Application of Monte Carlo algorithms to the calculation of dose and RBE for low energy brachytherapy

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**Application of Monte Carlo
algorithms to the calculation
of dose and RBE for
low energy brachytherapy**

Shane White

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Application of Monte Carlo algorithms to the calculation of dose and RBE for low energy brachytherapy

Dissertation

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Dedicated to the love of my life, Scarlett.

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Chapter 1:

Introduction and outline of thesis

Introduction

Brachytherapy is a form of radiotherapy that utilizes small encapsulated radiation sources placed close to or inside a target volume. As with other forms of radiotherapy, brachytherapy involves the delivery of a prescribed dose of radiation to a clinically relevant volume within the body for the purpose of killing cancerous cells. As one of the oldest forms of brachytherapy, the design of radiation sources has changed over the decades. Low energy brachytherapy, where photons with energy below 50keV are used to treat patients, has been a topic in a recent AAPM Radiation Therapy Task Group, TG-186(Beaulieu *et al.*, 2012). TG-186 has highlighted short-comings in the current protocol with regard to the water-based dose calculation models currently used as described in TG-43U1(Rivard *et al.*, 2004b).

Low energy brachytherapy can utilize high dose rate (HDR) and low dose rate (LDR) sources and can be further subdivided into the mechanism of photon emission. Traditional low energy brachytherapy sources have used radionuclides such as palladium-103 and iodine-125 in the treatment of breast and prostate brachytherapy(Blasko *et al.*, 2000; Pignol *et al.*, 2006a; Schellhammer *et al.*, 1977). These types of sources are typically LDR and are permanently implanted into the patient. Low energy HDR brachytherapy uses electronic brachytherapy sources (EBS) such as the Xofig Axxent(Rivard *et al.*, 2006b) and Zeiss Intrabeam(Kraus-Tiefenbacher *et al.*, 2005).

Current state of the art: TG-43U1

The current dose calculation platform used in the clinical environment, AAPM TG-43U1, uses water-based models to predict the dose distribution around sources. Dose to any 2D point around a source can be calculated using the equation (or: expression):

$$\dot{D}(r, \theta) = S_k \cdot \Lambda \cdot \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} \cdot g_L(r) \cdot F(r, \theta) \quad (1)$$

Where S_k is the source strength, Λ is the dose-rate constant, $G_L(r, \theta)$ is the correction to account for dose-rate falloff at distance r and angle θ along the sources transverse plane, due to the inverse square law compared to the reference distance r_0 (1cm) and angle θ_0 (90 degrees). $g_L(r)$ is the radial dose function and reflects the dose fall-off due to radiation absorption and scattering. $F(r, \theta)$ is the anisotropy function and corrects the change in dose-rate as a function of angle due to source construction. $F(r, \theta)$ and $g_L(r)$ originate from lookup tables derived for the particular brachytherapy source and are calculated using MC simulations and/or measured using experimental methods such as TLD, radiochromic film or ion chamber measurements. Dose-rates from multiple sources are calculated from the superpositions of individual sources. TG-43U1 is advantageous for its dose calculation speed and its reasonable accuracy in simple homogeneous water-equivalent geometries with single high energy sources such as Ir-192. Deviations in accuracy become more apparent at lower energies and in more complex heterogeneous setups.

Figure 1: CT-based TG-43 treatment plan of APBI patient calculated using BrachyVision. The dose distribution (coloured lines as a percentage of prescription dose 34Gy) ignores the effect of tissue heterogeneities (shown in HU scale, absence of skin backscatter and applicator effects). The air and rib do not perturb the dose distribution

Problems in brachytherapy

Tissue heterogeneity

The use of low energy brachytherapy sources presents greater challenges in relation to dose prediction than with high energy sources. While low energy photons have a steep dose fall-off due to higher attenuation, the degree of attenuation depends strongly on the tissue composition with tissue of a higher atomic number (Z), such as rib or calcium-rich breast tissue, more strongly attenuating than low- Z tissue like adipose. The sensitivity of low energy photons to population variations in adipose tissue has been demonstrated (Landry *et al.*, 2010b), where varying concentration of hydrogen, oxygen and carbon results in significant differences in the dose distribution around a brachytherapy source. TG-186 recommends the use of more advanced model-based dose calculation algorithms (MBDCA) which in turn require more detailed descriptions of the patient geometry and composition. Accurate patient modeling requires realistic patient geometrical models which can be obtained using CT imaging (Afsharpour *et al.*, 2012). As CT-imaging distinguishes tissue based on HU/ mass density, proper identification of different tissue types is required. Current treatment planning systems (TPS) for brachytherapy ignore tissue heterogeneity and patient geometry and assume the TG-43U1 approach, with all tissues assigned the composition and density of water. The patient geometry is assumed to be a sphere 15cm in radius with the source at the centre. This approach is advantageous for dose calculation due to its simplicity. TG-43U1 allows for an easy comparison of dose calculations between patients.

Dose reporting

The method of reporting absorbed dose in low energy brachytherapy is controversial (Walters *et al.*, 2010) (Tedgren and Carlsson, 2013) due to the different nature of the dose quantities calculated. While radiation can be attenuated by any medium in a phantom, how the locally deposited dose is reported in MC is still a matter of discussion. Arguments for scoring and reporting the dose in the same medium as it was transported in (Radiation transported in medium, dose scored in medium: $D_{m,m}$) are that it is the quantity inherently calculated in Monte Carlo platforms and accurately reflects the physical dose given to tissue. However an alternative method, dose to water (Radiation transported in medium, dose scored in water: $D_{w,m}$) has been used extensively in TG-43 and the most clinical experience exists. In TG-43U1, all tissue was treated as water for photon transport and dose reporting ($D_{w,w}$) Arguments for the continued use of reporting $D_{w,m}$ are that human cells, where the most clinically relevant dose is deposited, is composed mostly of water and bulk tissue composition does not make a good substitute (Liu *et al.*, 2002). Conversion from $D_{m,m}$ to $D_{w,m}$ is possible (Tedgren and Carlsson, 2013) but may introduce greater uncertainties due to inaccuracies in the conversion factors (Tedgren and Carlsson, 2013) (see Dosimetry) TG-186 recommends the continued use of TG-43U dose calculation alongside $D_{m,m}$ and $D_{w,m}$ results.

