measurements obtained in Experiment 1c from those of Experiment 1b, the contribution of collimator scatter could be calculated.

RESULTS

Figures 2a to 2e plot the doses measured in 5-cm increments from the field edge under the various experimental conditions. Figure 2a represents the total dose of scattered radiation from all sources. It can be appreciated that out-of-field dose is higher from IMRT than 3DCRT everywhere in the phantom. Integrating the area under the curves shows IMRT secondary dose to be 1.8 times higher than 3DCRT. The absolute difference is very small, however, being only about 0.14% of the prescribed dose.

Figure 2b illustrates the contribution of internal patient scatter alone. Integrating the areas under the graphs reveals that patient scatter from IMRT is 11% lower than from 3DCRT. However this represents a reduction of just 0.02% of the prescribed dose in absolute terms.

Figure 2c demonstrates the combined contributions from collimator scatter and head leakage. These measurements represent the total scattered radiation from the machine head (machine scatter). As expected, given the increased monitor units with IMRT, these values were on average 3.7-fold higher with IMRT. There is a prominent spike in the machine scatter over a distance of 5 cm, beginning approximately 15 cm away from the edge of the field. Although small in absolute terms, scattered radiation is more than doubled over this short distance. The same phenomenon is not observed in Fig. 2b, representing internal scatter. Although only a slight hump can be discerned in collimator scatter dose in Fig. 2d, a prominent spike in leakage radiation dose over this distance is clear from Fig. 2e. The spike is a product of the treatment head geometry, namely, leakage radiation penetrating through the Y-jaw of the secondary collimator before passing through a gap between the lateral edge of the MLC and the primary collimator. Leakage radiation traveling along ray lines closer than 15 cm from the field edge is attenuated by the MLC, whereas ray lines beyond 20 cm are attenuated by the primary collimator incorporated into the treatment head.

Collimator scatter is five times higher for IMRT than for 3DCRT because of longer beam-on times (Fig. 2d). The difference is, however, only 0.2% of prescribed dose in absolute terms at 6 cm from the field edge, and decreases exponentially with increasing distance. Given the longer beam on times with IMRT, it is not surprising that head leakage to tissues greater than 20 cm away may be many-fold higher than 3DCRT. Head leakage under the tested conditions was approximately 3 times higher with IMRT (Fig. 2e). Because of the efficient shielding of the primary collimator, however, the absolute dose at any point from head leakage is very low, usually under 1/1,000 of the prescribed dose.

Figures 3a and 3b show the relative contributions of each component to the total scatter dose for IMRT and 3DCRT, respectively. Figures 4a and 4b compare internal patient scatter to total machine scatter (collimator scatter plus head leakage). With 3DCRT, internal scatter is the dominant source of radiation dose for a distance of approximately 25 cm from the field edge. It is by far the major component of scattered dose until approximately 20 cm from field edge, findings that are in good agreement with previous reports (6, 7). In contrast, IMRT produces larger amounts of machine scatter (collimator scatter plus leakage) relative to internal/patient scatter. Machine scatter thus overshadows internal scatter as the major source of dose beyond 10 cm from field edge. For 3DCRT, total scattered dose is largely due to internal patient scatter (Fig. 4b), whereas, for IMRT, machine scatter is the dominant source (Fig. 4a), with internal scatter for the first 10 cm from field edge, collimator scatter for the next 10 cm and head leakage thereafter. Machine scatter contributes 65% of the secondary dose for IMRT and 30% for 3DCRT. Collimator scatter and head leakage contribute 33% and 32%, respectively, for IMRT and 11% and 19%, respectively, for 3DCRT. Internal scatter contributes 70% of the secondary dose for 3DCRT but just 35% for IMRT.

DISCUSSION

Our results confirm a reduction in internal patient scatter with IMRT. As expected, because of longer beam-on times with IMRT, head leakage and collimator scatter are several-fold higher than with 3DCRT. Although internal patient scatter is the dominant source of dose to tissues close to the beam edge, reductions in this component of scatter from IMRT are undone by increases in machine scatter and leakage. Scattered dose is thus always higher with IMRT, irrespective of distance from the field edge. IMRT results in an 80% greater out-of-field integral dose than does 3DCRT under the conditions tested. In absolute terms, this is a difference of just 0.14% of the prescribed dose.

The increase in machine scatter and leakage with IMRT appears to be proportional to monitor unit demand, in

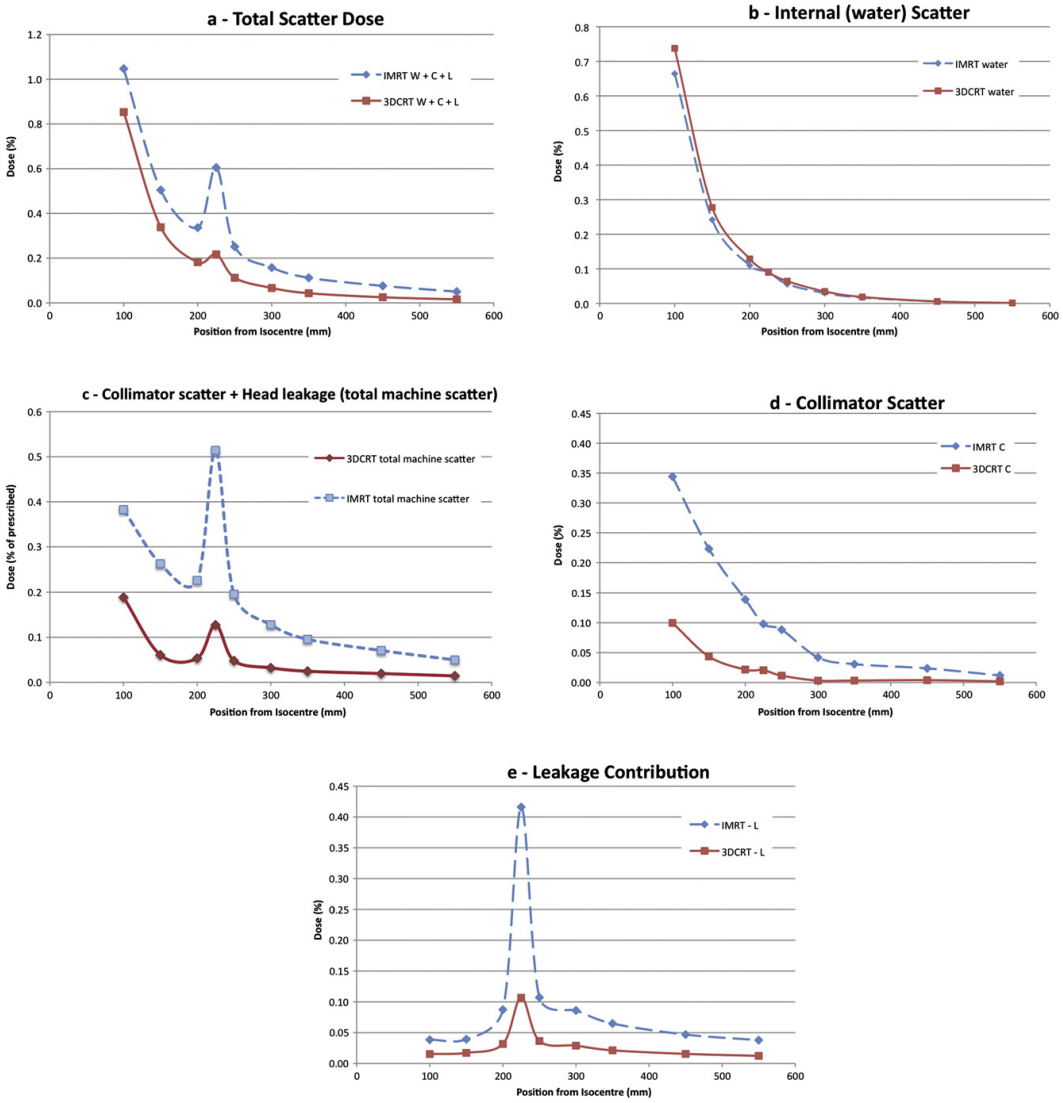

Fig. 2. (a) Total scatter dose from IMRT vs. 3DCRT. (b) Internal/water scatter dose from IMRT vs. 3DCRT. (c) Collimator scatter and head leakage from IMRT vs. 3DCRT. (d) Collimator scatter fom IMRT vs. 3DCRT. (e) Head leakage from IMRT vs. 3DCRT.

keeping with others' observations (14). However we found a disproportionate increase in IMRT collimator scatter relative to MU requirements. This may reflect inaccuracies in our measurement of sub-milligray doses in the presence of background activity at distances far from the field edge. On the other hand, the increase in collimator scatter may be real and could reflect increased exposure of MLC leaves to the beam during IMRT.

The relative contributions of the different scatter components depend on field size, MU demand, and measurement depth (6, 15, 16). The contribution of internal/patient scatter increases with increasing field size as this directly increases the irradiated volume (6). Internal scatter also increases with measurement depth (6), reflecting an increase in backscatter. Machine scatter increases in proportion to increasing MU demand. Because IMRT produces less internal scatter than 3DCRT and reduces integral dose to tissues within the primary beams (17–20), if the MU difference between the modalities is small enough to sufficiently minimize increases in machine scatter, and if fields are substantial enough to maximize reductions in internal scatter, then IMRT could theoretically produce a lower

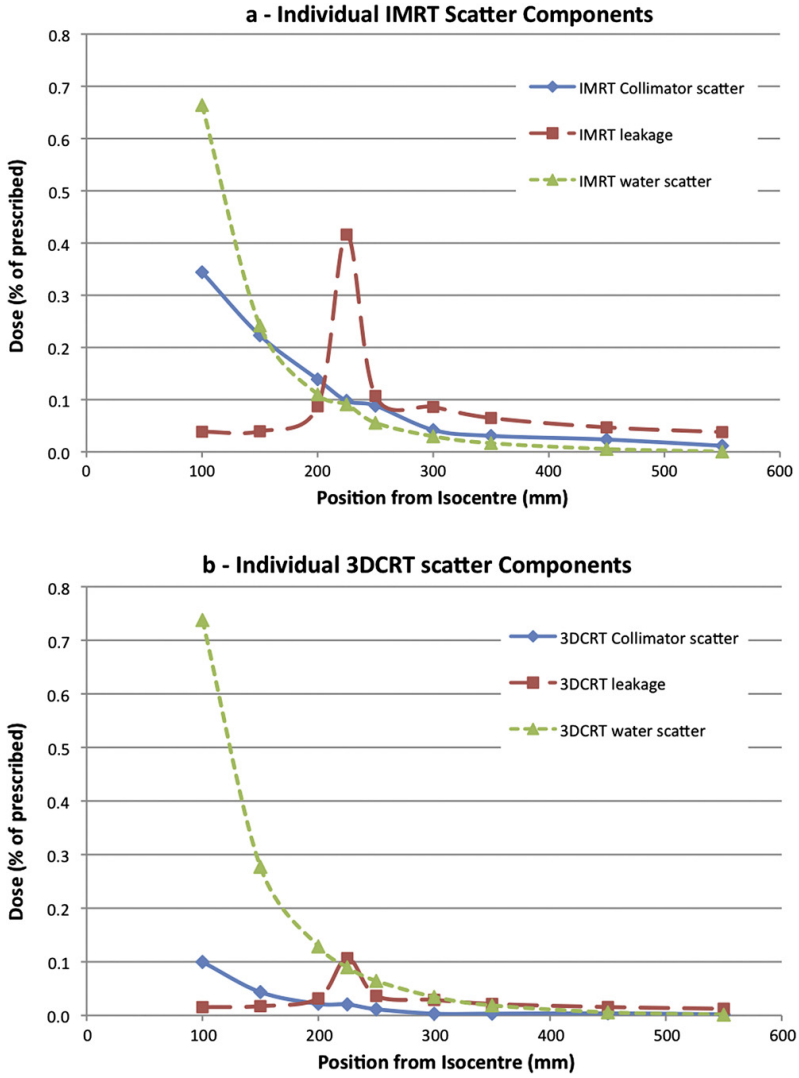

Fig. 3. (a) Individual components of scattered dose for IMRT. (b) Individual components of scattered dose for 3DCRT.

total integral dose to the patient. Previous measurements of ours using Plato v2.5 (Nucletron BV, Veenendaal, the Netherlands), for which the MU demand of IMRT was only twice that of 3DCRT, did in fact show a 15% reduction in total body integral dose for prostate and breast IMRT (data not shown). Similarly, effective dose from IMRT, which is a measure of carcinogenicity according to International Commission on Radiological Protection (ICRP)–65, was reduced relative to 3DCRT, according to work by Howell *et al.* (14).

The present study ignores the contribution of photoneutrons produced when high-energy radiation beams are used. Such photoneutrons have a high relative biological effectiveness (RBE) for radiocarcinogenesis (21). IMRT using photon energies of more than 10 MV greatly increases photoneutron production relative to 3DCRT secondary to prolonged head activation (14). This component of scattered dose has been investigated elsewhere (14). Because of attenuation in tissue, the measured neutron dose decreases with increasing depth within the patient (22).

