Consideration of the radiation dose delivered away from the treatment field to patients in radiotherapy

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ABSTRACT

Radiation delivery to cancer patients for radiotherapy is invariably accompanied by unwanted radiation to other parts of the patient’s body. Traditionally, considerable effort has been made to calculate and measure the radiation dose to the target as well as to nearby critical structures. Only recently has attention been focused also on the relatively low doses that exist far from the primary radiation beams. In several clinical scenarios, such doses have been associated with cardiac toxicity as well as an increased risk of secondary cancer induction. Out-of-field dose is a result of leakage and scatter and generally difficult to predict accurately. The present review aims to present existing data, from measurements and calculations, and discuss its implications for radiotherapy.

Key words: Monte Carlo calculations, out-of-field dose, radiation protection, radiotherapy, secondary cancers

Introduction

Contemporary external-beam radiotherapy treatment approaches are capable of conforming a focused radiation beam tightly to a defined target volume. Despite the high conformality achievable with modern methods, unwanted doses are nonetheless delivered to untargeted regions of the patient’s body. These doses from outside the primary beam are herein referred to as out-of-field doses, which arise from leakage from the medical linear accelerator (linac) treatment head, scatter from collimation devices and scatter from within the patient’s body itself. The increasing efficacy of modern radiotherapy techniques for treatment of cancers is successful in lengthening patients’ lifetimes. The unfortunate corollary of this is that there is therefore longer time in which treatment-induced health complications — such as secondary cancer — may become manifest. Radiation-induced cancer is of increasing clinical interest, as demonstrated by Figure 1.

In this review, an introduction to the mechanisms of, and influences on, radiocarcinogenesis is given, since this is typically considered the gravest potential consequence of out-of-field dose to untargeted organs. A review of studies that have measured or calculated out-of-field doses is also given, followed by a breakdown of individual contributing

![Figure 1: An illustration of the increasing number of publications in radiocarcinogenesis, as reflected by a PubMed search of the terms “radiation-induced cancer,” covering the past six decades](image-url)
Subclones can arise from clones of initiated cells in which the accumulation of a number of faults in the genome. This comes about by the acquisition of new properties, such as immortalization, known as initiation. The second stage, promotion, involves effectively the first stage of the carcinogenic process, comprising chromosomal abnormalities and gene mutations. The lesions in DNA that result from ionizing radiation include (i) double- or single-strand breaks of the DNA molecule itself, (ii) chemical alteration of the sugar moieties and (iv) cross-linking to DNA-related matrix proteins or nucleotides in the DNA molecule itself. Single-strand breaks are typically easily and rapidly repaired, whereas double-strand breaks are less readily repaired. The latter can eventuate from the simultaneous scission of both strands close together, or by the interaction of two adjacent single-strand breaks. About 25% of repairs are misrepairs in the case of double-strand breaks, depending on the mechanism of repair, and can result in mutations that may ultimately lead to cell death. In the case of damage not resulting in cell death, the daughter cells can carry a radiation-induced mutation. It is generally accepted that unrepaired or misrepaired double-strand breaks are of principal importance in terms of the induction of chromosomal abnormalities and gene mutations.

Such mutation resulting from ionizing radiation is effectively the first stage of the carcinogenic process, known as initiation. The second stage, promotion, involves the acquisition of new properties, such as immortalization, resistance to hypoxia and so on. This comes about by the accumulation of a number of faults in the genome. Subclones can arise from clones of initiated cells in which mutations have occurred. Amongst subclones, there is what Tubiana describes as “Darwinesque” competition, which allows the the subclones that exhibit rapid growth to gain dominance. Ultimately, new subclones emerge with greater autonomy, growing more rapidly, until finally a subclone of cells exists which may proliferate autonomously. Following this stage is progression, in which the cells proliferate frequently despite the absence of stimuli. Cells eventually gain the potential for invasion of peripheral tissues or metastasis.

The low doses to untargeted healthy organs in the human body that occur as a result of scattered and leaked radiation in radiotherapy have the potential to induce cancer (and other health complications) as a result of the treatment. This is a typical stochastic effect whereby the probability of cancer induction is dependent upon the dose whilst the severity is independent. Radiocarcinogenesis is the most serious potential consequence of out-of-field doses. There are several key influences on the risk of radiation-induced carcinogenesis.