Dosimetry

Accurate dose delivery in low energy brachytherapy also requires in-vivo dosimetry measurements, to ensure the prescribed dose has been delivered to the target, that dose to organs at risk has been minimized and to validate dose calculation algorithms particularly those using novel modeling techniques. Dosimetry measurements with low energy sources are inherently difficult and complex due to the high dose gradients and the large range of dose rates involved. Uncertainties in positioning of either the source or detector are magnified at close distances. For a linear source, the dose gradient is approximately 50%/mm at 4mm (Tanderup *et al.*, 2013), rendering even the dimensions of a small detector such as a thermoluminescence detector (TLD) important as they can no longer be considered to be point-objects. While the effect of the dose gradient decreases with distance (e.g. 9%/mm at 20mm), increased distance from the source reduces the signal to noise ratio (SNR).

Radiation detectors also must accommodate the energy dependence issues encountered when using detectors more commonly used in high megavoltage sources such as ion-chambers. To account for the physical and composition differences inherent with different heterogeneous chamber designs, a series of assumptions about how each detector measures dose are made. According to the Bragg-Gray Cavity theory, a gas filled cavity, serving as an ion chamber/detector, embedded in a medium can accurately measure the absorbed dose, provided the cavity is sufficiently small so that it does not alter the passage or fluence of electrons throughout the medium thereby allowing for charged-particle equilibrium (CPE). As the range of secondary electrons varies as a function of incident photon energy, the choice of cavity size required to achieve CPE in low energy brachytherapy sources can reach an impractically small nanometers. Photon-based detector using on mass-attenuation absorption co-efficients (large cavities) are more energy dependant as the photo-electric effect which dominates more at low energies (Tanderup *et al.*, 2013). Though ideal detectors should be

energy independent, the energy dependence of the detectors results in an over-response for low energies. . Low energy sources may also experience significant spectral changes with increasing distance from the source due to spectral hardening, where lower energy photons are filtered out of the photon spectrum more than higher energy photons. This creates a major challenge for energy dependent detectors. Detector types for brachytherapy dosimetry include MOSFET arrays (Bloemen-van Gurp *et al.*, 2009), TLDs (Perera *et al.*, 2005), Alanine detectors(De Angelis *et al.*, 1999), optically stimulated luminescence dosimeters(Sharma and Jursinic, 2013), Radiochromic film(Uniyal *et al.*, 2012) and plastic scintillation detectors(Kirov *et al.*, 1999; Thomadsen *et al.*, 2005). Each detector type has advantages and disadvantages in relation to its size, ease of use, availability, readout time, calibration, SNR, volume averaging, energy response, dose perturbations and biocompatibility. Readout time is an important factor in the use of detectors in permanent or single fraction brachytherapy as detectors requiring a long readout time, such as gafchromic film, TLDs and alanine, would not allow corrections to a treatment plan, should an under/over-dosing of a critical organ be measured.

Radiobiological effectiveness

The relative biological effectiveness (RBE) is defined as the ratio of the doses required by two radiation sources to cause the same level of biological effect. Sources with a higher RBE produce more cell damage per unit radiation. RBE is determined by the dose rate, total dose, level of fractionation and by a source's beam quality/spectrum. Currently, the International Commission on Radiation Protection have assigned a radiation weighting factor of unity for all photon emitting sources (ICRP, 2007), equating the biological effectiveness of high and low energy photon sources. Softer x-rays have been shown (Nikjoo and Lindborg, 2010) to increase the number of DNA strand breaks in cells, which is indicative of a greater RBE for low energy sources. As the spectrum of low energy sources may soften/harden with distance, the beam quality/RBE within the patient may vary throughout. Variations in RBE due to changes in beam quality are apparent in hadron therapy where the linear energy transfer (LET) of the beam increases with decreasing particle energy. LET mapping in particle therapy has been previously explored as a method of calculating the RBE-weighted dose maps (Grassberger *et al.*, 2011). Similar maps in low energy brachytherapy have not been generated.

Backscatter

For sources placed close to the surface of skin, the lack of radiation backscatter is not accounted for in TG-43U calculations. This can result in over-predicting the dose to critical organs and tumour volumes (ref) as many photons that are lost to the surroundings due to lack of attenuation are instead predicted to deposit dose locally. Lack of backscatter may also occur in regions close to low density regions in the body such as lungs and to a lesser extent, the rectum for prostate brachytherapy. The degree of under-dosage due to lack of backscatter material in HDR brachytherapy has been found to depend strongly (8-13% for depth from 1.5cm to 0.5cm) on the relative position of the prescription point with larger under-dosage at greater prescription depths(Raina *et al.*, 2005)..

Interseed attenuation

As well as tissue heterogeneities and backscatter, the impact of the source itself is unaccounted for in current TPS dose calculations algorithms. In the case of permanent brachytherapy for the prostate and breast, the sources involved in dose delivery, with a few exceptions(Khan *et al.*, 2008), are encapsulated in high-Z materials such as stainless steel or titanium for biocompatibility. The shape, composition and construction of the outer walls of these sources is accounted for in the anisotropic and radial dose function data used in the TPS. In the case of multi-seed implants, a shielding effect called inter-seed attenuation (ISA) occurs where one seed will attenuate radiation from another. As TG-43U1 calculates the dose-rate for multiple sources via the superposition of individual sources, the impact of the ISA is not calculated. Dose reduction due to ISA has been well-documented (Afsharpour *et al.*, 2008; Afsharpour *et al.*, 2010; Carrier *et al.*, 2006; Chibani *et al.*, 2005; Mason *et al.*, 2013). Post-implant dose calculations of LDR prostate brachytherapy patients using TG-43U1 and MC simulations have revealed a 5.8% to 12.8% decrease in D_{90} when ISA and tissue compositions are taken into account (Carrier *et al.*, 2006). The D_{90} impact of spectral and design variations of six different seed types was also explored using MC simulations where variations in the composition of the seed encapsulation influenced the degree of D_{90} reduction by between 4.8% to 1.5%. D_{90} reduction was the least for the polymer encapsulated Pd-103 OptiSeed (International Brachytherapy).