Thus out-of-field dose with IMRT would increase relative to 3DCRT with decreasing field size, increasing MU inefficiency, increasing distance from field edge, and diminishing depth of measurement; but would decrease relative to

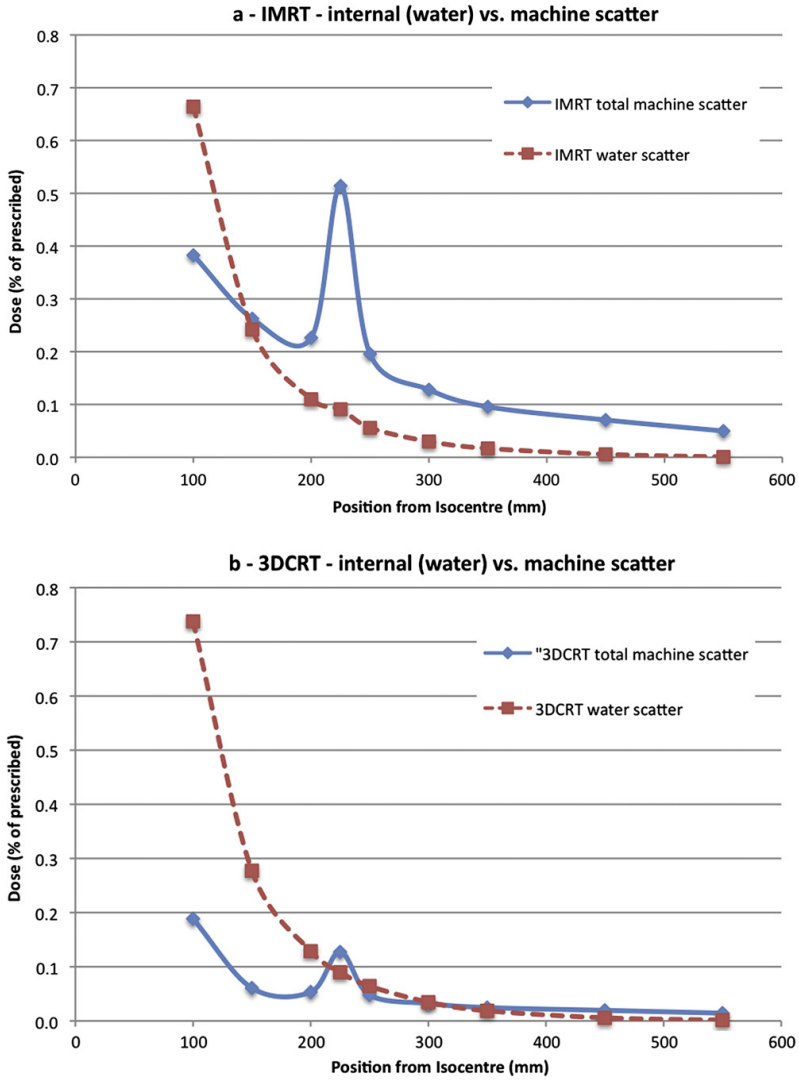

Fig. 4. (a) Internal scatter vs. machine scatter plus head leakage for IMRT. (b) Internal scatter vs. machine scatter plus head leakage for 3DCRT.

3DCRT with increasing field size, decreasing MU inefficiency, decreasing distance from field edge, and increasing depth of measurement.

Reduced internal patient scatter from IMRT helps to explain in part the differing results between studies comparing differences in second cancer induction between IMRT and 3DCRT. Differences in MU between studies, however, are also important. Those studies considering only dose to distant tissues, where dose consists almost exclusively of machine scatter, have shown large relative risks with IMRT (5, 23). In contrast, those studies considering both the dose to tissues within and around the primary beams, as well as dose to distant tissues, showed either much smaller differences in second cancer risk (11, 12) or a reduced risk with IMRT (12, 13). This can be partly explained by the findings of the present study, which shows that internal scatter, the dominant source of dose close to the beam edge, is actually reduced by IMRT. Total machine scatter, on the other hand, is increased. The increase in scattered dose with IMRT relative to 3DCRT thus increases with distance from field edge. In addition, IMRT has also been shown to reduce the integral dose to tissues within the primary beam (17–20), which would likely reduce its carcinogenic risk further (the magnitude of this reduction

depends heavily, however, on the dose–response relationship used in modeling such risks). Therefore, if the contribution of nearby tissues to the total second cancer risk is ignored and only distant tissues are considered, then risk estimate calculations for IMRT may be excessive.

CONCLUSION

As expected, based on our study findings, IMRT results in a higher total dose of scattered radiation to the patient than does 3DCRT. This increase is small in absolute terms and is due to an increase in dose to distant tissues because of greater collimator scatter and head leakage. The increase in machine scatter may be offset to varying degrees by a reduction in the dose to tissues within and immediately surrounding the primary beam. With IMRT, internal patient scatter is the dominant source of radiation dose for a distance of only 10 cm from the field edge, but with 3DCRT for approximately 30 cm, after which machine scatter predominates. This would be influenced by field size and the MU demand of IMRT. The contribution of photoneutrons to total scatter dose was not investigated in this study, which used 6 MV only. The relative contributions of different components of scatter and leakage are likely to vary with field size, beam energy, MU requirements of IMRT, and depth of measurement. Under conditions tested, total machine scatter contributed 65% of the secondary dose for IMRT but only 30% for 3DCRT. Importantly, collimator scatter and head leakage are also dependant on linear accelerator and collimator design.

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Chapter 4

Constituent Components of out-of-field Scatter Dose for 18MV IMRT vs. 3DCRT: A Comparison With 6MV and Implications for Carcinogenesis

An extension of chapter three, this chapter characterises the composition of out-of-field scatter for high energy IMRT and 3DCRT and compares them. It also explores the effect of beam energy on scattered dose including photoneutron dose. Implications for carcinogenesis are discussed.

The chapter is framed in terms of background context and its relationship to other thesis chapters on page thirteen of chapter one.

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Clinical Investigation

Constituent Components of Out-of-Field Scatter Dose for 18-MV Intensity Modulated Radiation Therapy Versus 3-Dimensional Conformal Radiation Therapy: A Comparison With 6-MV and Implications for Carcinogenesis

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Summary

This study measured and compared the constituent components of out-of-field dose for both high- and low-energy IMRT compared with 3D conformal radiation therapy. Internal patient scatter, collimator scatter, and head leakage were measured. Neutron dose was calculated. The effects of varying beam energies and techniques on second cancer risks are discussed.

Purpose: To characterize and compare the components of out-of-field dose for 18-MV intensity modulated radiation therapy (IMRT) versus 3-dimensional conformal radiation therapy (3D-CRT) and their 6-MV counterparts and consider implications for second cancer induction.

Methods and Materials: Comparable plans for each technique/energy were delivered to a water phantom with a sloping wall; under full scatter conditions; with field edge abutting but outside the bath to prevent internal/phantom scatter; and with shielding below the linear accelerator head to attenuate head leakage. Neutron measurements were obtained from published studies.

Results: Eighteen-megavolt IMRT produces 1.7 times more out-of-field scatter than 18-MV 3D-CRT. In absolute terms, however, differences are just approximately 0.1% of central axis dose. Eighteen-megavolt IMRT reduces internal/patient scatter by 13%, but collimator scatter (C) is 2.6 times greater than 18-MV 3D-CRT. Head leakage (L) is minimal. Increased out-of-field photon scatter from 18-MV IMRT carries out-of-field second cancer risks of approximately 0.2% over and above the 0.4% from 18-MV 3D-CRT. Greater photoneutron dose from 18-MV IMRT may result in further maximal, absolute increased risk to peripheral tissue of approximately 1.2% over 18-MV 3D-CRT. Out-of-field photon scatter remains comparable for the same modality irrespective of beam energy. Machine scatter (C+L) from 18 versus 6 MV

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is 1.2 times higher for IMRT and 1.8 times for 3D-CRT. It is 4 times higher for 6-MV IMRT versus 3D-CRT. Reduction in internal scatter with 18 MV versus 6 MV is 27% for 3D-CRT and 29% for IMRT. Compared with 6-MV 3D-CRT, 18-MV IMRT increases out-of-field second cancer risk by 0.2% from photons and adds 0.28-2.2% from neutrons.

Conclusions: Out-of-field photon dose seems to be independent of beam energy for both techniques. Eighteen-megavolt IMRT increases out-of-field scatter 1.7-fold over 3D-CRT because of greater collimator scatter despite reducing internal/patient scatter. Out-of-field carcinogenic risk is thus increased (but improved in-field dose conformity may offset this). Potentially increased carcinogenic risk should be weighed against any benefit 18-MV IMRT may provide.

Introduction

Radiation oncologists tend to concentrate on the dose distribution to target volumes and nearby critical organs, whereas scattered dose out of field receives little attention. This is because scattered dose more than a few centimeters from the field edge is very low. Furthermore, such dose is usually delivered in multiple, even tinier fractions, further reducing its biological effects.

In recent years, though, concerns have been raised about higher scattered dose to distant tissues with intensity modulated radiation therapy (IMRT) and the subsequently increased potential for second cancer induction (1, 2). This is because the longer beam-on time with IMRT increases collimator scatter and head leakage. There is, however, a third component of out-of-field scattered dose. This is radiation internally scattered by the patient's body tissues, or "phantom scatter" in physics terms. We theorized (3) and subsequently demonstrated using 6-MV beams that this component of scatter is actually reduced by IMRT (4). The risk of second cancer induction from IMRT may be somewhat mitigated by this phenomenon, although it ultimately depends on the reduction in phantom scatter relative to the larger increases in machine scatter, as well as on the altered dose distribution within the portals. Furthermore, photon beams of $\geq$10 MV produce highly carcinogenic photoneutrons through interactions in the linear accelerator head, couch, and patient tissues. This has implications for high-energy IMRT, for which beam-on time is several times longer than for 3D-CRT. Although some authors have reported dosimetric advantages to high-energy IMRT for targets that are deep-seated or within large breasts (5, 6), most studies show little difference, and the practice is not widespread.

The characterization of scattered dose in terms of its constituent components is of interest in radiation oncology because it may lead to improvements in shielding design and dose optimization. Such measurements have been performed for low-energy 3-dimensional conformal radiation therapy (3D-CRT) (4, 7) and IMRT (4). For high-energy 3D-CRT, Chofor et al (8) described phantom versus machine scatter, without differentiating collimator scatter from leakage, but no studies have been performed for high-energy IMRT as far as we are aware. Understanding the impact of such treatment on out-of-field dose is worthwhile given the potential of IMRT to induce second cancers in patients cured of their primary malignancy. In this work we characterize the constituent components of scattered dose for high-energy IMRT compared with 3D-CRT and compare them with their 6-MV counterparts. We also consider the implications for second cancer induction.

Methods and Materials

To compare scatter from 18-MV IMRT with that from 18-MV 3D-CRT, as well as with their 6-MV counterparts, we performed an experiment identical to our previous 6-MV experiment (4) but using 18-MV plans. Unfortunately, using the identical methodology produced excess scatter with 18-MV beams when blocking the treatment aperture, and this part of the experiment was consequently modified as detailed below.

Eighteen-megavolt IMRT and 3D-CRT plans were produced to complement existing 6-MV plans for the same target volume. All plans used 5 fields with identical gantry angles. All provided 95%-107% target coverage with acceptable spinal cord dose. Total monitor units (MUs) delivered per fraction were 241, 240, 742, and 697 for 6-MV 3D-CRT, 18-MV 3D-CRT, 6-MV IMRT, and 18-MV IMRT, respectively. Average field sizes were 36.65 cm^2 and 42.08 cm^2 for 18-MV IMRT and 3D-CRT, respectively, and 36.26 cm^2 and 41.55 cm^2 for 6-MV IMRT and 3D-CRT, respectively.

A 75 $\times$ 30 $\times$ 35-cm water tank was constructed from Perspex, with one end angled to match the divergent beam of a Varian 21EX linear accelerator and filled to a depth of 30 cm. A sliding Perspex clasp fitted along the length of the sidewall held a Farmer-type FC65-P ionization chamber (IBA Dosimetry, Schwarzenbruck, Germany). The chamber was positioned at 10 cm depth, and source-to-surface distance was set at 90 cm. All 5 fields were delivered at gantry angle 0° to coincide with the tank's divergent edge for each measurement position for each plan. The first measurement was performed 10 cm from the central axis (CA;

approximately 5.5 cm from field edge). The chamber was moved in 5-cm increments away from field edge for 4 subsequent measurements and 10 cm for the last 2 measurements. The process was performed using 3 different setup arrangements to separate out the individual contributions from head leakage (L), collimator scatter (C), and internal patient/water scatter (W), as described below (Fig. 1).