One factor is age. There is a higher risk at younger ages of irradiation, as shown in Figure 2. Furthermore, Figure 2 also shows that females are more susceptible to radiation-induced carcinogenesis than males. The average lifetime attributable risk of cancer mortality is 0.76% for women and 0.51% for men (for a 0.1 Gy dose). Time since the inception of irradiation is another key factor. Generally accepted as being of single-cell origin, the development of cancer occurs as a result of successive mutations and extensive proliferation. The development of cancer relies on the unregulated proliferation of mutated cells that are not removed over time via apoptosis or immune system action.

![Figure 2: The lifetime attributable risk of cancer mortality (expressed as a percentage of a population exposed to a single 0.1 Gy dose) as a function of age at time of exposure. The data for men (squares) and women (triangles) are shown separately; the average over the 80-year period is 0.76% for women (solid line) and 0.51% for men (dotted line). This figure indicates the age and gender dependency of radiation-induced cancer mortality, constructed using data from the BEIR Report VII (2006)](image-url)
A clinically-diagnosed cancer will typically be constituted by several billion cancerous cells. The small probability of particular mutations and the accumulation thereof means the process of radiation-induced carcinogenesis is very slow. For solid cancers, the latency is of the order of decades, with the exception of sarcomas (latency may be <10 years) and leukemia (latency may be <5 years). Different tissues exhibit different degrees of susceptibility to cancer induction. Figure 3 highlights the varying sensitivities of different organs; based on Biological Effects of Ionizing Radiation (BEIR) data, the relative risk is given for cancer of the stomach, colon, liver, lung, ovary, bladder and other solid cancers.

Obviously, another key factor affecting the incidence of secondary cancer is dose. The relationship between dose and radiocarcinogenesis is typically considered for dose regimes in two ranges: 0-2 Sv and >2 Sv. The linear no-threshold (LNT) dose-response relationship is generally accepted, and while there is some argument for nonlinear behavior (see, for instance, Tubiana and Aurengo), ultimately the only generic approach to radiation protection that can be broadly implemented at the present time is the LNT approach. Figure 4 illustrates this relationship.

To illustrate the relevant parameters considered in risk calculations, the BEIR VII–preferred risk model for solid cancer induction is shown below. For low doses, a linear fit is suitable, such as

\[
I_D = I_n [1 + (ERR)(D)]
\]

where \(I_D\) is the rate of incidence, \(I_n\) is the background rate (at zero dose), \(D\) is the dose in Sv and \(ERR\) is the excess relative risk per Sv, given by

\[
ERR = \alpha_s e^{-\frac{(a_e - 60)}{60}} \eta
\]

where

- \(\alpha_s\) is a sex-specific risk coefficient, which corresponds to the ERR for exposure at age 30 and 60 years attained age;
- \(a_e\) is the attained age (in years);
- \(\eta\) is the exponent of attained age;
- \(\gamma\) is the per-decade increase in the age at exposure over the range 0-30 years;
- \(a_e\) is the age at exposure (in years); and

\[
e^{-} = \begin{cases} 
\frac{1}{10}(a_e - 30), & a_e < 30 \\
0, & a_e \geq 30
\end{cases}
\]

This is an appropriate risk model for the calculation of site-specific cancer risks using the relative risk coefficients given in the BEIR report. However, it should be noted that there are different preferred models for leukemia and breast and thyroid cancers.

There is also a link between radiation exposure and non-cancer disease mortality. This is discussed in detail elsewhere. Preston et al. showed that a linear fit for the dose response is a suitable model, with the linear-quadratic model not fitting significantly better. Table 1 shows the...
cause-specific excess relative risk per Sv for mortality from non-cancer diseases, based on data from the atomic bomb cohort. All this demonstrates statistically significant risks — thus we cannot neglect out-of-field doses.

**Measurement and Calculation of Out-of-field Dose**

**Overview**

There have been a large number of studies over the past several decades that have investigated out-of-field doses. The majority of these involve measurement of such doses, but many also make calculations of such doses using Monte Carlo radiation transport simulation, analytical approaches, or combinations of these, as indicated in Figure 5. These studies are discussed in two subsections: the first devoted to conventional radiotherapy techniques; the second, to more contemporary methods (such as intensity-modulated radiation therapy) and small-field techniques such as stereotactic radiotherapy.

**Conventional techniques**

There has been increasing strong interest in the out-of-field radiation doses from different treatment units since about the 1970s. The focus of the studies is typically either dose from an occupational radiation safety perspective (particularly in early works; and for \(^{60}\)Co sources, where leakage is inevitable) or doses to untargeted critical structures in the patient’s body.