Applicator attenuation

HDR treatments typically involve a single source placed into multiple dwell positions until the desired dose distribution is achieved. As such there is no inter-source attenuation. HDR brachytherapy may require the use of applicators to ensure accurate positioning inside the patient or to avoid high dose gradients close to the source. Applicators used in high and low energy brachytherapy are ignored in TG-43U1. The neglect of applicator attenuation in high-Z uterine applicators has been shown to lead to appreciable over-dosing errors (3.5%) along the transverse plane for an Ir-192 source (Ye *et al.*, 2004). Similar MC studies have shown similar applicator effects on the dose to target volume in endorectal patients with applicator shields reducing the target volume dose from 97% to 94% in one study(Poon *et al.*, 2008b) and while tissue heterogeneities have not been shown to significantly alter predicted dose compared to TG-43U1 protocols in gynecological brachytherapy, the exclusion of air and applicator volumes has been noted as an important issue in another study(Desbiens *et al.*, 2013).

Applicators in low energy brachytherapy sources are utilized for skin (Rong and Welsh, 2010), rectal (Guo *et al.*, 2012; Richardson *et al.*, 2012) and breast (Dickler, 2009; Vaidya *et al.*, 2001). Of particular interest for this thesis are applicators used in accelerated partial breast irradiation (APBI). The Xofig[®] Axxent is an EBS used in APBI in a manner similar to MammoSite, a Ir-192 balloon catheter-based treatment used in breast irradiation (Edmundson *et al.*, 2002), with exception to the type of source used. The Axxent inflatable balloon applicator, designed to anchor itself inside the breast cavity during irradiation, contains high-Z elements which eases the delineation between the applicator surface and surrounding tissue during CT imaging for treatment planning. The impact of the Axxent balloon applicator on the dose distribution has been studied (Segala *et al.*, 2011). An applicator may be modeling

based on the outline visible during imaging but shortcomings in the modeling of applicators using CT-based voxelized descriptions have been highlighted (Fonseca *et al.*, 2014).

Table 1: classifying the significance of including dose modeling factors into dose calculation algorithms compared to TG-43 dose calculation

Source Significant?	Pd-103	I -125	Ir-192	EBS
Tissue heterogeneity	Yes	Yes	Bone/lung only	Yes
Interseed attenuation	Yes (minor in polymer seeds)	Yes	-	-
Applicator attenuation	-	-	Yes (Metal applicators) No (plastic applicators)	Yes (Axxent) No (Intrabeam)
Backscatter	Yes	Yes	Yes	Yes
Dose reporting ($D_{m,m}$, $D_{w,w}$ or $D_{w,m}$)	Yes	Yes	Bone/Lung dependant	Yes

Monte Carlo dose calculation

The TG-186 recommends the continued use of TG-43-based dosimetry alongside model-based dose calculation algorithms. Monte-Carlo (MC) based simulations have been recommended as one suitable alternative to the TG-43 formulation. MC dose calculation allows the simulation of photon and electron transport in realistic patient geometries. Patient information such as CT or MRI images, derived from pre-treatment/diagnostic scans can be used to construct patient geometries suitable for Monte Carlo dose calculation with delineated organs. . MC simulation requires considerable time (minutes to hours depending on the number of voxels used and required accuracy (Sarrut and Guigues, 2008)) for calculation precluding it from real-time use in clinical environments, but is considered the gold-standard in dose calculation(Beaulieu *et al.*, 2012) .

Objectives and outline of thesis

Influence of trace elements in human tissue in low-energy photon brachytherapy dosimetry

The impact on radiation dose of population variations in H, C, N and O percentage mass in breast tissue has been established for low energy brachytherapy sources (Landry *et al.*, 2010b). It has been shown (Carvalho *et al.*, 2007b) that the concentration of trace elements ($Z > 8$) in prostate and breast tissue are higher in cancerous tissue compared to healthy tissue. Current knowledge about the composition of tissue is derived from healthy human populations measured in studies widely used in ICRU reports (International Commission on Radiation Units and Measurements, 1992) (White, 1986). In addition, trace element concentration has not been measured with a high precision (rounded to 1 significant digit) with many low concentration of physiologically important elements such as iron and copper not measured at all. Given the larger photo-electric cross-section for trace elements (strongly dependant on photon energy and atomic number), it was investigated in this chapter whether the variations in the concentration of traces elements could bring a non-negligible change in a dose distribution in commonly treated tissues around a low energy brachytherapy source.

Comparison of TG-43 and TG-186 in breast irradiation using a low energy electronic brachytherapy source

In chapter 3, the recommendations described in TG-186 were applied to a series of clinical cases. 7 APBI patient cases, treated with the Xofig Axxent, underwent dose re-calculation for a more realistic model of the patient using TPS CT images. Using a Monte Carlo calculation platform, Geant4 (Agostinelli *et al.*, 2003b), the dose distribution was determined for each patient, taking into account applicator attenuation, tissue heterogeneity and backscatter correction, as recommended by TG-186. Tissue segmentation was used to distinguish breast voxels into separate tissues, given the complex gland structure and the Axxent balloon applicator was modeled using a novel mesh-based technique (Fonseca *et al.*, 2014). Variability in breast size allowed the impact of lack of backscatter to be explored compared to all-water models. A comparison was made between dose to the planning treatment volume (PTV) and skin organ at risk (OAR) calculated with the older TG-43 and the newer TG-186.