To measure the total dose of scattered radiation (head leakage plus collimator scatter plus patient scatter), the water tank was positioned so that the beam passed through the water in the tank to ensure full scatter conditions (Fig. 1a). For the second experiment the tank was moved to align its angled edge with the divergent edge of the primary beam. The beam thus did not pass through or interact with the water in the tank, eliminating the contribution of internal scatter. Resultant dose thus reflected only L+C (Fig. 1b). By subtracting doses obtained in experiment 1b from 1a, internal patient scatter was calculated. The water tank remained in the same position for the third experiment, but the Y-jaws of the secondary collimator parallel to the long axis of the tank were closed and, as in our previous 6-MV experiment, the beam aperture was initially plugged with a lead block (Fig. 1c). The measured dose out of field was thus expected to represent head leakage only (treatment beam being blocked to prevent interaction with the collimator system or with the water in the tank). By subtracting the measurements of 1c from those of 1b, the contribution of collimator scatter was calculated (7).

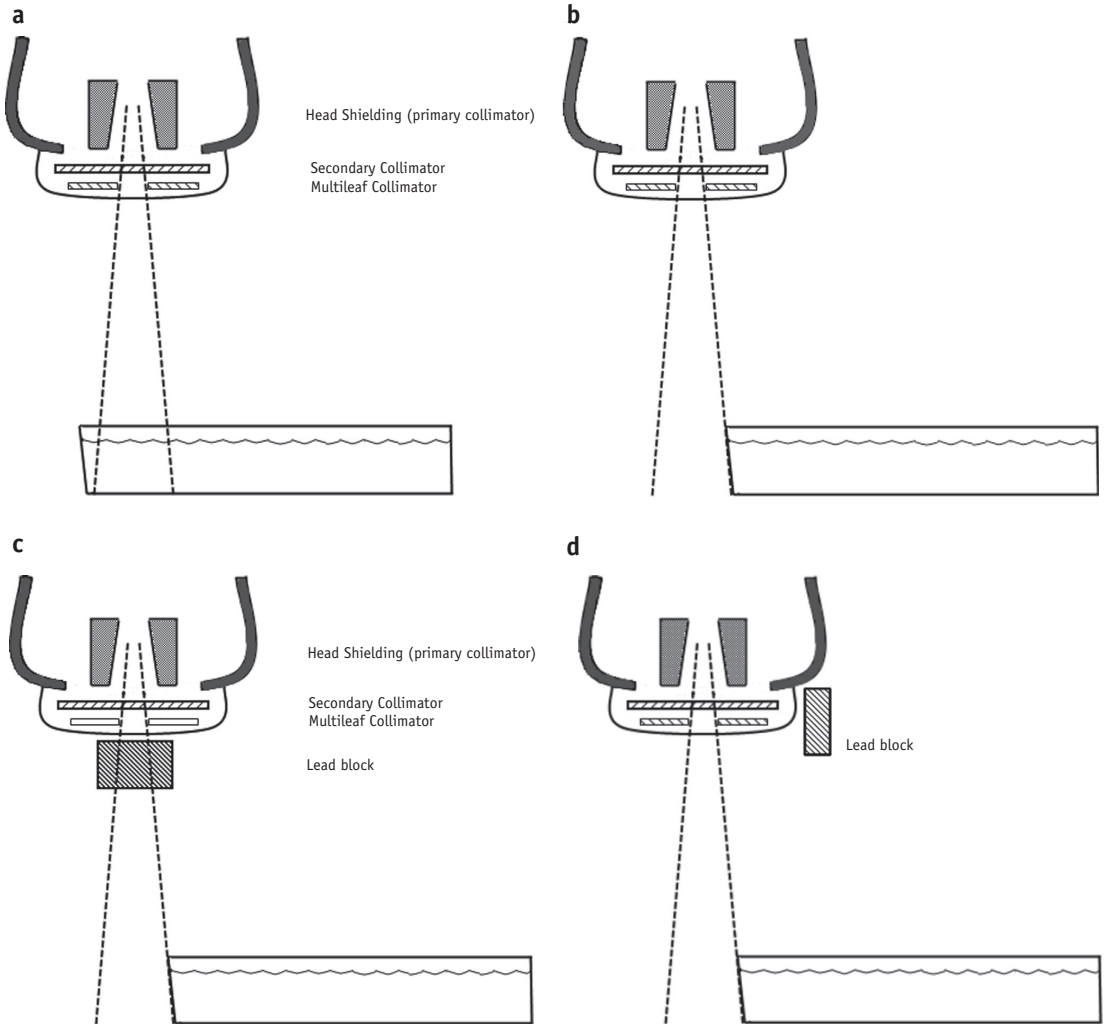

Fig. 1. Experimental setup to measure (a) W+C+L; (b) C+L; (c) L (used for 6-MV measurements but abandoned for 18-MV); and (d) C (used for 18-MV measurements). L, head leakage; C, collimator scatter; W, internal patient/water scatter.

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However, these measurements showed that there was significant scatter from the lead block due to the high-energy photons, which was not the case in our previous 6-MV experiment. The setup was thus modified to circumvent this problem as follows (Fig. 1d). The tank remained in the same position. Lead blocks were placed immediately adjacent to the collimator system and beneath the linear accelerator head to absorb head leakage. This arrangement eliminated both W and L and reflected only scatter emanating from the secondary and multileaf collimators. By subtracting this measurement from those of 1b, head leakage was calculated. Plotted results for each experiment were integrated using Matlab software (Mathworks, Natick, MA).

Identical apparatus and methods were used to measure water and "machine scatter" (C+L) in the current 18-MV experiment and our previous 6-MV experiment (4). The treatment plans for respective photon energies and techniques were highly comparable in terms of field size and MU demand. This allows us to compare W and C+L for low- versus high-energy IMRT and 3D-CRT. However, because of the different methods used to discriminate between head leakage and collimator scatter for the present 18-MV and previous 6-MV experiments, these scatter components cannot be compared between the 2 studies.

Results

18-MV IMRT versus 18-MV 3D-CRT

In Figure 2 we compare 18-MV IMRT with 3D-CRT in terms of overall scattered photon dose as well as individual scatter components.

Total photon scatter dose is 1.7 times higher from 18-MV IMRT compared with 18-MV 3D-CRT (Fig. 2a). This is mainly due to a 2.6-fold increase in collimator scatter (Fig. 2b and c). True head leakage contributes very little (Fig. 2c), with the absolute increase of $<0.001\%$ of CA dose from IMRT being less than the inherent error in experimental setup and measurement.

Internal patient scatter, on the other hand, is reduced by IMRT by 13% (Fig. 2d). Internal scatter predominates for just the first approximately 6 cm from field edge with 18-MV IMRT, compared with approximately 10 cm with 6-MV IMRT (4). This is because of increased collimator scatter from 18-MV IMRT, which contributes most to scattered dose from approximately 6 cm onward (Fig. 2b and e). By contrast, for 18-MV 3D-CRT, internal scatter predominates for 16 cm from field edge (Fig. 2f).

In relative terms, the difference in scattered dose between modalities is modest: approximately 8% close to field edge. Relative increased scatter with IMRT becomes more marked with increasing distance from field edge, approximately 1.6 times greater at 150 mm and 2.6 times greater 300 mm from isocenter. This is because increased collimator scatter from IMRT is mitigated close to the field edge by reduced internal patient scatter relative to 3D-CRT, but the contribution of internal scatter relative to total diminishes over distance. In absolute terms, however, the increase in overall scattered dose is extremely small, approximately 0.1% of CA dose.

Implications for second cancer induction in peripheral tissues

As endorsed by *International Commission on Radiological Protection* report 103 (ICRP 103), we may assume linearity of dose response for second cancer induction at the low doses seen from radiation therapy scatter (9). The average dose to peripheral tissues within 400 mm of field edge is 0.33% and 0.22% of CA dose for IMRT and 3D-CRT, respectively, or 0.23 Gy and 0.15 Gy, respectively, for a 70-Gy course. Multiplying these by the ICRP 103 nominal lethality-adjusted cancer risk coefficient for the "whole population" of 5.5% Sv^{-1} and applying a dose and dose-rate effectiveness factor of 2 as per ICRP 103 recommendations to account for fractionation, predicts a lifetime risk of second cancer induction of approximately 0.64% to distant tissues from IMRT, and 0.40% from 3D-CRT. This must be added to the risk to tissues inside the portal to obtain the whole-body risk. The effect of IMRT on in-field tissues depends on the dose distribution and the dose-response model used and has been considered elsewhere (1, 3, 10, 11).

The second source of risk for cancer induction is from neutron dose. Neutrons have a carcinogenesis weighting factor of up to 21 (9). Acknowledging the difficulties and potential inaccuracies inherent in neutron measurement, recent studies suggest that peripheral neutron dose secondary to 15- to 18-MV IMRT is 1.2-2.3 times higher than with 18-MV 3D-CRT (12-15). The absolute values are very low, however. Thus it is reasonable to assume a linear dose relationship for radiocarcinogenesis in this dose range. The highest ratio of peripheral neutron dose reported by (Howell et al [15]) for IMRT versus 3D-CRT is 2.3 times higher, corresponding to 0.37 Sv versus 0.16 Sv over a 70-Gy radiation therapy course. Applying the whole-body risk coefficient of 5.5% recommended by ICRP 103 predicts a maximal absolute increase in risk to peripheral tissue of approximately 1.2% over 3D-CRT. The same study reports a total body neutron dose 1.6 times higher for 18-MV IMRT versus 3D-CRT.

6-MV versus 18-MV beam energy for 3D-CRT and IMRT

In Figure 3a-c we compare scatter measurements from 18-MV IMRT with those from previous work using 6-MV. Because of differences between the current experiment and the previously reported 6-MV experiment, we can only validly compare 18-MV versus 6-MV in terms of internal patient scatter (W), machine scatter (C+L), and total

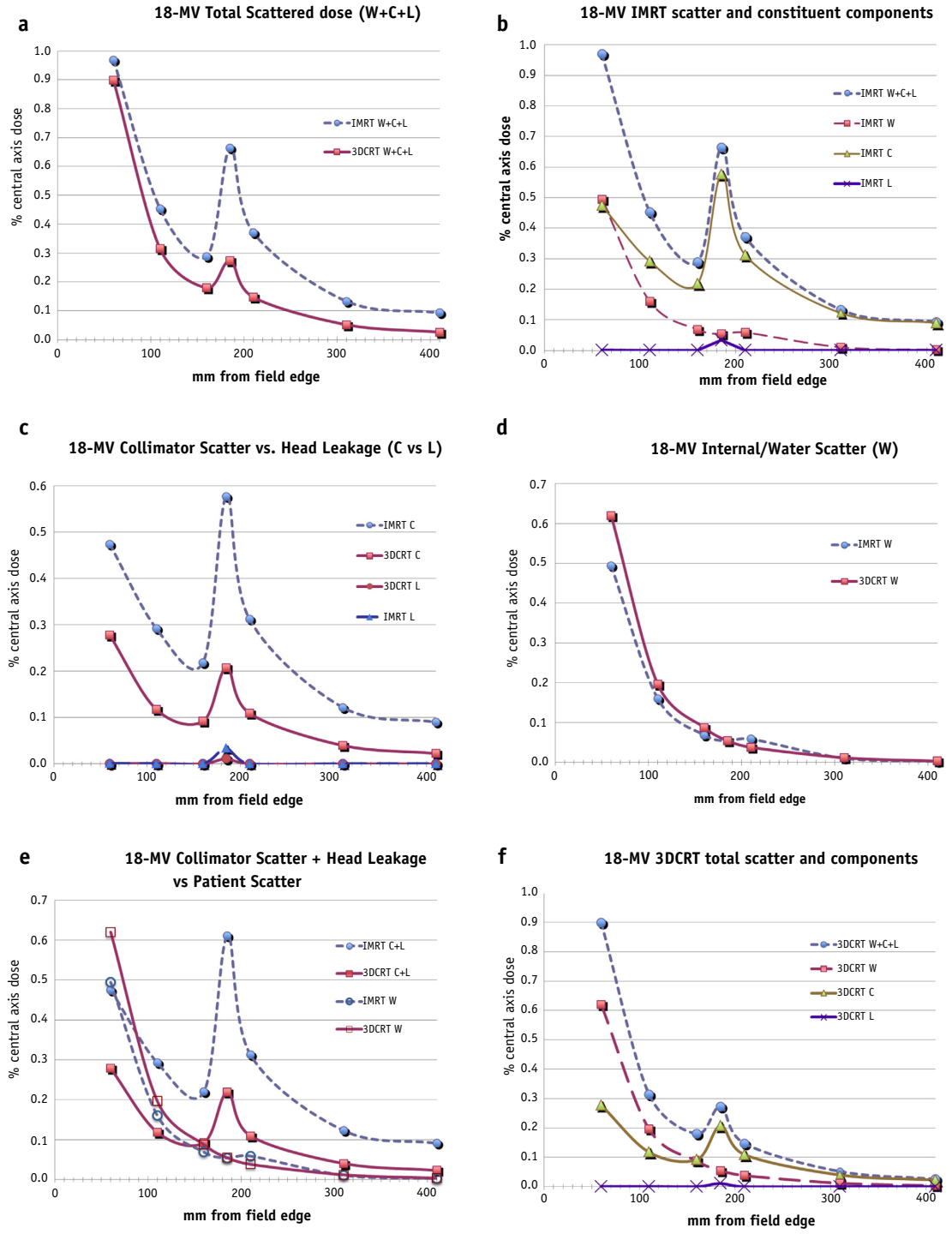

Fig. 2. Eighteen-megavolt intensity modulated radiation therapy (IMRT) versus 3-dimensional conformal radiation therapy (3DCRT): scatter and its constituent components. L, head leakage; C, collimator scatter; W, internal patient/water scatter.