Fraass and Van de Geijn\(^{24}\) investigated the peripheral dose for a \(^{60}\)Co beam, as well as 4-MV, 6-MV and 8-MV photon beams. Doses were reported for water tank measurements for multiple field sizes at a range of distances from the field edge. Transmission and in-patient scatter were separated, which were found to be of similar magnitude. Thermoluminescent dosimetry (TLD) was also performed during treatment of patients. Kase \textit{et al.}\(^{25}\) similarly studied a \(^{60}\)Co beam, as well as 4-MV and 8-MV photon beams. Kase \textit{et al.} also attempted to differentiate head-leakage and scattered radiation, finding that collimator scatter may contribute up to about 40% of the dose outside the treatment field. Francois \textit{et al.}\(^{26}\) parameterized dose distributions for different beam energies as a function of depth, distance from the edge, field size and shape. An algorithm was thus developed to determine the dose to organs outside the beam at a distance of 10-50 cm from the field edge. The measurements were undertaken with TLD in an anthropomorphic phantom. Measurements were also taken in a large water phantom for the various fields. Limited Monte Carlo calculations were also performed. The American Association of Physicists in Medicine (AAPM) report TG-36\(^{27}\) reported fetal doses in pregnant women treated with radiotherapy, for a range of delivery conditions. Van der Giessen\(^{28}\) measured doses in a water phantom for 4 Cobalt machines and 37 linear accelerators to investigate variation in peripheral doses amongst machines from 7 different manufacturers. Variation of leakage radiation dose was found to be small amongst the varying designs; however, collimator dose was found to vary up to 50%, depending on the collimator / flattening filter design. In his PhD thesis, Van der Giessen\(^{29}\) provides results from studies of various machines (with a focus on \(^{60}\)Co), mostly using water phantoms to collect data or by evaluation of published data and leakage / collimator scatter data provided by other clinics / institutions. Dose was also measured on patients’ perinea using TLD. The studies constituting his thesis were published separately as articles, mostly in \textit{Int. J. Radiat. Oncol. Biol. Phys.}\(^{28,30-33}\)

Broadly, regarding photon doses outside the treatment volume for ‘classical’ methods, one may conclude that the photon dose decreases with decreasing field size and drops approximately exponentially away from the field edge, and neutron doses are more dependent on beam energy than distance from the field edge.

**Intensity-modulated radiotherapy and small-field delivery**

The advent of intensity-modulated radiotherapy (IMRT)
has given rise to concerns over the fact that the total number of monitor units used is often greater than that for treatments for equivalent cases using, for instance, three-dimensional (3D) conformal radiotherapy. The additional monitor units may result in additional leakage dose and thus increase the dose to untargeted critical structures. Contemporary IMRT delivery is typically undertaken with multileaf collimators (MLCs) or mini-multileaf collimators (MMLCs) replacing, or attached as, tertiary/quaternary collimators on a linear accelerator. Many of the works discussed here involve measurements to investigate the influence of the MLC on out-of-field doses, also in the specific context of IMRT. Note that the focus of the discussion is on peripheral photon doses.

Followill et al.\textsuperscript{[34]} undertook a study of doses outside the treatment fields for IMRT with 6-MV, 18-MV and 25-MV beams, for which the photon whole-body equivalent doses per cGy were 80 \(\mu\)Sv, 6.5 \(\mu\)Sv and 10 \(\mu\)Sv, respectively. The respective neutron doses were 0 \(\mu\)Sv, 46 \(\mu\)Sv and 76 \(\mu\)Sv. Using risk values recommended by the National Council on Radiation Protection and Measurements (NCRP), they calculated worst-case scenario risks of cancers to be between a minimum of 0.4\% (for a conventional nonwedged 6-MV beam) and 24.4\% (for a 25-MV tomotherapy beam). Stern\textsuperscript{[35]} investigated whether the presence of an MLC would influence the peripheral dose when positioned at the field edge defined by the jaws. For 6-MV and 18-MV beams at all depths and distances studied, configuring the MLC leaves at the field edge yielded a reduction in peripheral dose of 6\% to 50\% compared to the MLC leaves fully retracted. In the latter case, peripheral doses matched those for a linac without an MLC. As mentioned earlier, the AAPM report TG-36 can be used to estimate the peripheral dose distributions.\textsuperscript{[27]} Matic and Klein\textsuperscript{[36]} undertook a number of measurements with an ionization chamber in a water-equivalent plastic phantom with various MLC leaf settings, including full retraction. Peripheral dose distributions with the MLC fully retracted and collimator rotated to 180\(^\circ\) were similar to TG-36 data, but lower with MLC field shaping. They also showed that rotating the collimator to 90\(^\circ\) with full MLC retraction may reduce the peripheral dose up to a factor of 3 (compared to TG-36).