Measurement of absorbed dose to water around an electronic brachytherapy source. Comparison of two dosimetry systems: lithium formate EPR dosimeters and radiochromic EBT2 film

Accurate dosimetry is a very important factor in the quality assurance of radiotherapy treatments. As well as providing MC experimental validation, the absence of MBDCa-based dose calculation in some clinical treatments renders dosimeters provide the only dose verification method. This is particularly true in single fraction intra-operative radiotherapy

(IORT) where imaging or re-planning is neither available nor practical. In addition to the high dose gradients, inherent energy dependency, detector size and positioning uncertainties, the intrinsic efficiency (signal per absorbed dose) of a dosimeter may influence measurement accuracy. The accuracy of two dosimetry systems, gafchromic film (EBT2) and new EPR-based lithium formate, was explored for the Axxent 50kV source in chapter 4.

A comparison of the relative biological effectiveness of low energy brachytherapy source in breast tissue

In addition to tissue and applicator considerations in TG-186, the potential variation of RBE due to spectral and tissue changes may also impact dose treatment accuracy. Radiation quality influences the number of DNA strand breakages caused by radiation at a cellular level. These breakages are responsible for cell inactivation and cell death. It has been shown (Nikjoo *et al.*, 2002) that decreases in photon energy result in increased RBE. The extent to which this is true for EBS is unexplored.

Chapter 5 explores the RBE variations between two low energy EBS, the Xofig Axxent and the Zeiss Intrabeam, which output different spectra due to their respective design. Variations due to attenuation from each source's respective applicator as well as the changes in RBE in tissues at different distances away from the source were explored using DNA damage simulators.

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Chapter 2: Influence of trace elements in human tissue in low energy photon brachytherapy dosimetry

This work was part of an invited presentation at the “International Workshop on Recent Advances in Monte Carlo Techniques for Radiation Therapy”, held in Montreal, June 8-10, 2011

Abstract

Purpose

To determine the dosimetric impact of trace elements in human tissues for low energy photon sources used in brachytherapy.

Methods and materials

Monte Carlo dose calculations were used to investigate the dosimetric effect of trace elements present in normal or cancerous human tissues. The effect of individual traces (atomic number $Z=11$ to 30) was studied in soft tissue irradiated by low energy brachytherapy sources. Three other tissue types (prostate, adipose and mammary gland) were also simulated with varying trace concentrations to quantify the contribution of each trace to the dose distribution. The dose differences between cancerous and healthy prostate tissues were calculated in single and multi-source geometries.

Results

The presence of traces in a tissue produces a difference in the dose distribution that is dependent on Z and the concentration of the trace. Low- Z traces (Na) have a negligible effect ($<0.3\%$) in all tissues while higher Z (K) had a larger effect ($>3\%$). There is a considerable difference in the dose distribution between cancerous and healthy prostate tissues (4%) and even larger if compared to the trace-free composition (15%) in both single and multi-sourced geometries.

Conclusion

Trace elements have a non-negligible effect on the dose in tissues irradiated with low energy photon sources. This study underlines the need for further investigation into accurate determination of the trace composition of tissues associated with low energy brachytherapy. Alternatively, trace elements could be incorporated as a source of uncertainty in dose calculations.

Introduction

Low energy photon brachytherapy is an increasingly popular form of radiotherapy in prostate cancer as low dose rate transperineal permanent seed implantation (Nath, 1995) and as a form of radiation boost in breast cancer patients (Pignol *et al.*, 2006b). Low energy brachytherapy currently relies on the protocol of the AAPM Radiation Therapy Committee Task Group 43 (TG-43) (Nath, 1995; Rivard *et al.*, 2004a) to perform dosimetric evaluations of brachytherapy implants and other procedures. The TG-43 protocol considers a uniform water geometry 30 cm in diameter with a source positioned at the center and uses dose kernels based on this geometry to calculate the dose in clinical scenarios. This calculation method works well for high energy sources such as Ir-192. However dose calculations for low energy sources are sensitive to a number of factors such as tissue heterogeneities, rendering this form of dose calculation inaccurate. Low energy photons (< 50 keV) interact primarily through the photoelectric effect, a process which is highly dependent on the composition of the medium and the energy of the incident photon.

The AAPM Radiation Therapy Committee Task Group 186 (TG-186) is investigating model based dose calculation algorithms as an alternative to the current TG-43 protocol. Monte Carlo (MC) calculations are a potential alternative due to their ability to accurately simulate low-energy photon interactions in realistic geometries. MC simulation methods require voxel-by-voxel knowledge of tissue density and composition. The accurate determination of composition data has been shown to be challenging due to the significant degree of overlap of Hounsfield Units between different media in modern CT scanners (Schneider *et al.*, 2000). The elements found in tissues can be separated in two categories. Hydrogen, carbon, nitrogen and oxygen (HCNO) form the basis of soft tissues, each with concentrations in fractional weight greater than 1%, accounting for over 99% of the total weight, while other higher atomic number (Z) elements such as Na, S, P, Cl and K are present at a trace level ($< 1\%$). A recent study (Landry *et al.*, 2010a) has demonstrated that uncertainties and variations in the HCNO human tissue composition could have a significant effect on MC dose distributions. In that work, compositions were varied according to population distributions reported by Woodard and White (Woodard and White, 1986), with no special attention to the significance of trace elements. No study has been found that assesses the specific contribution of traces to the MC dose calculation, which potentially could lead to uncertainty in the dose. As low energy photons such as those found in permanent implant brachytherapy interact mainly through the photoelectric effect, we hypothesize that dose distributions could be sensitive to changes in concentration of higher-Z (> 8) elements. Small inter-patient variation of trace element levels could thus contribute disproportionately to dosimetric uncertainty.