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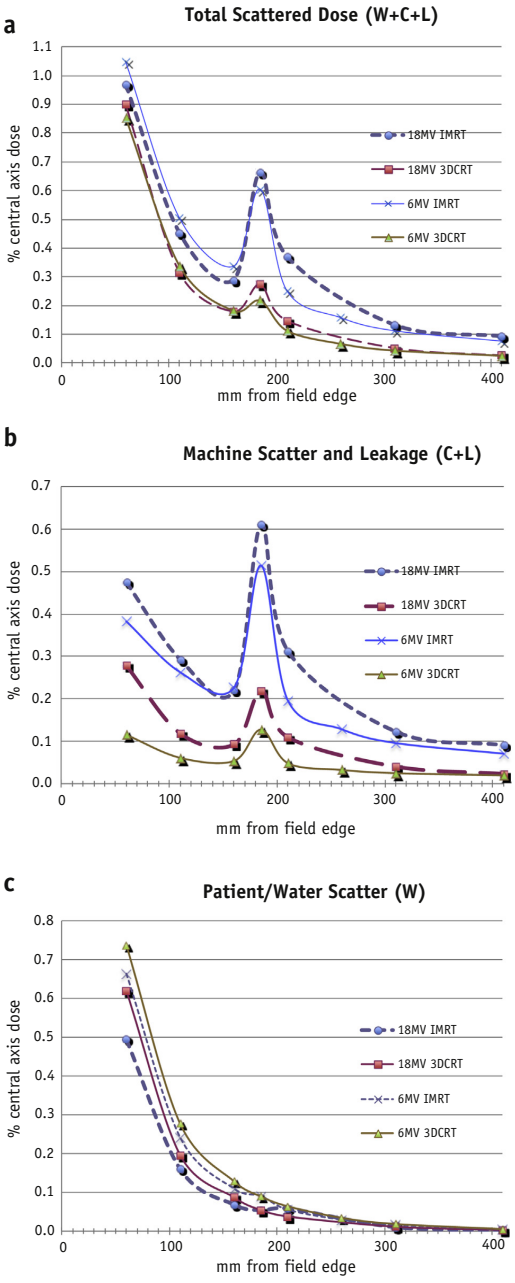

Fig. 3. Eighteen- versus 6-MC and intensity modulated radiation therapy (IMRT) versus 3-dimensional conformal radiation therapy (3DCRT): scatter and its constituent components. L, head leakage; C, collimator scatter; W, internal patient/water scatter.

scattered dose (W+C+L). We cannot compare C or L as individual components.

Figure 3a demonstrates that beam energy does not affect total photon scatter, but technique does. Total scatter remains comparable for the same technique (3D-CRT or IMRT) irrespective of energy, but IMRT generates more total scatter than 3D-CRT. This can be appreciated in quantitative form in Table 1, which tabulates W+C+L versus C+L versus W for each energy and technique using 6-MV 3D-CRT as the reference dose. Table 1 illustrates that compared with 3D-CRT, IMRT increases total scatter by a factor of 1.7 and 1.8 for 18-MV and 6-MV, respectively. Figure 3b and Table 1 illustrate that machine scatter (C+L) is higher with IMRT; and higher for 18-MV than for 6-MV for both treatment techniques (1.2 times higher for IMRT and 1.8 times higher for 3D-CRT). From Table 1, the increased machine scatter with 18-MV versus 6-MV is 1.2 and 1.8 times higher for IMRT and 3D-CRT, respectively, and 4 and 2.6 times higher for 6-MV and 18-MV IMRT versus 3D-CRT, respectively. In contrast, internal patient scatter is reduced by IMRT irrespective of energy and reduced with 18-MV compared with 6-MV for both IMRT and 3D-CRT (Fig. 3c). From Table 1, the reduction is 13% and 11% for 18-MV IMRT and 6-MV IMRT, respectively. The reduction in internal scatter with 18-MV versus 6-MV is 27% for 3D-CRT and 29% for IMRT. The effects of different techniques and beam energies on the components of peripheral scatter are summarized in Tables 2 and 3.

Internal scatter predominates for just 6 cm from beam edge for 18-MV IMRT, compared with 25 cm for 6-MV. This is because of the increased collimator scatter with 18 MV that dominates from 6 cm onward and contributes 75% of total photon scatter.

6 versus 18 MV: Implications for second cancer induction

Photon scatter from18-MV 3D-CRT is not clinically significantly different from 6-MV 3D-CRT, but 18-MV IMRT increases 6-MV 3D-CRT risk 1.8 times. This may,

Table 1 Total out-of-field dose and contribution of individual components relative to 6-MV 3D-CRT

Voltage	W+C+L	C+L	W
6-MV			
3D-CRT	1.00*	0.29	0.71
IMRT	1.78	1.16	0.63
18-MV			
3D-CRT	1.05	0.52	0.52
IMRT	1.79	1.34	0.45

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; C = collimator scatter; C+L = machine scatter; IMRT = intensity modulated radiation therapy; L = head leakage; W = internal patient/water scatter; W+C+L = total scattered dose.

* 6-MV 3D-CRT is the reference dose and represented as unity.

Table 2 Differences in out-of-field scatter between energies and techniques

Variable	W+C+L	W	C+L (machine scatter)	C	L
18-MV IMRT	1.7 × higher than 18-MV 3D-CRT but comparable to 6-MV IMRT	13% lower than 18-MV 3D-CRT and 29% lower than 6-MV IMRT	1.2 × higher than 6-MV IMRT, and 2.6 × higher than 18-MV 3D-CRT	2.6 × higher than 18-MV 3D-CRT	Comparable to 18-MV 3D-CRT
6-MV IMRT	1.8 × higher than 6-MV 3D-CRT	11% lower than 6-MV 3D-CRT	4 × higher than 6-MV 3D-CRT	Not compared with 18-MV	
18-MV 3D-CRT	Comparable to 6-MV 3D-CRT	27% lower than 6-MV 3D-CRT	1.8 × higher than 6-MV 3D-CRT	Not compared with 6-MV	
6-MV 3D-CRT	Reference technique				

Abbreviations as in Table 1.

however, be compensated for through improved dose conformity and lower doses to in-field organs (10, 15).

Regarding photoneutrons, the whole-body neutron dose for a 35-fraction course of radical IMRT is reported as 0.05-0.47 Sv (10, 14-16). The corresponding increase in second cancer induction is approximately 0.28%-2.6% compared with 6-MV, where no photoneutron production occurs. Considering peripheral tissues only, the corresponding risk for 18-MV IMRT is approximately 0.28%-2.2% versus 0 for 6-MV (14, 15, 17).

Discussion

Both 18-MV IMRT and 3D-CRT produce less internal/patient scatter than their 6-MV counterparts. This is rational because scatter vectors for higher-energy photons remain closer aligned to their original direction of motion than lower-energy photons, which are more prone to lateralized scatter out of field. It is also rational that machine scatter is greater for 18-MV beams for both techniques, as observed, because higher-energy photons are less readily attenuated by the collimator system and so are more likely to reach out-of-field tissue. It seems that the reduction in internal scatter from 18-MV relative to 6-MV IMRT (25% vs 35% of total) is counterbalanced by increased collimator scatter (75% vs 65% of total). The net result is that the total out-of-field dose is closely comparable between low- and high-energy IMRT.

Possible explanations for the reduced internal scatter from IMRT include the smaller field sizes required for coverage of the same target volume compared with 3D-CRT (18), as well as the shielding of portions of the field by the moving multileaf collimator leaves for part of the beam-on time. Machine scatter is markedly increased with IMRT, roughly proportional to the increased MU demand. Out-of-field dose with IMRT relative to 3D-CRT increases with decreasing field size, increasing MU inefficiency, increasing distance from field edge, and diminishing depth of measurement (4).

Although neutron dose is low relative to photons, neutrons are particularly important from a carcinogenic perspective, carrying a weighting factor as high as 21 compared with photons (9). Intensity modulated radiation therapy produces more neutrons than 3D-CRT—roughly proportionate to MU demand. This is due to the increase in IMRT beam-on time, possibly exacerbated by increased interaction of primary beam photons with the multileaf collimator leaves. Accurate assessment of effective neutron dose is extremely difficult owing to uncertainties about neutron energy spectra and the specificity, sensitivity, and accuracy of neutron dosimeters. As a result there is significant variation in published results and general scepticism in accepting any as completely reliable. Linear accelerators from different manufacturers produce varying proportions of photoneutron contamination (13, 17).

Taken as a whole, several recent studies suggest that peripheral neutron dose secondary to 15- to 18-MV IMRT is 1.2-2.3 times higher than with 18-MV 3D-CRT (12-15). Peripheral neutron doses may be in the range of 4.7-11 μSv/MU (13, 14) or 5.2-5.4 mSv/Gy of prescribed dose (15,

Table 3 Effect of treatment technique (irrespective of beam energy) and beam energy (irrespective of technique) on the components of out-field-scatter

Comparison	W+C+L	W	C	L	C+L
IMRT vs 3D-CRT	Increased with IMRT	Reduced with IMRT	Increased with IMRT	Comparable (for 18-MV)*	Increased with IMRT
6-MV vs 18-MV	No difference	Reduced with 18-MV	—	—	Increased with 18-MV

Abbreviations as in Table 1.
* Leakage <0.001% of central axis dose higher with 18-MV IMRT versus 18-MV 3D-CRT.

17) or 0.04-0.43 Sv over a 70-Gy IMRT course (10, 12, 14, 15, 17). If these values are correct, then out-of-field neutron dose is low and of modest clinical significance. Although neutron dose may be higher within the primary beam, this finding is inconsistent and relatively modest (2, 10, 14, 15). In-field neutron doses of 0.05-0.47 Sv over a treatment course have been reported for 15- to 18-MV IMRT (10, 14-16), and according to reported measurements, the whole-body neutron dose for a 35-fraction course of IMRT is similarly 0.05-0.47 Sv (10, 12-14, 16, 19). Even if we consider the highest of these point doses reported, corresponding to 0.47 Sv over a 72-Gy IMRT course (15), it is evident that neutron dose from high-energy IMRT may not be as clinically significant as previously feared. On the basis of this highest reported point dose and assuming the maximum reported increase in neutron point dose for IMRT relative to 3D-CRT of 2.3 (15), using ICRP 103 risk coefficient of 5, 5% Sv^{-1} (9), the extra 0.22-Sv neutron dose would carry a lifetime risk of second cancer induction of approximately 1.1% over and above 18-MV 3D-CRT. Compared with 6-MV radiation therapy, neutrons may add up to 2.5% excess risk, although at least 2 studies incorporating both photon and neutron contributions have calculated a comparable or lower overall cancer risk from 15- to 18-MV versus 6-MV IMRT despite their additional photoneutron dose (10, 15). This was because the photon dose to in-field organs was reduced with higher-energy IMRT, which compensated for the additional neutron risk. The phenomenon seemed to be magnified when comparing IMRT with 3D-CRT, whereby the relative risks were even lower with IMRT regardless of energy (15). The maximum measured neutron point dose used for the above calculations is unlikely to represent the true overall body dose, which is more likely between 0.05 and 0.39 Sv (10, 12-14, 16) and corresponds to 0.28%-2.15% absolute risk. Because observed results suggested second cancer risks of only 1.4%, values toward the lower end of this range are more likely correct than higher ones (20). Our neutron estimates are in keeping with the published literature reviewed by Takam et al (21), and the maximum risk is also congruent with Chibani et al, whose risk estimate of 2% is based on the highest (calculated) neutron dose published (21, 22). Although scattered dose (photon and neutron) is low, increasing work suggests the possibility that bystander effects may play a role in carcinogenesis and bystander effects are highest in the scatter dose range (23). Bystander radio-carcinogenic mechanisms are not considered proven by ICRP 103, and because ICRP risk coefficients are based mostly on observed data, they incorporate all involved mechanisms anyway.

Conclusions

IMRT increases overall scatter compared with 3D-CRT for both 18 and 6 MV—by a factor of 1.7 and 1.8, respectively—despite reducing internal scatter. This is because collimator scatter is disproportionately higher for IMRT and outweighs the reduction in internal scatter. The effect of head leakage on out-of-field dose seems to be minimal.

The effect of intensity modulation on out-of-field scatter for 18-MV energy is similar to that for 6 MV, but 18-MV IMRT further reduces W while further increasing C+L. These 2 phenomena effectively compensate for each other though, so that the total out-of-field photon dose remains relatively constant and essentially independent of beam energy. This is the case for 3D-CRT as well.