Chibani and Ma\textsuperscript{[37]} employed Monte Carlo N-Particle eXtended (MCNPX) to study the dose from photon-induced nuclear particles (neutrons, protons and alpha particles). Varian beams are found to produce more particles than the Siemens beams, due to higher primary electron energies. Neutrons are found to contribute more than 75\% of the total dose-equivalent ratio. Chibani and Ma compared the model to measurements. The dose-equivalent from leakage neutrons (at 50 cm off-axis distance) represents 1.1\%, 1.1\% and 2.0\% likelihood of fatal secondary cancer from a 70-Gy treatment delivered by the Siemens 18-MV, Varian 15-MV and Varian 18-MV beams, respectively. Vanhavere et al.\textsuperscript{[38]} performed measurements in air, at different depths in a plexi-phantom and using a Rando-Alderson phantom for gammas and neutrons with an 18-MV linac. Organ equivalent doses and effective doses (estimated by different methods) were evaluated for a range of organs. For a prostate cancer IMRT treatment, the effective dose (using Rando-Alderson phantom) was found to be about 30 mSv per 2 Gy target dose, 13\% of which is attributed to neutrons.

Sharma et al.\textsuperscript{[39]} noted that dynamic fields (consisting of constant-width strips moved from one bank to the other) required between 2 and 14 times as many monitor units as static fields to achieve the same dose at isocenter, for various arrangements. Peripheral doses were between 2 and 15 times higher for the dynamic case, depending on field size, etc. They also compared patient-specific intensity-modulated fields with dynamic MLC fields with similar jaw settings and discovered that the two are sufficiently similar to use the dynamic MLC data to predict out-of-field doses for comparable patient-specific cases.\textsuperscript{[40]} Kry et al.\textsuperscript{[41]} highlighted that determination of such out-of-field doses requires tedious measurement or calculations that exhibit high uncertainty. They used the MCNPX Monte Carlo code to model a Varian Clinac 2100 operated at 6 MV, modeling dose distributions away from the central axis and measuring dose distributions with an ionization chamber (in a water phantom) and TLD (in an acrylic phantom). In a different publication, Kry et al.\textsuperscript{[42]} describe a similar study for 18-MV photons. In the latter work, discussion of neutron dose was also included.

Wiezorek et al.\textsuperscript{[43]} performed point dose measurements at different depths in a solid phantom at 29 cm off-axis distance, for a Siemens Oncor Impression linac with energies of 6 and 15 MV. Peripheral doses associated with artificial fluence distributions were compared with open beam contributions. Measurements were performed with two types of TLDs to quantify photon and neutron doses separately. Neutrons were only detected for 15 MV. The photon contribution to peripheral dose increased (compared to open field) when using segmented multileaf modulation (sMLM) for IMRT, and even further when using compensators.

Also of interest are the out-of-field doses from the small fields used in stereotactic radiotherapy (SRT). The doses involved in SRT are generally much higher than those in IMRT treatments, and are delivered in relatively few fractions. (Note that stereotactic radiosurgery involves a single fraction only.) Another point worth noting is that patients often receive stereotactic treatment for nonmalignant lesions — and thus have relatively long potential lifetimes. The out-of-field doses from these high-dose treatments are thus of significant interest.

Ioffe et al.\textsuperscript{[44]} quantified the dose rate as a function of
distance from the isocenter in a RANDO phantom for 
Gamma-Knife treatments. Hasanzadeh et al.\textsuperscript{[45]} constructed 
an anthropomorphic phantom and undertook TLD measurements of dose in untargeted organs for Gamma-
Knife radiosurgery. Petti et al.\textsuperscript{[46]} developed Cyber-Knife plans 
for a thorax lesion and brain lesion in an anthropomorphic 
phantom and measured the dose at various depths and 
distances outside the treatment field using TLD. Peripheral 
doses were found to be 2 to 5 times higher than those in 
a comparable Gamma-Knife treatment, and up to 4 times 
higher than those in an IMRT treatment. The relatively large 
peripheral dose is attributed to greater leakage of the 
Cyber-Knife unit. Chuang et al.\textsuperscript{[47]} investigated reduction of out-
of-field doses from the Cyber-Knife system resulting from a 
shielding upgrade, with the observation that doses were 
generally reduced by 20\% to 55\%.