The trace composition of human tissues has been shown to vary considerably depending on the clinical state of the tissue such as the presence and stage of cancer (Carvalho *et al.*, 2007a). If trace elements have an impact on the dose distribution, individual variations in the concentration could produce uncertainties in the dosimetry. Megavoltage photons interact primarily through Compton scattering which is Z-independent and hence the trace composition can be largely ignored for high energy radiotherapy.

A study was performed to investigate the importance of trace elements in low energy photon brachytherapy in healthy and cancerous human tissues using MC simulation techniques.

Methods and materials

The software package used for the simulations in this study was Geant4 v9.3. Geant4 is an all purpose MC simulation toolkit that provides a diverse set of software components that can be employed in a variety of settings, including the simulation of photon transport from low energy sources (Agostinelli *et al.*, 2003a). This paper uses the Lawrence Livermore National Laboratory low energy electromagnetic model which simulates the low energy photon interactions of the Photoelectric effect, Compton scattering and Rayleigh scattering. The model uses the EPDL (Cullen *et al.*, 1997), and EADL (Perkins *et al.*, 1997) evaluated libraries. All secondary electrons are made to deposit their energy locally due their short range compared to typical voxel sizes; hence dose is approximated by collision kerma. In view of the current debate over dose reporting (Ma and Li, 2011a), both dose to medium ($D_{m,m}$) and dose to water ($D_{w,m}$) should be reported (both methods transport photons in medium (Landry *et al.*, 2011)), but as this study is a demonstration, the majority of the results are reported in $D_{m,m}$.

Composition of tissues

The elemental constitution of the human tissues used in the first part of the study were taken from a commonly cited review paper on compositions (Woodard and White, 1986) unless otherwise stated. Four tissue types were used in this study (Table 1). These were selected due to their association with low energy brachytherapy. All compositions in table 1 were taken from healthy adult tissues. While it has been shown that uncertainties in the composition of HCNO can affect low energy brachytherapy (Landry *et al.*, 2010a), the objective of this study is the investigation of the effects of trace element variations, and hence throughout the study the proportionality between H, C, N, and O in each tissue remained fixed however the trace component varied. In addition to this, the density of each tissue was also kept constant.

In the later part of the study, a simulation was performed using a trace composition derived from a study which describes a series of trace compositions measured to correlate their concentration to tumor stage (Kwiatk *et al.*, 2005). Among the tissues sampled was the prostate. The data provided describes the concentrations of trace elements ranging from Cl ($Z=17$) to Zn ($Z=30$). The effective atomic number Z_{eff} for each of the compositions was also calculated by:

$$Z_{\text{eff}} = \left(\sum_i w_i Z_i^{3.5} \right)^{1/3.5}$$

Where w_i is the mass fraction of the element i with atomic number Z_i .

In the final part of the study the composition from Kwiatek *et al* was applied to the CT geometry of a CT scan of a patient who underwent brachytherapy seed implantation.

Table 1: Composition of human body tissues relevant to low energy photon brachytherapy (derived from Woodard and White unless stated otherwise).

Elemental composition (by % weight)

Body tissue	Element with $Z \leq 8$				Trace elements with $Z > 8$					Density / kg m^{-3}
	H	C	N	O	Na	P	S	Cl	K	
soft tissue*	10.1	11.1	2.6	76.2	-	-	-	-	-	1000
prostate	10.5	8.9	2.5	77.4	0.2	0.1	0.2	-	0.2	1040
mammary gland	10.6	33.2	3.0	52.7	0.1	0.1	0.2	0.1	-	1020
adipose	11.4	59.8	0.7	27.8	0.1	-	0.1	0.1	-	950

* (ICRU Report 46, 1992)

Simulations

Using Geant4 v9.3, a spherical phantom 20cm in radius was modeled. The phantom contained a selected uniform composition and had a low energy isotropic point source placed at the center. The source had the photon spectral characteristics of one of three clinical sources, the 2301 I-125 source, the 2335 Pd-103 source (Best Medical, Springfield VA) and the Xofig Axxent electronic brachytherapy source (Xofig, Sunnyvale, CA) operated at 50 kV. The spectral characteristics of the Best seeds and Axxent source were derived using MC techniques (Landry *et al.*, 2010a; Liu *et al.*, 2008)

The source chosen depended on the clinical relevance it had to the tissue type, with 2301 (I-125) and 2335 (Pd-103) seed models being used in permanent seed prostate brachytherapy (Machtens *et al.*, 2006) and the Axxent source and Pd-103 seed used in breast brachytherapy (Hepel *et al.*, 2010b; Pignol *et al.*, 2006b). All MC simulations calculated the dose per particle in 1mm thick concentric spherical shells with the mid-radius of the first shell at 0.1 cm and last shell at 10 cm with the inverse square law dependence factored out (Landry *et al.*, 2010). Simulating 10^6 photons reduced the relative statistical uncertainty to less than 1% within a distance of 10cm of the source (Landry *et al.*, 2010a).

0.2% high-Z composition

Using the *soft tissue* composition from table 1, the MC phantom was filled with a fictitious medium where 0.2% of the composition was re-allocated to a single trace element with the *soft tissue*'s HCNO ratio remaining fixed. A total of 8 high-Z constituents were used (Table 2). The traces were chosen based on two reviews (Carvalho *et al.*, 2007a; Woodard and White, 1986), where these elements were the most abundant traces in tissues. Two special cases were also simulated; one excluding all traces (0%) and another including all the traces given an equal percentage to a total of 0.2%. 0.2% was chosen as it approximately corresponds to the weight fraction of the traces in several human tissues of several of the traces (Woodard and White, 1986). However it is likely an overestimation of the

concentration of other less abundant high-Z traces like Zn and Fe as well as an underestimation of the concentration of more abundant traces like Na, P and K.

Table 2: *Soft tissue* with a 0.2% trace component.