Effective neutron dose from 18-MV IMRT is likely to be <0.5 Sv. This corresponds to a maximal possibly increased total body cancer risk of approximately 0.28%-2.59% compared with 6-MV IMRT. In terms of cancer risk to peripheral tissues, 18-MV IMRT neutron risks are 1.2-2.3 times higher than with 3D-CRT; this is in addition to the 1.7 times higher risk from higher out-of-field photon doses. Eighteen-megavolt IMRT would thus be expected to increase second cancer risk in peripheral tissue over 18-MV 3D-CRT, although absolute values are small. This increase out of field seems to be offset by reductions in dose to organs at risk within the field, however, so the net whole-body risk might actually be reduced or only modestly increased (10, 15).

Ultimately, given the uncertainties around neutron dosimetry and radio-carcinogenic dose response to in-field doses, no firm conclusions can be drawn, and a potentially increased risk of second cancer induction from 18-MV IMRT cannot be excluded. This possibility should be weighed against any dosimetric benefit IMRT may provide.

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Chapter 5

Effect of Intensity-Modulated Pelvic Radiotherapy on Second Cancer Risk in the Postoperative Treatment of Endometrial and Cervical Cancer

Building on chapter one, this chapter investigates the dosimetric and carcinogenic implications of IMRT in the gynaecological setting using a finessed method for in-field risk calculation.

The chapter is framed in terms of its background context and relationship to preceding thesis chapters on page thirteen of chapter one. As noted there, the findings of this chapter are even more relevant today than when they were first published given the subsequent publication of RTOG 0418. RTOG 0418 was a phase II trial examining adjuvant pelvic IMRT in high-risk gynaecological settings. Its positive outcomes included both favourable toxicity and tumour control, and hence IMRT is now more widely adopted in this clinical context. This makes the findings of the present chapter more widely applicable and clinically relevant than ever [54,55].

The footnote to the title page of the resultant publication acknowledges the equal first author contributions of my friend and colleague Dr. Daniel R. Zwahlen and myself to the paper.

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BIOLOGY CONTRIBUTION

EFFECT OF INTENSITY-MODULATED PELVIC RADIOTHERAPY ON SECOND CANCER RISK IN THE POSTOPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

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Purpose: To estimate and compare intensity-modulated radiotherapy (IMRT) with three-dimensional conformal radiotherapy (3DCRT) in terms of second cancer risk (SCR) for postoperative treatment of endometrial and cervical cancer.

Methods and Materials: To estimate SCR, the organ equivalent dose concept with a linear-exponential, a plateau, and a linear dose–response model was applied to dose distributions, calculated in a planning computed tomography scan of a 68-year-old woman. Three plans were computed: four-field 18-MV 3DCRT and nine-field IMRT with 6- and 18-MV photons. SCR was estimated as a function of target dose (50.4 Gy/28 fractions) in organs of interest according to the International Commission on Radiological Protection

Results: Cumulative SCR relative to 3DCRT was +6% (3% for a plateau model, −4% for a linear model) for 6-MV IMRT and +26% (25%, 4%) for the 18-MV IMRT plan. For an organ within the primary beam, SCR was +12% (0%, −12%) for 6-MV and +5% (−2%, −7%) for 18-MV IMRT. 18-MV IMRT increased SCR 6–7 times for organs away from the primary beam relative to 3DCRT and 6-MV IMRT. Skin SCR increased by 22–37% for 6-MV and 50–69% for 18-MV IMRT inasmuch as a larger volume of skin was exposed.

Conclusion: Cancer risk after IMRT for cervical and endometrial cancer is dependent on treatment energy. 6-MV pelvic IMRT represents a safe alternative with respect to SCR relative to 3DCRT, independently of the dose–response model. 18-MV IMRT produces second neutrons that modestly increase the SCR. © 2009 Elsevier Inc.

Cervical cancer, Endometrial cancer, Second cancers, Intensity-modulated radiotherapy, Comparative treatment planning.

INTRODUCTION

Postoperative radiotherapy (RT) is recommended in endometrial and cervical cancers if findings in the surgical specimen indicate a high risk of pelvic recurrence. Randomized trials have demonstrated that whole-pelvic RTafter hysterectomy reduces the rate of pelvic recurrence (1, 2).

Traditional whole-pelvic RT, commonly delivered in a four-field technique, irradiates large volumes of organs at risk (OAR), such as rectum, bladder, bone marrow, and small bowel, which tend to fall into the space left after hysterectomy. This increases the risk of bowel toxicities (3, 4) and limits the dose that can be delivered to target structures.

In 2006, the Radiation Therapy Oncology Group (RTOG) commenced prospective trial (RTOG 0418) evaluating postoperative pelvic intensity-modulated RT (IMRT) in endometrial and cervical cancer. Consensus guidelines for delineation of the clinical target volume (CTV) were published (5). The IMRT reduces doses to OAR significantly and decreases rates of gastrointestinal and hamatologic toxicities (6). Another potential benefit may be the ability to dose-escalate while minimally increasing toxicity to the OAR (7). This may translate into improved local tumor control and increasing cancer cure rates, and hence larger numbers of long-term cancer survivors are expected.

Second cancers may be a consequence of more successful primary cancer cure, and Chaturvedi *et al.*(8) showed that after RT, long-term survivors of cervical cancer presented with increased second cancer risk (SCR).

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There are several reasons why IMRT may increase SCR relative to three-dimensional conformal RT (3DCRT) (9). First, a change from 3DCRT to IMRT involves more fields, and therefore a larger volume of normal tissue is exposed. Second, IMRT requires a longer beam-on time because more monitor units (MU) are needed (10). Patient dose may increase because of head leakage and collimator scatter (9, 11). Third, the dose from secondary neutrons produced with photon energies >10 MV contributes to integral dose and increases carcinogenic risk (9, 10, 12). Secondary neutron production is greater for 18-MV IMRT than for 3DCRT (13).

The aim of this study was to estimate the SCR for pelvic IMRT compared with 3DCRT in the postoperative treatment of gynecologic cancers using consensus guidelines for CTV definition (5).

METHODS AND MATERIALS

Treatment planning

After ethics approval, a 68-year-old woman, weighing 65 kg after total abdominal hysterectomy and bilateral salpingo-oophorectomy, underwent a planning computed tomography (CT) scan that included the neck, chest, abdomen, pelvis, and proximal lower extremities. The CTV was contoured according to the recommendations of the RTOG 0418 published by Small *et al.* (5). The CTV included the common, external, and internal iliac lymph nodes and the presacral lymph nodes (approximately 1–2 cm of tissue anterior to the S1, S2, and S3 segments), as recommended for patients with cervical cancer, or endometrial cancer with cervical stromal invasion. Bone and small bowel were excluded from the CTV.

The 18-MV 3DCRT consisted of a standard four-field technique (anteroposterior, posteroanterior, and two lateral fields). Both 6-MV and 18-MV IMRT plans were produced, and they used a dynamic multileaf collimator technique (sliding window) using nine equispaced fields. Five- and seven- field plans were abandoned because of significant hotspots. The dose prescribed was 50.4 Gy, at 1.8 Gy per fraction to the isodose encompassing at least 97% of the planning target volume. The field limits used for IMRT were defined as follows (5): CTV upper border, 7 mm below the L4/L5 interspace; CTV lower border, 1 cm above the inferior extent of the obturator foramen. For the planning target volume, a 7-mm margin was added around the CTV.

Photon dose distributions for both 3DCRT and IMRT were calculated using the Pencil Beam Convolution 7310 algorithm (Eclipse External Beam Planning Software 6.5, Varian Medical Systems, Palo Alto, CA). Differential dose volume histograms (DVHs) were generated for the whole CT-stack. For distant tissues not included in the CT scan, a homogeneous dose bath of phantom scatter, collimator scatter, and neutron dose was assumed. Photon scatter dose was estimated from measured data at a point 50 cm away from the center of a 10- × 10-cm treatment field at a depth of 10 cm (14). Measured neutron dose data on medical electron accelerators were taken from d'Errico *et al.* (15). Photon scatter and neutron dose were weighted with the applied MU for each treatment plan.

Calculation of risk estimates

Calculations of SCR are based on effective dose (16) (sum of the equivalent doses in all specified tissues and organs of the body, each multiplied by its respective tissue weighting factor). The calculation of effective dose, however, is based on the premise of low doses and homogenous dose distributions, neither of which is applicable to RT. Doses to nearby organs are high and heterogeneous; thus, simple dose averaging in organs of interest is not a valid method of obtaining an effective dose. In this work we used the concept of organ equivalent dose (OED) to organs of interest, to calculate a realistic effective dose that would more accurately reflect carcinogenic risk than one relying only on an average dose to each organ. The OED is derived from the DVH and is proportional to SCR (17). The OED is an overall organ dose derived from the sum of homogenous dose voxels within the organ, weighted with an appropriate dose–response relationship for radiation-induced cancer and divided by the total organ volume. The major uncertainty in using this method is the dose–response relationship for carcinogenesis at higher doses (18). For doses <2 Gy, the linear-no-threshold model applies with good precision. For doses >2 Gy, two extreme possibilities exist for the shape of the dose–response curves: the curve remains linear (19), or the curve decreases linearly-exponentially with increasing dose, owing to cell kill at higher doses (17, 18, 20). A plateau dose–response model was included, which lies midway between the other two, accounting for repopulation effects from fractionation (20, 21).

In Table 1, the organs of interest with the corresponding tissue weighting factors ω_T and CT volumes are reported according to the 2007 recommendations of the International Commission on

Table 1. Organs of interest according to ICRP 2007 with the corresponding tissue weighting factors and volumes

Organ/tissue	Volume in CT (cm^3)	Volume out CT (cm^3)	Volume total (cm^3)	Weighting factor ω_T
Bone marrow	1301.3	775.9	2077.2	0.12
Colon	399.6	0	399.6	0.12
Lung	3121.9	0	3121.9	0.12
Stomach	238.9	0	238.9	0.12
Breast	930.1	0	930.1	0.12
Remainder tissues	25787.5	15376.8	41164.3	0.12
Bladder	40.5	0	40.5	0.04
Esophagus	15.7	0	15.7	0.04
Liver	1340.2	0	1340.2	0.04
Thyroid gland	6.8	0	6.8	0.04
Brain	-	-	-	0.01
Skin	2945.3	1756.2	4701.5	0.01
Salivary glands	-	-	-	0.01
Bone surface	5.1 m^2	3.0 m^2	8.1 m^2	0.01

Abbreviations: ICRP = International Commission on Radiological Protection; CT = computed tomography.

Table 2. Absolute and relative OED with 3DCRT and IMRT for the organs of interest according to ICRP 2007 for a linear, plateau and linear-exponential dose–response model

		Absolute OED (Gy)			Relative OED (3DCRT=1)	
Organ/Tissue	Model	3DCRT	6-MV IMRT	18-MV IMRT	6-MV IMRT	18-MV IMRT
Bone marrow	Linear	7.391	7.568	7.896	1.02	1.07
	Plateau	1.724	1.721	2.059	1.00	1.19
	Linear-exponential	1.805	1.751	2.092	0.97	1.16
Colon	Linear	15.687	14.741	15.045	0.94	0.96
	Plateau	4.534	4.553	4.607	1.00	1.02
	Linear-exponential	5.172	5.233	5.273	1.01	1.02
Lung	Linear	0.102	0.107	0.652	1.05	6.40
	Plateau	0.101	0.107	0.624	1.05	6.17
	Linear-exponential	0.101	0.107	0.634	1.05	6.25
Stomach	Linear	0.341	0.421	0.722	1.23	2.12
	Plateau	0.332	0.404	0.687	1.22	2.07
	Linear-exponential	0.335	0.410	0.699	1.22	2.09
Breast	Linear	0.105	0.107	0.652	1.02	6.23
	Plateau	0.104	0.106	0.624	1.02	6.00
	Linear-exponential	0.104	0.107	0.634	1.02	6.08
Remainder tissues	Linear	6.329	7.091	7.119	1.12	1.12
	Plateau	2.000	2.268	2.508	1.13	1.25
	Linear-exponential	2.237	2.568	2.820	1.15	1.26
Bladder	Linear	47.940	42.411	44.386	0.88	0.93
	Plateau	7.181	7.155	7.052	1.00	0.98
	Linear-exponential	5.810	6.511	6.079	1.12	1.05
Liver	Linear	0.229	0.221	0.670	0.97	2.93
	Plateau	0.225	0.216	0.639	0.96	2.85
	Linear-exponential	0.226	0.218	0.650	0.96	2.87
Esophagus	Linear	0.107	0.107	0.652	1.00	6.09
	Plateau	0.106	0.106	0.624	1.00	5.87
	Linear-exponential	0.106	0.106	0.634	1.00	5.95
Thyroid	Linear	0.091	0.107	0.652	1.18	7.17
	Plateau	0.090	0.106	0.624	1.17	6.90
	Linear-exponential	0.091	0.106	0.634	1.18	7.00
Skin	Linear	1.558	2.131	2.331	1.37	1.50
	Plateau	0.821	1.003	1.388	1.22	1.69
	Linear-exponential	0.947	1.158	1.551	1.22	1.64
Bone surface	Linear	7.391	7.568	7.896	1.02	1.07
	Plateau	1.724	1.721	2.059	1.00	1.19
	Linear-exponential	1.805	1.751	2.092	0.97	1.16
Brain	Linear	0.091	0.107	0.652	1.18	7.17
	Plateau	0.090	0.106	0.624	1.17	6.90
	Linear-exponential	0.091	0.106	0.634	1.18	7.00
Salivary glands	Linear	0.091	0.107	0.652	1.18	7.17
	Plateau	0.090	0.106	0.624	1.17	6.90
	Linear-exponential	0.091	0.106	0.634	1.18	7.00

Abbreviations: OED = organ equivalent dose; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; ICRP = International Commission on Radiological Protection.