Maarouf et al.\textsuperscript{[48]} examined the radiation exposure of 
organs at risk and assessed the risk of late effects (such 
as secondary tumors or hereditary disorders) following 
stereotactic linac radiosurgery of intracranial tumors. TLDs 
were placed superficially on patients’ (n = 21) eyelids, 
thyroid, breast and regions of the ovary / testes. The organ 
receiving the highest doses was the eye lens (276 ± 200 
mGy), followed by the thyroid (155 ± 83 mGy), breast (47 
± 22 mGy), ovary (12 mGy) and lastly the testes (9 ± 3 
mGy). The absorbed doses thus ranged between 0.025\% 
and 0.76\% of the target dose. They recommended the use 
of conformal beams employing micro-multileaf collimators 
and avoiding beams directed toward the trunk. Solberg et 
al.\textsuperscript{[49]} compared conventional noncoplanar arc, static field 
conformal and dynamic arc field shaping approaches to 
radiosurgery. In terms of peripheral dose, it was found to 
decrease as additional beams or arc degrees were added with 
either of the conformal approaches. Ultimately, dynamic 
arc shaping was found to be preferred for its efficiency and 
efficacy in delivery of a homogenous dose whilst minimizing 
peripheral dose, for radiosurgery applications. More recently, 
Taylor et al.\textsuperscript{[50]} investigated out-of-field doses from mini-
multileaf collimator–shaped fields, and described a number 
of simple techniques for the minimization of out-of-field 
dose and its associated risks. The authors found doses of 
the order of 50 mGy in out-of-field regions — a substantial dose 
in radiation protection terms — and observed that simple 
treatment techniques such as aligning the craniocaudal 
direction of the patient with the x-plane of the collimator 
can reduce dose by up to an order of magnitude. The latter 
result was confirmed in a later study of doses in small-field 
radiotherapy of pediatric patients, whereby Taylor et al.\textsuperscript{[51]} 
found that doses are, on average, 40\% less along the x-plane 
(compared to the y-plane). Furthermore, the authors also 
found that far from the primary field, about half the out-
of-field dose is due to leakage; that the use of a linac with 
a bending magnet resulted in dose about 40\% higher than 
the straight waveguide unit; and that coplanar treatments 
with beams avoiding the trunk of the body can reduce dose 
to organs at risk by an order of magnitude.

Tomotherapy is another modality of interest in terms of 
out-of-field doses. Tomotherapy almost invariably involves 
a larger number of ‘monitor units’ than an equivalent 
treatment delivered by conventional radiotherapy, with 
leakage being a major possible source of out-of-field doses 
delivered to patients.\textsuperscript{[52,53]} There have also been studies 
on proton beam therapy in relation to out-of-field doses. 
These methods are not discussed in any greater detail here 
because the focus of this work is conventional external-
beam radiotherapy, which is far more widely employed than 
the latter methods.

IMRT treatments often require between 3 and 5 times 
the number of monitor units to deliver (compared to a 
conventional treatment). Kry et al.\textsuperscript{[54]} measured the photon 
and neutron out-of-field dose equivalents to various 
organs using different treatment strategies, energies 
and accelerators. Photon dose decreased exponentially 
away from primary field; neutron dose was found to be 
independent of the distance from treatment field. 
Neutrons contributed significantly to out-of-field dose for 
E > 15 MeV. Considering out-of-field doses, Kry et 
al.\textsuperscript{[55]} found that the maximum risk of fatal secondary 
malignancy was 1.7\% for conventional radiation, 2.1 \% 
for IMRT with 10-MV x-rays and 5.1\% for IMRT with 
15-MV x-rays. Kry et al.\textsuperscript{[56]} also examined the uncertainty 
in risk estimates relating to out-of-field doses, with the 
result that risk estimates for secondary malignancy were 
subject to very large uncertainties. It was shown, however, 
that it is possible with relatively good accuracy to identify 
preferable modalities based on the ratio of risk estimates. 
In a recent study, Ruben et al.\textsuperscript{[57]} compared IMRT with three-
dimensional Conformal Radiation Therapy (CRT) in terms 
of carcinogenic risk. Equivalent plans were constructed for 
prostate, breast and head-and-neck treatments. The risk of 
radiation-induced malignancies in organs outside the target 
volume was calculated using two dose-response models for 
radiocarcinogenesis. Ultimately, the risks were found to be 
comparable between the two modalities. Depending on the 
technique and region of interest, risks ranged between 1\% 
and 2\% for one risk model, and between 0.5\% and 1\% for 
the other model. There is a significant body of literature 
covering epidemiological studies of cancer induction in 
radiotherapy patients, an overview of which is given in the 
subsequent section. Reft et al.\textsuperscript{[58]} performed in vivo patient 
and phantom measurements of the secondary out-of-field 
photon and neutron dose equivalent for 18-MV IMRT 
treatments. It was found that the photon dose dropped by 
a factor of two for distances of 10 and 20 cm from the field 
edge, while the neutron dose remained the same (within 
experimental uncertainties). There is an indication that 
18-MV IMRT results in higher neutron doses (factor of 
2 or 3) compared to three dimensional CRT (3DCRT). 
Klein et al.\textsuperscript{[59]} collected peripheral dose data in a phantom 
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at distances ranging from 5 to 72 cm away from the field edges of small (2 to 10 cm) IMRT fields. Micro-ionization and cylindrical ionization chambers were arranged in a phantom representing a 3-year-old child at locations corresponding to the thyroid, breast, ovaries and testes. Distant peripheral dose (dominated by head scatter) was higher than predicted. For example, doses to the testes were 3 to 5 times higher for IMRT compared to conventional treatment.