Scenario	Fraction by weight of trace (%)	HNCO (%)			
		H	C	N	O
Single trace element: Na, P, S, Cl, K, Ca, Fe, Zn	0.2	10.0798	11.0778	2.5948	76.0476
All traces present (Na-Zn)	0.2 (0.025x8)	10.0798	11.0778	2.5948	76.0476
HCNO only	-	10.1	11.1	2.6	76.2

Prostate, adipose and mammary gland

For simulating *prostate*, *adipose* and *mammary gland*, published tissue compositions listed in table 1 were used. The trace elements component for each tissue was modified by excluding one of the traces at a time and redistributing the percentage to HCNO accordingly. The aim of the exclusion was to determine the individual contribution of each trace to the dose distribution. The calculation was also performed for the exclusion of all traces. Differences in dose per particle for trace variations were assessed by first comparing inverse square law corrected radial dose profiles.

The differences were also quantified by plotting the mean dose deposited in a spherical volume against incremental increase to the radius (R) of the sphere, from a sphere of R = 0.1cm to a sphere with a radius of 10cm. Each mean dose value for successive radii was compared for all compositions and the percentage differences between them and the reference composition analyzed. This method allows for a more realistic representation of the dosimetric impact of trace compositions in a 3-D volume, rather than using a simple 1-D radial dose function profile which does not take into account the geometric effects on dose distributions.

Healthy versus cancerous prostate tissue

No recent comprehensive study into tissue composition with a full spectrum of elements could be found. However many studies into the concentration of trace elements present in human tissue have been done (Carvalho *et al.*, 2007a; Kwiatek *et al.*, 2005; Sarafanov *et al.*, 2008; Zaichick and Zaichick, 2012). These studies investigate variations in concentrations of traces for the purpose of diagnosing the presence and stage of cancer. Of particular interest is the variation in the concentration of traces between healthy and cancerous tissue in the prostate (Kwiatek *et al.*, 2005). The majority of the elemental composition, the HCNO component, was not reported. Kwiatek *et al.* reported the average trace concentrations of each element in healthy prostate tissue, prostate tissue classified as adenocarcinoma with Gleason score 5 and one with Gleason score 3. All samples were taken from healthy and cancerous segments of the prostate of six cancer patients.. Only the Gleason score 5 (CA-5) and healthy prostate tissue trace concentrations were used in our study. The Woodard and White prostate (*W&W prostate*) was updated to include the new trace data (Table 3). The trace composition was added at the equal expense of the HCNO components with the ratio between H, C, N, and O maintained in order to ensure a fair comparison to other simulations. Kwiatek *et al.* did

not include some trace elements that were present in the *W&W prostate* and so these elements were not adjusted or removed. Of all the traces measured in both studies, there was only one overlap, potassium (K) where both papers reported different percentages. In such cases of conflicting data, Kwiatek *et al.* values were used. Each composition from table 3 was simulated. The method used to determine the trace concentration in Kwiatek *et al.*, synchrotron radiation induced X-ray emission (SRIXE), is described as having a statistical uncertainty of 15-20% in a related paper (Kwiatek *et al.*, 2001). Kwiatek *et al.*'s (2005) reports large standard deviations in the concentrations recorded in the average of all the patients due to the variations between patients and though the standard deviations among some of the concentrations can be as large as 20% for some of more abundant traces, we feel that given the exploratory nature of this study, our chosen concentrations are acceptable. As with the previous section, the dose per particle profiles were integrated over a spherical volume and the percentage difference, relative to the *W&W prostate*, was plotted against the radii of the integrating spherical volume.

Table 3: Composition and effective atomic number (Z_{eff}) of four healthy and cancerous prostate tissues with varying trace concentrations.

	W&W prostate (Woodard and White, 1986)	No traces (HCNO only)	Healthy prostate (Kwiatek <i>et al.</i> , 2005)	Cancerous prostate (Prostate CA-5) (Kwiatek <i>et al.</i> , 2005)
Element	%	%	%	%
H	10.500	10.574	10.482	10.4558
C	8.900	8.962	8.885	8.8625
N	2.500	2.517	2.495	2.4894
O	77.400	77.945	77.272	77.0742
Na	0.2000	-	0.2000	0.2000
P	0.1000	-	0.1000	0.1000
S	0.2000	-	0.2000	0.2000
K	0.2000	-	0.1475	0.3620
Cl	-	-	0.18000	0.18300
Ca	-	-	0.01200	0.04100
Zn	-	-	0.01580	0.01760
Fe	-	-	0.00520	0.01145
Cu	-	-	0.00127	0.00121
Co	-	-	0.00038	0.00054
Ni	-	-	0.00045	0.00051
Mn	-	-	0.00018	0.000345
V	-	-	0.000041	0.000202
Cr	-	-	0.00013	0.000087
Z Effective	7.50	7.34	7.53	7.63

Effect of trace composition in a multi-source patient geometry

Of clinical interest is the dosimetric impact that trace concentration variation could have on a realistic patient geometry with multiple sources. A previous study (Landry *et al.*, 2010a) had described the effect of HCNO variation in a multi-source geometry. In Landry *et al.*, 4 post-implant CTs of prostate brachytherapy seed patients were converted into a voxelized

geometry using an in-house CT image conversion tool, BrachyGUI (Poon *et al.*, 2008a). The CT images gave a complete visualization of the prostates, which were contoured by a clinician. During the voxelization each voxel was assigned adjustable elemental composition and the corresponding density. As the tumour volume could not be delineated on the CT images the entire prostate was assigned a single composition. The number of seeds and their position were measured using Seedfinder (VariSeed, Varian, Palo Alto, CA). In the case of this study the patients had between 51 and 99 I-125 2301 seeds implanted.