Radiological Protection (ICRP) (16). The tissue-weighting factor ω_T is the factor by which the equivalent dose to each organ is weighted to represent the relative contribution of that organ to the total cancer risk. According to the 2007 ICRP recommendations, ω_T for breast has been increased from 0.05 to 0.12, and two more tissues (brain and salivary glands) have been included. Calculations were adjusted for incompletely scanned organ volumes (bone, bone marrow, skin, brain, salivary glands, and ''remainder tissues''). The DVHs of radiosensitive ICRP organs were calculated using the computed dose distribution in the CT scan. The DVHs were then convoluted with the three different dose–response models, and separate OED for ICRP organs were obtained in the following fashion:

The linear dose–response model, which is the conventional way to obtain the average organ dose:

$$OED_T = \frac{1}{V_T}\sum_i DVH(D_i)D_i \quad (1)$$

where *DVH* (D_i) is the volume that corresponds to the dose D_i and the summation is done for all voxels of organ T of volume V_T.

The OED for the linear-exponential dose–response curve is calculated from the DVH as follows:

$$OED_T = \frac{1}{V_T}\sum_i DVH(D_i)D_i\, e^{-\alpha D_i} \quad (2)$$

where $\alpha = 0.044$ Gy^{-1} (22).

For a plateau dose–response relationship with α model parameter $\delta = 0.139$ Gy^{-1} the OED is as follows:

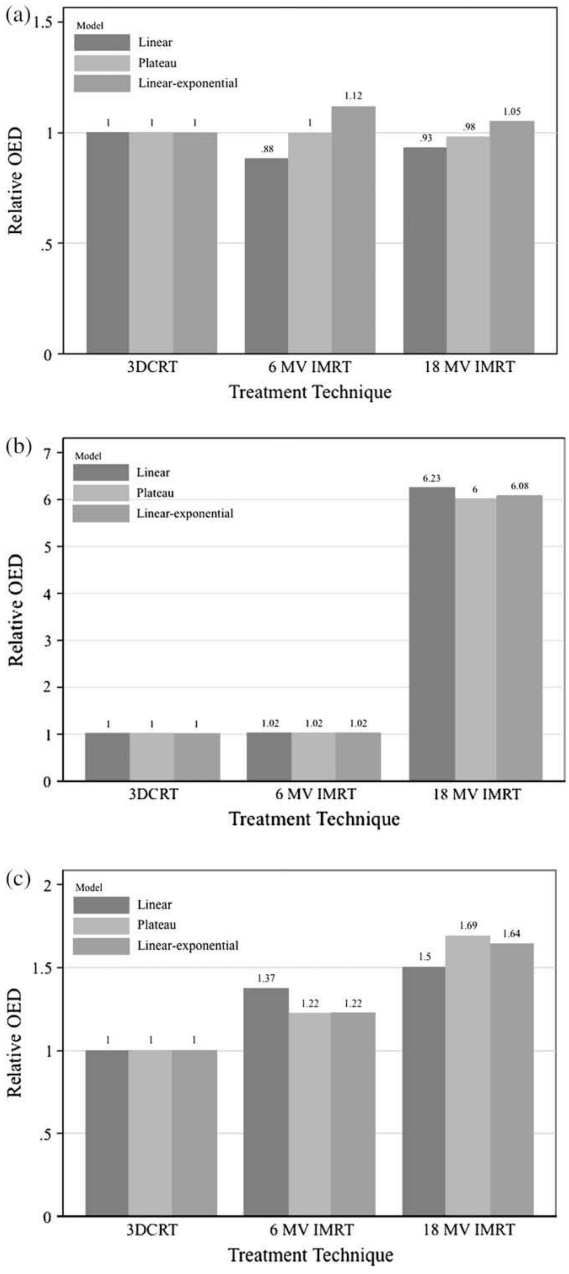

Fig. 1. Relative organ equivalent doses (OED) for (a) bladder, (b) breast, and (c) skin as function of three-dimensional conformal radiotherapy (3DCRT), 6-MV intensity-modulated radiotherapy (IMRT), or 18-MV IMRT technique using linear, plateau, and linear-exponential dose–response model.

$$OED_T = \frac{1}{V_T}\sum_i DVH(D_i)\left(1 - e^{-\delta D_i}\right)/\delta \qquad (3)$$

The model parameters α and δ were estimated from a combined fit to the Japanese A-bomb and Hodgkin cohorts (22).

The effective OED, which is directly proportional to whole-body SCR, is calculated by summing up the OED in the various organs of interest (OED_T) multiplied by their corresponding weighting factors ω_T, as recommended in the ICRP report 103 (16).

$$effective\ OED = \sum_T \omega_T\ OED_T \qquad (4)$$

RESULTS

Table 2 shows absolute OED in organs of interest for 3DCRT and IMRT plans using the linear, plateau, or linear-exponential dose–response model. For each model, the relative OED compared with the OED of the 3DCRT plan is depicted. Figure 1a demonstrates the relative OED for the bladder, an organ of interest close to the primary beam. Compared with 3DCRT, the linear dose–response model indicates a decrease in SCR of 12% and 7% for 6-MV and 18-mV IMRT, respectively, whereas the linear-exponential model shows increases of 12% and 5%. Applying the plateau dose–response model, a 2% decrease in SCR is noticed for 18-mV IMRT. Figure 1b demonstrates the relative OED for breast, an organ of interest far away from the treatment volume. All three dose–response models show that 6-MV IMRT increases the SCR by 2% relative to 3DCRT. The SCR is increased sixfold using 18-MV IMRT, most likely because of increased second neutron production. Similar findings were noted for lung, esophagus, thyroid, brain, and salivary glands (Table 2). Figure 1c shows the different relative OED for skin for all three dose–response models. The 6-MV IMRT increased OED by 22–37% relative to 3DCRT depending on the dose–response model used. The 18-mV IMRT increased the relative OED by 50–69%. This reflects the fact that a larger volume of skin is exposed when using IMRT. To indicate the whole-body SCR for the different treatment plans, the absolute and relative effective OED, which is the tissue-weighted sum of the OED in all specified organs of interest according to ICRP, are listed in Table 3. When 6-MV IMRT was compared with 3DCRT, a 3–6% increase in the effective OED was found for the plateau and the linear-exponential dose–response model. Using the linear dose–response model, the effective OED for 6-MV IMRT relative to 3DCRT was −4%. When 18-MV IMRT was compared with 3DCRT, increases of 25% and 26% were evident for the plateau and linear-exponential dose–response relationship models, respectively (Fig. 2).

DISCUSSION

Our results show that the SCR from postoperative pelvic IMRT for endometrial and cervical cancer is dependent on treatment energy (Fig. 2). The 6-MV IMRT increases SCR by only 3–6%, but up to 26% for 18-MV IMRT (exponential dose–response relationship). Although 18-MV photon energy is often avoided because of the production of second neutrons (23), an optimized 6-MV pelvic IMRT plan represents a safe alternative with respect to SCR. Provided sufficient 6-MV beams are used, dosimetry is not adversely affected (24). It should be borne in mind that the overall risks

Table 3. Absolute and relative effective OED (whole body) with 3DCRT and IMRT for a linear, plateau, and linear-exponential dose–response model

	Absolute effective OED (Sv)			Relative effective OED (3DCRT=1)	
Model	3DCRT	6-MV IMRT	18-MV IMRT	6-MV IMRT	18-MV IMRT
Linear	5.620	5.417	5.820	0.96	1.04
Plateau	1.387	1.432	1.737	1.03	1.25
Linear-exponential	1.449	1.530	1.827	1.06	1.26

Abbreviations: OED = organ equivalent dose; Sv = Sievert; 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; ICRP = International Commission on Radiological Protection.

of a radiation-induced cancer are low in absolute terms, and a relative increase of 3–6% (6-MV IMRT) or even 25% (18-MV IMRT) represents a <1% increase in absolute risk (25). The difference in SCR between the two energies is significantly lower than estimates from other studies (26) and might be not clinically significant.

Epidemiologic studies demonstrate that pelvic RT increases the SCR (8, 25, 27, 28). Extrapolating these results to pelvic IMRT is not possible, given the differences in dose distribution, MU requirements, and scattered radiation dose between 3DCRT and IMRT. Because IMRT is a relatively new technique, and radiation-induced second cancers are a late event, clinical studies addressing SCR from IMRT have not yet been performed, to our knowledge. There is thus debate about the carcinogenic risks for IMRT vs. 3DCRT (9, 10, 29–31). Predictive models for SCR must be used because risk estimation is imprecise, owing to the uncertainty of the radiation dose–response curve for therapeutic doses >2 Gy (18). Some modeled estimates of SCR from pelvic IMRT have concluded that SCR doubles in comparison with 3DCRT (10, 18). However, those estimates were based on a linear dose–response relationship model and considered only the scattered low doses to distant tissues while ignoring the high and moderate doses to tissues in and around the primary beam (20, 29, 32, 33). Such estimates based only on scattered radiation (and neutrons) tend to overestimate SCR (30). The SCR model used in the present work is thus based on the concept of OED (17), which incorporates the contribution from the primary beam because most second malignancies occur within or adjacent to high dose regions (8, 25, 34). In addition, OED also accounts for the ''out-of-field'' low dose because SCR is body wide. Last, in addition to the linear model, we included a linear-exponential and a plateau dose–response function for therapeutic doses >2 Gy, because at greater doses cell killing and sterilization of already mutated cells becomes important, and the linear-no-threshold model tends to overestimate SCR (18, 19, 22).

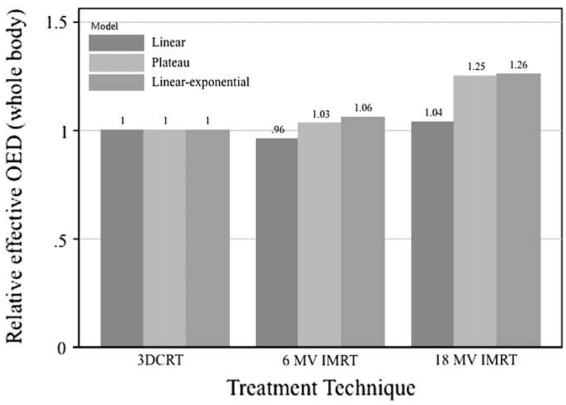

Fig. 2. Relative effective organ equivalent doses (OED) (whole body) as function of three-dimensional conformal radiotherapy (3DCRT), 6-MV intensity-modulated radiotherapy (IMRT), or 18-MV IMRT technique using linear, plateau, and linear-exponential dose–response model.

We could not demonstrate that IMRT doubled or tripled SCR in comparison with 3DCRT, as reported by others (9, 10, 35). The estimated variation in SCR with 6-MV IMRT was between −4% and +6%, depending on the dose–response model applied (Table 3). This is despite the unavoidably higher head leakage with 6-mV IMRT caused by higher MU demand. Ruben *et al.* (29) demonstrated similar findings and hypothesized that smaller field size and reduced average field intensity with IMRT reduced internal patient scatter more than enough to compensate for any increase in head leakage. Others have reached similar conclusions when SCR estimates included the body in totality (31). With 18-MV IMRT, SCR varied between 4% and 26%. This is attributable to the large increase in MU with IMRT and a consequential increase in secondary neutrons, which is proportional to the total MU demand (36).

Most second cancers occur in organs adjacent to or near the target volume (8, 9, 25, 34). In our study, little if any increase in SCR was found for both bladder and colon (Table 2). The 6-MV IMRT did not increase bladder SCR (Fig.1a) in comparison with 3DCRT (plateau dose–response model), and for 18-MV IMRT the SCR was even lower because of improved dose conformality (37). Therefore, for organs adjacent to or near the target volume, there was no detriment with IMRT because of better dose conformation within the target volume. For organs distant from the primary beam, SCR is mainly due to neutron dose and photon scatter. These tissues may be represented in our study by the breast (Fig.1b). Here, 6-MV IMRT increased SCR marginally despite a greater MU requirement compared to 18-MV 3DCRT. This indicates that SCR with 18-MV 3DCRT must be mainly due to the production of secondary neutrons, and that any increase in head

leakage and collimator scatter from 6-MV IMRT is less relevant. It is also likely that 6-MV IMRT reduces internal patient scatter, which is the main component of dose <18 cm from the field edge (11, 38). With 18-MV IMRT, however, the SCR increases by a factor of 6. This is largely due to the longer beam-on time with IMRT and the associated increase in photoneutron production. Followill *et al*. (35) arrived at a similar risk estimate for a point 50 cm from the center of a pelvic field, and concluded that the magnitude of such risk was directly dependent on photoneutron production.