There are a range of influences on the out-of-field dose, which are detailed in the following section.

**Contributions to out-of-field dose**

Out-of-field dose is essentially the combination of leakage from the accelerator head, scatter from collimators, from within the patient’s body and from the rest of the treatment room. It is possible to reduce out-of-field doses (and corresponding risks to the patient) by careful choice of treatment arrangement. To help facilitate this, the main influences on out-of-field dose are discussed here.

**The influence of accelerator type**

Because out-of-field dose to untargeted regions of a patient’s body is a result of a combination of leakage and scatter, it is likely that different linac models (having different shielding designs) will generate different out-of-field doses. Figure 6 illustrates this quite clearly for a Siemens Primus, Varian 2100 and Philips SL-C operated at 18 MV (listed in order of decreasing out-of-field dose).

Figure 7(a) also shows very interesting consequences for choice of linac. This data\[51\] shows that even when operated in the same energy mode (6 MV), there is a significant difference between the out-of-field doses from the (multi-mode) Varian 2100 and the (single-mode) Varian 600C. The dose from the Varian 2100 is up to 250% higher for far out-of-field regions than that from the Varian 600C. This discrepancy is likely to be due to the larger horizontal waveguide of the Varian 2100 and the presence of a bending magnet (the latter acting as a further source of bremsstrahlung). The Varian 600C has a vertical waveguide directed at the isocenter and no bending magnet. Figure 8 illustrates the differences between Siemens and Varian machines, with the latter delivering out-of-field doses only 20% to 50% of those delivered by the Siemens Primus.\[37\] Neutron doses are clearly higher with the Varian machine, however [Figure 6]. The different contributions to out-of-field dose from collimator scatter for a range of machines are given in Figure 9. Kry et al.\[51\] found that intensity-modulated radiotherapy (IMRT) in 6-MV mode with Varian and Siemens linacs resulted in risks of fatal secondary cancer of 2.9% and 3.7%, respectively.

**The influence of field size**

Intuitively, one would expect that for larger field sizes, higher dose would be delivered to out-of-field regions, as a result of increased patient-scatter. Generally this is indeed the case. Taylor et al.\[51\] showed that in the context of linac-based stereotactic radiotherapy, the out-of-field dose tends to (approximately) increase with the increase in side length of the field. For example, a square field of side length 9.8 cm is roughly four times greater than a field of side length 2.4 cm, and the out-of-field dose is about four times greater. However, the difference in out-of-field dose between different field sizes decreases with increasing out-of-field distance. This is made clear from Figure 7(b) — in particular, the subplot showing the ratio of a 5×5-cm² field to a 0.5×0.5-cm² field, which approaches unity with increasing distance from isocenter.\[31\] A similar result is shown in Figure 8. (Note that Figure 10 shows the distance from field edge, not from isocenter.) This means that at large distances, head leakage is the dominant influence on out-of-field dose. Figure 11 also shows the influence of field size on patient-scatter\[30\] and collimator scatter and leakage.\[31\]