In our study, each composition from table 3 was simulated as the prostate composition for each patient. In all cases the remaining voxels outside of the prostate were assigned as water. A separate simulation using a prostate with a water composition was also simulated to enable a comparison to TG-43 parameters. In all cases the inter-seed attenuation was ignored by using a phase space file as the particle source. The minimal dose to 90% of the prostate volume (D_{90}) in each simulation was calculated post-simulation using BrachyGUI.

Results and discussion

For all of the MC simulations, the results were plotted with $D_{m,m}$ per photon against radial distance from the source. The dose was multiplied by the square of the radial distance to factor out the inverse square law to clarify the effect of the traces.

Effect of trace elements in soft tissue

soft tissue with 0.2% trace

Figure 1: The dose profile for $D_{m,m}$ for Pd-103 (A), Axxent (B) and I-125 (C) sources in *soft tissue* using a varying Z trace. Different dose reporting methods are shown for an I-125 source as $D_{m,m}$ (C) and $D_{w,m}$ (D).

As can be seen in Figures 1 A-C for the three brachytherapy sources the lower Z trace elements such as Na and S have a smaller effect on the dose profile than higher Z elements like Zn and Fe for a 0.2% weight concentration, due to their lower photoelectric effect cross section. The $D_{m,m}$ from the I-125 and Pd-103 sources show a Z-dependent maximum within a few millimeters from the source. In figure 1A, the Pd-103 source exhibits a sharp peak and steep falloff. The I-125 source exhibits a flatter Z-dependent dose falloff due to the slightly higher photon energy of this isotope compared to Pd-103. The Axxent source has its maximum in the first shell (0-1mm). Both brachytherapy radioisotopes have a discrete spectrum while the Axxent source has a continuous spectrum. As can be seen in the figure from A-C the differences in the appearance of all graphs demonstrate the strong spectral dependence on the dose profile, and the varying magnitude that different traces has on them. In general, and as expected, the addition of higher Z elements causes $D_{m,m}$ to increase near the source. Due to the increased attenuation, the dose gradient also becomes steeper with increasing Z leading all the profiles in each figure to cross-over at a certain distance from the source

Figures 1CD show the difference between $D_{w,m}$ and $D_{m,m}$ for an I-125 source for different traces. The dose pattern is different when scoring $D_{w,m}$ with lower Z compositions. The slopes are similar between $D_{w,m}$ and $D_{m,m}$ but the dose in the first shell differs by the ratio of mass energy absorption coefficients. The difference occurs because the photons are transported and attenuated in the medium but $D_{w,m}$ is scored in water. For all cases the photon fluence close to the source can be assumed to be the same, when scoring $D_{w,m}$ the mass energy absorption coefficients of water are used, resulting in almost identical doses close to the source (Fig 1D). For scoring $D_{m,m}$ the photon fluence close to the source is effectively multiplied by different mass energy absorption coefficients for different media, resulting in different doses (Fig 1A-C). This section shows that dose differences caused by traces can be quite different close to the source for $D_{m,m}$ or at larger distances if $D_{w,m}$ is considered. It is therefore important to report the dose scoring scheme used.

Effect of trace elements in prostate, adipose and mammary gland

Prostate

The results for the MC simulation in *prostate* are found in figure 2. The removal of the lower Z component, Na, from the *prostate* composition has a relatively small effect (<0.5%) on the dose profile while the removal of higher Z (S and K) reduce the peak dose per particle by 4%. If all traces are removed this difference increases to 7% (Fig 2A). The difference between the curves decreases with increasing distance to a crossover point before they increase again in the opposing direction.

Figure 2B shows the mean dose $D_{m,m}$ in spheres of increasing radius centered on the source . It can be seen that the relative difference between compositions is greatest close to the source. Also it can be seen that low Z elements have an almost negligible effect on the dose per particle for all distances as opposed to higher Z materials. The absence of all traces has the largest impact on the average dose per particle in a volume, as more of the photons pass through the medium unattenuated. This shows that the presence of the high Z elements induces a greater energy deposition as a function of distance. It should be noted that the

difference in integrated energy in all cases approaches zero at a large enough distance due the conservation of energy (i.e. the total energy deposited will eventually be equal).

Figure 2: (A) The $D_{m,m}$ profiles of the I-125 source in *prostate* tissue with and without trace elements. (B) The dose difference between each variation, relative to *all traces*, integrated over a spherical volume.

Figure 3: $D_{m,m}$ profiles in adipose for (A) Pd-103 and (B) Axxent sources and in mammary gland (C) Pd-103 and (D) Axxent with and without trace elements

Figure 3AB shows the dose profile for two sources in *adipose* for varying trace elements. The Pd-103 seed and the Axxent source demonstrate similar profiles in both figures, with a similar response to the removal of trace elements. The maximum percentage difference between *All traces* and *HCNO only* in figure 3AB is similar for both sources (4% for Pd-103 and 4% for the Axxent).

Figure 3CD for mammary gland possesses the same characteristics of the two other tissues *prostate* and *adipose* with a gradual decrease in the maximum of the dose profiles as higher Z traces are removed. The maximum difference between the *HCNO only* and *all traces* is 5% and 4% for Pd-103 and the Axxent respectively. *Adipose* has a lower trace content than *mammary gland* but has a similar maximum percentage difference when the traces are removed due to *adipose*'s lower average Z compared to *mammary gland*. This gives *adipose* a greater sensitivity to changes in the trace composition. It has also been shown that the composition of adipose tissue can vary significantly between samples and so the effect that each trace has on the dose can vary (Landry *et al.*, 2010a). It is worth noting that as real breast tissue is a complex mixture of adipose and mammary tissue (Nelson *et al.*, 2008) and not homogenous as in this case, the results from these tissues are not based on a realistic case. A more detailed study should use a composition based on a segmented breast geometry such as those described in Afsharpour *et al* and Nelson *et al* (Afsharpour *et al.*, 2011b). However our study demonstrates clearly that traces have a non-negligible effect on dose distributions in addition to the uncertainties related to tissue segmentation