Kry *et al*. (10) reported a twofold to threefold increase in fatal secondary malignancy with IMRT based exclusively on photon scatter and neutron dose to distant tissues. That large an increase in SCR could be ascribed to the fivefold increase in MU demand with IMRT. Those risks estimates, however, are associated with large uncertainties because they are based on risk estimates from atom bomb survivors and assume a linear dose–response relationship. Based on dose to nearby tissues, Hall and Wuu (9) also concluded that 6-MV IMRT might almost double the SCR from 1% to 1.75%, stating that most second malignancies would develop close to the center of the treatment field. Our results are in contrast to these studies (9, 10) and that of Followill *et al*. (35) but are in agreement with other previously published studies that accounted for carcinogenesis in both nearby and distant tissues (as opposed to either one or the other) (29, 31).

The IMRT reduces the high dose volumes in neighboring normal tissues by using a larger number of fields to achieve conformal dose distribution. However, the high dose equivalent is redistributed elsewhere and is spread out over a larger volume (38). Consequently, both 6- and 18-MV IMRT plans deposited a larger amount of dose into the skin than with 3DCRT (Fig.1c). The SCR for skin therefore increases by 22–37% for 6-MV IMRT and by 50–69% for 18-MV IMRT because of neutron production. Inasmuch as the SCR is body-wide (29), this is only a relative disadvantage for IMRT because the integral dose to tissues remains relatively constant (12).

Modern cancer treatment often combines RT with sequential or concomitant chemotherapeutic agents. The impact on SCR is unknown, and extended follow-up is needed to record this late event and was beyond the scope of this work.

One limitation of this study was that the parameters α and δ for the OED model were obtained from the combined Japanese atom bomb and Hodgkin's disease cohorts (22, 30). To extrapolate the results to other patient groups, therefore, has its limitations. Another further limitation, common to all studies using risk modeling, is the unknown shape of the dose–response curve for radiocarcinogenesis above doses of 2 Gy. In this study, therefore, linear, linear-exponential and plateau models were used. It might be expected that the real dose–response curve for second cancer induction lies between the linear and linear-exponential models. There is growing evidence that models accounting for cell killing at higher doses (>2 Gy) fit best with the epidemiologic data (19, 22, 29).

CONCLUSION

The effect of 6-MV pelvic IMRT on SCR seems to be small relative to that of 3DCRT and clinically insignificant in absolute terms. The SCR for 6-MV IMRT seems to be independent of the dose–response model applied. As expected, the increase in beam number with IMRT increases skin exposure and hence skin-specific SCR risk. In terms of overall SCR, 6-MV IMRT is an acceptable alternative to 3DCRT for gynecologic malignancies and offers advantages in terms of sparing adjacent bowel and bladder (6). This is especially relevant for cervical cancer patients, the majority of whom are <50 years old, and long-term survivors are common (8, 25). When using 18-MV IMRT, the increase in photoneutron production resulted in an increase of approximately 25% in relative SCR, which is still only a small increase in absolute terms. Nevertheless, an adequate IMRT plan may be achieved using 6 MV, provided sufficient beams are used (24), and may be preferred from a radiocarcinogenesis perspective.

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Chapter 6

Concluding Remarks

6.1 The thesis in the context of the current literature

The thesis represents an ordered examination of the altered dosimetry of IMRT compared to 3DCRT both in- and out-of-field, for a range of clinically relevant anatomical sites and beam energies as used in clinical radiotherapy. These findings are used to calculate the risk of second cancer induction from the use of intensity modulation and are compared to those from 3DCRT. The thesis also compares the effect of altered beam energy on out-of-field scatter from IMRT as well as 3DCRT and the consequences for second cancer induction.

At the time the work was begun, there was limited data on the subject of carcinogenic risk from IMRT, and that data was incomplete and hence inaccurate, since each study was limited to either in-field or out-of-field tissue and was not representative of the entire body. Just two groups had considered the radio-carcinogenic implications of IMRT on the body as a whole, although the methodology employed was imperfect. These studies were limited only to prostatic IMRT. Schneider et al did not actually measure scattered dose throughout the body. Rather a single measurement 50cm from isocentre was used as representative of the dose range over all out-of-field tissues, which is suboptimal [52,53]. Furthermore, those two papers (the second paper using a slightly expanded data set) were published well after the present work was underway. Howell et al did consider dose to organs within and out-of-field [35], but point doses were used for determining organ-related risks rather than accounting for the dose gradients actually encountered in organs, especially those within or close to the edges of the fields. More importantly, although an elegant work, results were reported only for effective dose rather than for actual carcinogenic risk associated with prostatic IMRT. This study was similarly published while the current work was already underway.

Since the publication of the results in the second chapter, several subsequent studies have been published examining the carcinogenic implications of IMRT compared to 3DCRT. Some limited their analyses to in- or out-of-field tissue alone or relied on previous non-representative measurements of peripheral dose. Others used various Monte Carlo simulations of both in- and out-of-field dose distributions. Their results are hence

understandably heterogeneous, no doubt reflecting the differences in methodology, in addition to the varying dose-response models and correction factors used. A recent, convenient review, although limited to the prostatic setting is provided by Murray et al. [39]. Its conclusions are in agreement with the findings presented in this thesis.

When comparing the results of other studies to the present thesis, it is important to bear in mind the beam energies used for the comparative plans. Only one other study adopted the same approach of directly comparing high-energy prostate 3DCRT to 6MV prostate IMRT. This is the most valid methodology since these beam energies are realistic and representative of the energies used for the respective techniques in everyday clinical practice [39]. Two additional studies report risks for a range of energies and hence they too facilitate comparison of low energy IMRT to high-energy 3DCRT. All three studies are in agreement with the findings of chapter two. The first study only considered out-of-field risk and found that risks were generally comparable between modalities in this situation [56]. The second study included risk from both the primary beam and out-of-field scatter, although it used a point dose as representative of all peripheral tissues[51]. It compared 15MV 3DCRT to 6-, 15- and 18MV prostate IMRT. Depending on the dose-response curve used, risk was either unchanged or 15% higher with IMRT. The final study compared a range of energies for both modalities and actually showed marginally lower risks from IMRT (from improved in-field dose conformity) [35]. Two other reports are also illuminating in this regard, and both are also in agreement with the findings of chapter two. First is an update from Kry *et al.* of their 2005 paper. In 2007 after the work in chapter two had already been submitted for publication, this group updated their previously reported results for out-of-field risks from IMRT vs. 3DCRT using more realistic MU figures and risk models [57]. They too found no significant differences between 18MV 3DCRT compared to 6MV IMRT. This was in contrast to their earlier study which had predicted a doubling of risk [3]. The second report is in the form of a letter by Schneider criticizing the 2005 Kry study for not considering the impact of the primary beams on carcinogenic risk. It presents risk calculations showing little difference between 18MV 3DCRT and 6MV IMRT - again in keeping with the predictions in chapter two [52]. Chapter five, of the thesis, although dealing with gynaecological pelvic radiotherapy, is also consistent with the contemporary literature in finding little difference between 6MV IMRT and 18MV 3DCRT in terms of second cancer induction.

In contrast, when comparing IMRT to 3DCRT of the same energy, studies usually report a higher carcinogenic risk from IMRT although such increases are small in absolute terms and lower than postulated in the early studies preceding this thesis [38,58,59]. These include studies on breast cancer radiotherapy using different beam arrangements and modalities [58,60]. Thus the current literature is mostly well in keeping with the findings of chapter two, as unexpected as they were at the time of publication. It is fair to note though, that at least one study showed a potential doubling of 3DCRT risk from IMRT of the same energy [61], although a more recent update from the same group revised these risks downward to a the level predicted in chapter two of the thesis [59].

In summary therefore, when considering radiogenic risks from IMRT, most contemporary studies have been in keeping with the findings of this thesis, especially and

perhaps most importantly, those studies which considered the body in its entirety [35,51-53,59].

Chapters three and four are unique in the literature in that they separate out the components of scattered dose from IMRT. In as much as they can be compared with similar literature they appear to be in excellent agreement with other studies [34,62-64]. Three studies report that low energy IMRT produces more scatter than higher energy IMRT [34,63,65], while chapter four of the thesis concludes that total scatter for the two energies is comparable. However, these apparently conflicting statements are easily reconciled. A closer inspection reveals that, firstly, the experiments in chapters three and four *do* demonstrate that 6MV radiotherapy does produce more scatter than 18MV – the increase is just very small in absolute terms and therefore comparable from a clinical point of view. Secondly, the differences between energies in those three papers are similarly tiny in absolute terms. Thirdly, those authors demonstrate these differences in the scattered dose only relatively close to the field edge. Since 18MV reduces internal scatter which predominates close to the field edge, its scattered dose is certainly lower than 6MV in this region and this is well demonstrated in figure 3 of chapter four. Lastly, the studies use linacs from varying manufacturers. Wiezorek *et al* elegantly show that linacs from different manufacturers produce different amounts of scatter as alluded to in the first chapter [63]. Such reports are therefore entirely compatible with the results of the present thesis.

Along with describing the components of scatter for 18MV 3DCRT and analysing the influence of beam energy, chapter four predicts that increased radiogenic risk from excessive photoneutrons from high energy IMRT might not be as high as was previously feared. These findings sit well with the most recent literature [34,35,62,66]. It must be noted though that uncertainties around neutron energy spectra and dose equivalents at various distances and depths in the patient preclude firm conclusions. Chapter four does demonstrate that high energy IMRT carries the highest *out-of-field* risks due both to increased scatter from the high-energy photons, as well as to photoneutron production, despite lower MU demand. Interestingly, other studies have suggested that improved *in-field* conformity may mitigate these out-of-field phenomena [34,35]. Until further data is available, prudence is advised in the application of high-energy IMRT.

An interesting observation from the work in chapter five relates to the considerable contribution of the skin to second cancer risk from IMRT as an organ at risk. This appears to be consequent to the increased skin volumes exposed to multiple IMRT beams compared to 3DCRT but excess collimator scatter may also play a role. A corroborating study is that of Zelefsky et al who compared prostate IMRT to brachytherapy. They found no increased risk of second cancer; except in the form of non-melanomatous skin cancer in IMRT patients [67]. These two findings thus agree well with the findings of both chapters two and five.

6.1.1 Controversies

Since IMRT had only entered mainstream clinical practice a few years before the thesis was begun, the present research concentrates on the *modelling* of carcinogenic risk from the new technology, since reliable epidemiological data takes decades to mature. Tubiana argued in a 2009 review paper that we should "base second primary cancer reduction on solid data and not on speculation or models built on debatable hypotheses regarding the dose-carcinogenic effect relationship" [68]. An unassailable position: yet inadequate regarding the subject of second cancer induction from IMRT. Not because it is incorrect about the superiority of observed data over modelled data, but rather because such observed data do not yet exist. What are we to do in the considerable meantime? Accumulating sufficient patient data to demonstrate such postulated, minimally increased absolute risks that take ten years or more to manifest takes decades [69]. Yet, when introducing a new technology with no demonstrable survival advantage, we must endeavour to fully understand its capacity for harm and the risks it entails for our patients in the present. The uncertainties in dose-response models are well acknowledged, but by including the full range of plausible dose-response relationships, from one extreme possibility to the other, we can know with a high level of certainty the maximal possible risk involved, as well as the most likely range of risk, and base our practice on that. Since adequate epidemiological data still do not exist many years after the publication of various modelling papers, such papers remain a relevant and important source of information regarding the important consideration of radiation induced second cancer in patients receiving radiotherapy [39]. Lastly, although adequate epidemiological data require many, many thousands of patients followed up for many years, a single epidemiological study recently published facilitates comparison of observed second cancer risk between IMRT vs. 3DCRT. Reassuringly, the observed, epidemiological data from this large, single-centre study of 2120 prostate radiotherapy patients and 14309 matched surgical controls actually confirm the modelled predictions made in chapter two of this thesis -as its authors acknowledge [70].

6.2 Looking forward

IMRT has become ever-wider adopted and more frequently used in clinical practice since chapter one was written. These trends are likely to continue. However, new developments in technology are likely to erode the role of IMRT in many clinical contexts. Specifically volumetric modulated arc therapy (VMAT) and proton radiotherapy are increasing in uptake.

VMAT was formally known as intensity modulated arc therapy (IMAT), which alerts us to the fact that it is simply a form of IMRT that uses arcs rather than multiple discrete beams. Its main advantages over IMRT are rapidity of treatment (no need to set up multiple fields in turn), and the ease of planning and flexibility of treating multiple targets simultaneously. VMAT also reduces MU demand compared to conventional IMRT but

spreads out lower doses even further [71]. Limited studies have compared carcinogenic risk between the two modalities and results are conflicting, often with overlapping estimates. Reported differences were small [60,72,73].