**The influence of beam quality**

The energy mode also influences out-of-field dose, as evidenced by Figure 6, Figure 8(b) and Figure 9. Lower-energy beams tend to result in greater out-of-field photon doses than higher-energy modes. This is because lower-energy photons are less forward-scattered than higher-energy photons.\[90\] As such, one would expect patient-scatter in low-energy modes to result in greater out-of-field dose. One would also expect, however, that this would be pronounced at intermediate distances but less so at far distances, since from the previous section we expect patient-scatter to be less influential far out-of-field. Indeed, from Figure 9, it is clear that the Varian linacs in 15-MV and 18-MV modes generate comparable

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*Figure 6: Data from Reft et al. (2006)\[96\] shows the difference between linac models in terms of out-of-field dose for 18-MV IMRT of the prostate. In vivo measurements were undertaken measuring both photon (solid) and neutron (cross-hatched) doses; the data shown here corresponds to doses at a distance of 20 cm from the field edge. Measurements were performed for the same-model accelerator at different centers (reflected by the number n).*
Figure 8: An indication of the variation in neutron dose that exists between operating at 15- and 18-MV modes, and between different linac manufacturers. This data shows MCNPX-calculated neutron doses along the plane of the couch for a Varian 2160C (15 MV and 18 MV) and Siemens Primus (18 MV) (Chibani and Ma 2003). Also shown are several measured data points for the Varian 15 MV. The subplot below the primary figure shows the ratio of these doses to the Siemens 18 MV case.

out-of-field doses at far off-axis distances. The problem with high-energy modes, however, is that the photonuclear effect may generate neutrons that contribute to the out-of-field dose. This is illustrated in Figure 6. It has been shown that neutron doses may not significantly increase the risk of radiocarcinogenesis for IMRT with a linac operated in 18-MV rather than 6-MV mode.\[60\]

The influence of leakage, collimator scatter and patient-scatter

As discussed, the influence of leakage, collimator scatter and patient-scatter may be inferred to some extent by the influence of field size [Figure 7(b)]. A number of authors have made explicit attempts to determine separate influences of these. Figure 10(a) directly indicates that the (percentage of central axis, CAX) dose attributable to patient-scatter decreases with increasing distance. Figure 10(b) shows that the different field sizes converge far from the primary beam, and the contribution to out-of-field dose “plateaus.” The orientation of the collimator has been shown to have a significant effect on out-of-field dose. Taylor et al.\[51\] found that preferentially aligning the craniocaudal axis of the patient with the x-plane (defined by the direction...
of jaw motion and effected by rotating the collimator appropriately) can reduce the out-of-field dose by up to an order of magnitude for a Varian 600C linac. In a study of out-of-field dose in pediatric radiotherapy, it was shown that alignment with the x-plane on other Varian linacs can also achieve a significant reduction in out-of-field dose. The percentage contribution to out-of-field dose (relative to central axis dose) due to collimator scatter generally differs amongst machines, as indicated by Figure 11.

The influence of treatment type

The nature of the treatment affects the out-of-field dose. Intensity-modulated radiotherapy (IMRT) is of particular interest in this regard, as discussed earlier, because it typically involves a greater number of monitor units than other delivery methods. Wang and Xu found that out-of-field doses are indeed significantly higher for an IMRT treatment than for conformal radiotherapy (CRT), as shown in Figure 12(a). Sharma et al. showed that achieving an equivalent field size with a sliding field rather than a static MLC can result in an increase in out-of-field dose of up to an order of magnitude; see Figure 12(b). Hall and Wu found that IMRT of prostate cancer rather than conventional radiotherapy resulted in double the risk of fatal secondary cancer (3\% Sv⁻¹ compared to 1.5\% Sv⁻¹). Kry et al. found that 18-MV IMRT with a Varian unit resulted in a risk of fatal secondary cancer of 5.1\% Sv⁻¹, while the risk for 18-MV conventional radiotherapy was 1.7\%.

Clinical implications and simple means of reducing out-of-field dose

There is strong evidence for radiation-induced cancer, even at low dose levels, such as those due to out-of-field dose from radiotherapy procedures. The International
Commission on Radiological Protection[6] does not assign specific dose limits to patients undergoing radiotherapy, precisely because it is the cell-killing function of ionizing radiation that is the desired effect, and restricting any dose may reduce the efficacy of the treatment. Few would argue with the notion that the curative effects of radiation therapy outweigh the potential detrimental consequences; nonetheless, there is clearly a need to maintain an awareness of out-of-field doses and the risks they pose to patients. This is of particular importance in certain contexts, such as the treatment of pediatric patients.