Protons offer the advantage of reduced integral dose because of the absence of exit radiation. Protons offer consistently lower cancer induction risks than VMAT [73,74] and IMRT [51,73,75,76], yet also offer excellent dose conformity. Their role is especially important in paediatric practice where carcinogenic risks are highest. Although proton radiotherapy requires an on-site cyclotron, commercial units are diminishing in both size and price with the passage of time. Their uptake will no doubt increase in the future.

It is not just in the area of hardware that improvements will be made. Improvements in treatment planning systems and in the accuracy of the algorithms used for dose calculation enable ever-increasing accuracy of dose calculation and data collection. This in turn allows for the creation of better databases and hence the creation of more accurate dose-response models for radiocarcinogenesis. An ESTRO initiative with the acronym ALLEGRO (eArLy and Late hEalth risks to normal/healthy tissue from the use of existinG and emeRging techniques for radiatiOn therapy) aims to systematically investigate methods of out-of-field dose measurement as well as to accurately measure dose outside the treatment volume and to investigate models of second cancer induction using existing databases of treatments and their outcomes. This will hopefully produce meaningful insights into peripheral dose and radiocarcinogenic dose response. Better understanding of late effects including radiocarcinogenesis will also arise through genomic studies to identify genes responsible for late effects. Such work has already begun under the auspices of the Radiogenomics Consortium.

Summary

IMRT reduces the volume of in-field tissue receiving higher doses while spreading lower doses to greater volumes and increasing out-of-field scatter. The effect of IMRT on carcinogenesis is thus very complicated and subject to many variables. Chief among them is the shape of the risk-response curve for the dose range above 4Gy fractionated dose which is relevant to tissues at the periphery of the field and close to field margins where most second cancers develop [16,30]. Also important is the site treated; MU imbalance between IMRT and 3DCRT; planning algorithm; beam energy; and linac design [63]. The age of the patient and possibly gender are also material although independent of modality used.

Low energy IMRT produces comparable risks to high-energy 3DCRT in absolute terms. In relative terms, risks generally appear to be modestly higher, although it is possible that

they may be similar or even lower depending on the true radio-carcinogenic risk-response relationship, the site treated and the MU imbalance between modalities.

IMRT is generally reported to produce slightly higher carcinogenic risks than 3DCRT of the same energy. The in-field carcinogenic risk is generally modestly increased with IMRT of similar energy compared to 3DCRT, irrespective of risk-response curve used. It is important to note though that in keeping with the findings of the present thesis, appropriately designed studies considering the body in totality suggest that increases to total body risk are modest, especially if considered in absolute terms. At least one study has actually shown a reduced risk estimate with IMRT [35]. This goes to show that the difference between the modalities us unlikely to be a great as originally feared when concerns were first raised in the literature.

With regard to out-of-field tissue, IMRT as a technique increases peripheral scatter compared to 3DCRT, but:

- In absolute terms the magnitude of the increase and hence carcinogenic risk is limited

- Peripheral tissues manifest only a limited proportion of second cancers anyway because of the low scattered dose to these tissues. Most second cancers develop within or close to high dose regions [16,30-32].

- Compared to low energy IMRT, the use of higher energy beams for 3DCRT which are usually the alternative to IMRT in clinical scenarios other than head and neck cancer, increases photon scatter too as demonstrated in chapter three, and also adds photoneutron dose. These variables probably account for the similar risk to out-of-field tissue for low-energy IMRT and high-energy 3DCRT.

Increased scatter from IMRT is due to the machine scatter component while internally scattered radiation is reduced. For low energy IMRT, the reduction in internally scattered radiation which predominates for the first 20cm from field edge, might have a significant effect on carcinogenic risk, since a significant proportion of second cancers develop in tissues receiving doses of 6Gy or less [16] which lie in this region. For high energy IMRT, a similar pattern is observed whereby internal scatter is reduced but machine scatter is significantly increased. However, internal scatter predominates for just 6cm from field edge for 18MV IMRT so the benefits of its reduction may be less pronounced. Compared to 6MV 3DCRT and IMRT, as well as 18MV 3DCRT, the excess photoneutron production secondary to increased MU demand of 18MV IMRT is likely to result in excess carcinogenic risk. Based on the most recent literature regarding neutron dosimetry, these risks may however, be lower than previously feared [35,62,77]. One caveat is that higher energy IMRT requires less MU's than low energy IMRT and so may involve less head activation and photon scatter. It may also improve dose distribution to radiogenic in-field organs which can mitigate other disadvantages [34,62]. Since the balance of evidence still favours some increased risk from high-energy IMRT, prudence is warranted in its application.

Chapter 7

Required Statements

7.1 The relationship of the thesis to my previous work

In 2007, I presented a thesis in partial fulfilment of a Master of Medicine (MMed) degree. The title of that thesis was "A Planning Study Comparing Intensity Modulated Radiotherapy to Conformal Therapy: Effect on Integral Dose, Volume of Tissue Receiving Low Doses of Radiation, and Possible Implications for Carcinogenesis."

The subject of that thesis differed from the present work in all respects but for the fact that the MMed work did incorporate a superficial analysis of carcinogenic risk from IMRT and 3DCRT as a minor component. The carcinogenesis estimations were however, peripheral to the two main subjects of that thesis, which were the effect of IMRT on integral dose and its effect on spreading out low radiation dose while constricting higher isodoses. The Master's thesis examined those two issues in detail both theoretically and experimentally. In contrast, the carcinogenic risk modelling was a small component, considered for completeness sake but acknowledged as superficial and requiring further exploration. The present thesis is therefore a natural extension of the Master's thesis and in no way repeats any analysis or data interpretation from that work.

While the second chapter of the present work does reanalyse data collected in an experiment described in the Master's thesis, the data are analysed and therefore interpreted in an entirely novel way, producing an original, more complex, comprehensive and accurate assessment of the radio-carcinogenic risks from IMRT. The present thesis is therefore an entirely original work in terms of intellectual and scientific content.

The second chapter of the present thesis is original work and distinct from the previous thesis because:

- The method used for carcinogenic risk modelling in the present work is completely novel and considerably more detailed and complex than the simple approach of the previous Master's thesis. In that work, the average dose to the lungs and to the

"rest of the body" was used to calculate risk – clearly an inadequate over simplification given the heterogeneity of radiation dose, especially to tissues within and closely surrounding the treatment portals. In the present work, heterogeneity of dose within the DVH volume is accounted for and built into the risk calculations. These calculations account for both the variation in absorbed dose to tissues due to dose gradients within and close to the treatment field, as well as the varying volumes of tissue exposed to different doses.

- The previous thesis simply multiplied the average dose to the lungs and "rest of body" by the National Council on Radiation Protection (NCRP) risk coefficients to calculate carcinogenic risk, while chapter two uses a novel, more complex method incorporating multiple risk-response relationships for carcinogenesis.

- The present thesis includes carcinogenic risk from photoneutrons in its risk calculations. This was not accounted for in the Master's research – a shortcoming acknowledged therein.

- Resultant Carcinogenic risk estimates are markedly different between the two theses, reflecting the different methodologies used, with those from the current work agreeing better with epidemiological data (which is available for 3DCRT).

The second chapter of the present thesis is thus original work and does not repeat any data analysis or interpretation of previous work. Apart from that chapter, there is no possible area of overlap with prior work submitted for a degree.

7.2 The extent to which the thesis advances knowledge

The thesis comprises original work, presenting observations and predictions previously unreported. These can be summarised as follows:

- The only comprehensive estimation of carcinogenic risk from IMRT for a variety of tumour sites based on whole-body risk. Although two previous works examined this for the prostatic setting alone, one did not report carcinogenic risk [35], and the other did not actually measure out-of-field dose throughout the body, but assumed dose at a single point to be representative of all peripheral doses [51].

- The first reported carcinogenic risk estimates for tonsillar IMRT.

- The first reported carcinogenic risk estimates for nasopharyngeal IMRT.

- The first reported carcinogenic risk estimates for gynaecological pelvic IMRT.
- The first reported carcinogenic risk estimates for prostatic IMRT based on body-wide assessment of dose distribution
- The first reported carcinogenic risk estimates for breast IMRT based on body-wide assessment of dose distribution
- The only analysis of all three constituent components of scattered dose for either low- or high-energy IMRT
- The only reported analysis of all three constituent components of scattered dose for high energy 3DCRT
- A comprehensive assessment of out-of-field scatter from IMRT compared to 3DCRT for both high and low energy radiotherapy, and an assessment of the influence of varying beam energy on scatter for both modalities with reference to radio-carcinogenesis.

At time the work was begun, there were no studies of the effect of IMRT on radio-carcinogenesis that were methodically adequate to provide credible risk estimates to inform clinical practice. This is because none had measured radiation dose and its variation throughout the whole body for risk calculations. While the present work was underway, a single study was published which did measure the radiation dose to the entire body, however the study was restricted only to the prostatic setting and only presented results for effective dose, not carcinogenic risk [35]. Another study reported whole-body risks based on just a single out-of-field measurement 50cm from the isocentre, and was similarly limited to the prostatic setting [52]. As the current thesis demonstrates, carcinogenic risk differs depending on the nature of the dose distribution which is inhomogeneous both in- and out-of-field, and thus precise assessment of dose throughout the body is vital. The thesis also demonstrates varying carcinogenic risk for different treatment sites and techniques; hence information from just one site is of limited utility when considering other clinical scenarios. Each tumour site needs to be analysed individually.

The current work was thus the first to provide plausible risk estimates based on a range of credible dose-response relationships for a variety of tumour sites using current radio-therapeutic techniques. Its risk estimates for breast and gynaecological IMRT were the first published results in the field, and its results for prostate and head and neck IMRT were the first based on adequate data for both in- and out-of-field dose. Although risk estimates for prostate and general head and neck IMRT had been published by the time this work was published, they were not definitive, since none had reliably measured dose throughout the body upon which to base calculations. Furthermore the work in this thesis was already underway by the time of their publication (with the exception of Verellen *et al* [4]).

Aside from modelling carcinogenic risk at multiple sites, the thesis also provides analyses of scattered dose to out-of-field tissues for IMRT and 3DCRT and quantifies the contribution of the individual scatter components to the total scattered dose. This has implications for the design of linac shielding and gives impetus to the development of monitor-unit efficient planning algorithms.

Although several studies had considered peripheral dose from IMRT alone [4,50,63,78,79], or both 3DCRT and IMRT [80-83], most either measured or modelled (using Monte Carlo algorithms) point doses at just one or two distances from the field and few went on to analyse implications for carcinogenesis . Furthermore, all studies were limited to pelvic radiotherapy except for two: one investigating the paediatric brain setting over two papers [81,83], and the other measuring a single point dose on the sternum to predict risk from head and neck IMRT [4]. In contrast, the present work incorporates the dose throughout the entire body in its risk calculations and deals with a variety of anatomical sites.

Additionally, no previous study had purposefully examined the composition of peripheral scatter from IMRT nor provided a detailed examination and comparison of scatter from IMRT vs. 3DCRT throughout the periphery of the body. Certainly none had described the three components of scattered dose for either low or high energy IMRT. The present thesis thus provides novel information in this area.

The composition of low energy scatter had been well described in 1983 [84], although data for modern linacs were not well characterised. Furthermore, no investigation into the components of high-energy photon scatter for 3DCRT was published until 2010. Even that study made no attempt to quantify collimator scatter and head leakage, treating them both as a single entity [64]. The thesis thus provides novel analysis of the composition of peripheral scatter for IMRT and high-energy 3DCRT and updates previous data on low energy 3DCRT for modern linacs. It also provides estimates of the effects of such scatter on second cancer induction.

Furthermore, the thesis examines in detail, the effect of beam energy on the various constituent components of scatter both for 3DCRT as well as for IMRT. Although other studies have considered scatter for multiple beam energies, none have done so in enough detail or used a method that allows analysis of the alteration in each constituent component of scatter with varying beam energy. This is a unique feature of the thesis.

The thesis then takes this a step further by investigating the effects of the alterations in scattered dose from intensity modulation and varying beam energy on radio-carcinogenic risk. The analysis includes an assessment of risk from photoneutron production secondary to the use of high-energy photon beams.

In summary, the thesis is novel in a number of ways and sheds new insights into the effect of IMRT on second cancer risk at a number of sites – many of which had never been previously considered, and others which had not been examined in sufficient detail to provide representative data for body-wide risk. The thesis also provides new detail regarding the composition of out-of-field scatter and the effect of both high and low

energy IMRT on such scatter, as well as the effect of different beam energies on the individual components of out-of-field scattered dose.

Abbreviation List

IMRT	intensity modulated radiotherapy
MU	monitor unit
3DCRT	three dimensional conformal radiotherapy
DVH	dose volume histogram
MLC	multi-leaf collimator
LSS	Life Span Study
ICRP	International Commission for Radiation Protection
BEIR	Biological Effects of Ionizing Radiations
Sv	Sievert
LNT	Linear No Threshold
Gy	Gray
ESTRO	European Society of Therapeutic Radiation Oncology
MV	megavolt
RTOG	Radiation Therapy Oncology Group
VMAT	volumetric arc radiotherapy
IMAT	intensity modulated arc therapy
NCRP	National Council on Radiation Protection

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