What has been demonstrated in the present work is that there are a range of contributors to out-of-field dose. As such, it may be possible — by careful selection of treatment parameters — to minimize out-of-field dose and the associated risks thereof. The day-to-day transference of patients between linacs in a clinic is routine, because there...
is an understanding that a treatment on a different linac is equivalent provided the treatment plan is the same. For the in-field doses, this should indeed be the case, since linacs are individually commissioned and linac-specific data is incorporated into the treatment planning system (TPS). For this reason, anecdotal evidence suggests that oncologists and other clinicians are often surprised that there may be significant differences in out-of-field dose, and that in this regard treatments on different machines may not be identical. Treatment planning systems are generally commissioned using data that extend only centimeters beyond the field edge, with penumbra defined as 80% to 20% of the maximum dose for the field. Dose beyond this field is not intended to be incorporated into the overall dose calculation or to contribute to the inverse optimization procedure, and indeed it has been shown that treatment planning systems significantly miscalculate doses far from the primary field.\textsuperscript{[50]}

In cases where out-of-field doses may be more critical, such as treatment of a pediatric patient or pregnant female, it is worthwhile considering the various influences on out-of-field dose. Where possible, attempts should be made to choose delivery parameters that result in an equivalent treatment to the targeted lesion but are likely to generate less out-of-field dose. A summary of parameters that influence out-of-field dose is given in Table 2.

| Parameter               | Suggestions for reducing out-of-field dose |
|-------------------------|-------------------------------------------|
| Accelerator model       | Philips and Varian linacs generate less OF photon dose than Siemens, though the Varian generates more neutron dose. Vertical waveguide linacs should be used in preference to horizontal waveguide (multiple-energy mode) linacs. |
| Collimator              | Particularly on Varian machines, alignment of the craniocaudal axis with the x-plane of the collimators may result in reduction in OF dose of up to an order of magnitude. Collimator scatter varies between machines but becomes less important at large distances. |
| Energy                  | OF photon doses are generally lower in high-energy modes. High-energy modes generate neutron doses, but there is high uncertainty in neutron dose equivalents, and the actual increased risk due to neutrons may not be significant. |
| Treatment technique     | Intensity-modulated radiotherapy generally results in significantly higher OF dose than conformal radiotherapy. Stereotactic radiotherapy generates similar OF doses far from the primary field, where leakage begins to dominate over scatter. |
| Shielding               | The dominance of leakage over patient-scatter far from the primary field indicates shielding around the patient may reduce OF dose. Care must be taken that backscatter from shielding does not introduce additional OF dose. |

There is an increasing awareness of out-of-field doses and their corresponding long-term risks in radiotherapy. One can consider 3 broad regimes of out-of-field dose, illustrated in Figure 13. Close to the primary field, where deterministic effects are relevant, the treatment planning systems typically calculate doses well. Centimeters beyond the penumbra (where stochastic effects are dominant) is best calculated by Monte Carlo methods. Far from the primary field (where low-risk stochastic effects are relevant), measurement of the leakage dose would best inform risk assessment — since it is relatively difficult to construct a Monte Carlo model that very accurately determines leakage dose at large distances.

Note that these are not strict rules, but merely general observations based on the data presented in the present review. It is strongly recommended that each institute / clinic undertake its own measurements of out-of-field dose using equipment available, and use these measurements to inform clinical decisions.

**Outlook**

There is an increasing awareness of out-of-field doses and their corresponding long-term risks in radiotherapy. One can consider 3 broad regimes of out-of-field dose, illustrated in Figure 13. Close to the primary field, where deterministic effects are relevant, the treatment planning systems typically calculate doses well. Centimeters beyond the penumbra (where stochastic effects are the relevant risk), planning systems tend not to predict dose accurately, and a Monte Carlo model that accurately calculates collimator scatter and patient-scatter would be the preferable option for dose determination. Far from the primary field, where low-risk stochastic effects are relevant, measurement of the leakage dose would best inform risk assessment — since it is difficult and computationally-intensive to achieve accurate Monte Carlo predictions of leakage dose at large distances.

It is conceivable that the increasing efficacy of radiotherapy, which serves to increase patients’ lifetimes, will result in greater consideration of potential late effects, such as radiation-induced cancer. There are notable relationships between out-of-field dose and treatment parameters, which indicates that plan optimization in terms of out-of-field dose reduction is achievable.
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