Healthy versus cancerous prostate tissue

Figure 4AB shows the different dose profiles of four prostate compositions and the mean dose differences, relative to *W&W prostate*, when they are integrated over a spherical volume. It is worth noting, in figure 4B, the difference between *prostate CA-5* and *HCNO only* of 15% at 0.5cm. Another notable difference is the variation between Kwiatek *et al.*'s *healthy prostate* and cancerous *prostate CA-5* dose profiles which has a maximum difference of 4% at 0.5cm. This shows that the trace concentration difference between healthy and cancerous tissue may be large enough to produce a considerable dose difference. It should be mentioned that Kwiatek *et al.* measured only certain trace elements (missing most notably Na, P and S) and therefore, their data may be incomplete. This may cause an unquantifiable systematic error and as such the results from this section should not be seen to quantify the exact differences in dose profiles between healthy and cancerous tissue, but it should demonstrate that potential changes in trace concentration may have a non-negligible effect on dose distributions. A cancerous prostate is also not composed entirely of cancerous tissue and is actually a mixture of both healthy and cancerous tissue. This constitutes another source of uncertainty as a CT image cannot make any distinction between cancerous and healthy tissue. However advances in dual energy CT (DECT) may allow for better delineation of prostate tissue or perhaps even a elemental breakdown of the tissue itself (Liu *et al.*, 2009). Kwiatek *et al* also possesses large standard deviations in its measured trace compositions due to inter and intra patient composition variations as well as uncertainties with the measurement modality, SRIXE. However this study is merely a demonstration and the uncertainties and variations emphasize the necessity for further study.

Figure 4: (A) $D_{m,m}$ profiles in four prostate tissues using different trace compositions derived from Woodard and White (W&W) and Kwiatek *et al.* (B) The difference in mean dose between the different tissues, relative to *W&W prostate*, over a spherical volume.

Effect of trace composition in a multi-source patient geometry

Table 4 shows the D_{90} for various compositions, in absolute and relative to a water composition. The D_{90} for all 4 prostate compositions from table 3 increase with increasing trace composition with a maximum difference of 9-12% (14-16Gy) between a zero-trace composition (*No traces*) and cancerous prostate tissue (*Prostate CA-5*) for all patients.

It can be seen here that trace elements can cause a notable dose variation, not only in single source geometries but also in a multi-source clinical scenario. However there are some significant sources of uncertainty in this study. Again these simulations assume a prostate of uniform composition of either healthy or cancerous tissue, which is unrealistic, but is a necessary assumption if only CT images are available. Among the other heterogeneities that are present in the prostate are calcifications, small regions with a high concentration of calcium, observable on CT and ultrasound. Calcifications are not present in all prostates and can be confused for seeds and so constitute a source of uncertainty. It is unknown how calcification affects the concentration of calcium in the whole prostate but the effects of calcifications on the dose distribution have been explored (Chibani and Williamson, 2005) .

Table 4: The D_{90} for the 4 prostate compositions ,in absolute and relative to a water-based composition

Patient/ No. of seeds	Composition	Water	W&W prostate	No traces	Healthy prostate (Kwiaterek <i>et al</i>)	Cancerous prostate (Kwiaterek <i>et al</i>)
Patient 1 N=75	D_{90} (Gy)	141.6	140.1	133.2	142.5	146.4
	% of Water	100	98.9	94	100.6	103.4
Patient 2 N=77	D_{90} (Gy)	154.3	152.6	144.6	155.9	160.4
	% of Water	100	98.9	93.7	101	104.5
Patient 3 N=51	D_{90} (Gy)	145.3	143.9	136	146.2	151.2
	% of Water	100	99	93.6	100.6	104
Patient 4 N=99	D_{90} (Gy)	146.1	144.2	137.4	146.4	150.1
	% of Water	100	98.6	94	100.2	102.7

Conclusion

Dose distributions were obtained from MC simulations for low energy brachytherapy sources in human tissues with varying trace element content. The simulations, scored with dose to medium $D_{m,m}$, show a strong dependence to the Z and the concentration of the trace present. The absence of low Z traces like Na from a tissue has a negligible effect on the dose calculation when compared to higher Z traces like Fe and Zn. The effect of a trace is also dependent on the mean energy and photon spectrum of the source being simulated, with lower mean energy sources exhibiting a greater sensitivity. Results from this study show that the trace component of a tissue is not negligible in low energy brachytherapy MC calculation and therefore should not be excluded from MC calculations. The variation in trace concentration between healthy and cancerous prostate tissue was shown to alter the dose distributions.

Further study of the trace elements in human healthy and cancerous tissues is needed, as well as studies into the potential variability between compositions in a population of patients. While it may be possible that the next generation CT scanners will be able to determine the tissue composition, it is unlikely that trace component will be measured to a high (or any) level of accuracy nor that patients will have individual biopsies to determine the elemental composition of their tissues. As such, the potential dose uncertainties caused by trace element composition uncertainties should be quantified.

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Chapter 3:

Comparison of TG-43 and TG-186 in breast irradiation using a low energy electronic brachytherapy source

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Abstract

Purpose

The recently updated guidelines for dosimetry in brachytherapy in TG-186 have recommended the use of model-based dosimetry calculations as a replacement for TG-43. TG-186 highlights shortcomings in the water-based approach in TG-43, particularly for low energy brachytherapy sources. The Xofig Axxent is a low energy (<50kV) brachytherapy system used in accelerated partial breast irradiation (APBI). Breast tissue is a heterogeneous tissue in terms of density and composition. Dosimetric calculations of 7 APBI patients treated with Axxent were made using a model-based Monte Carlo platform for a number of tissue models and dose reporting methods and compared to TG-43 based plans.

Methods and materials

A model of the Axxent source, the S700, was created and validated against experimental data. CT scans of the patients were used to create realistic multi-tissue/heterogeneous models with breast tissue segmented using a published technique. Alternative water models were used to isolate the influence of tissue heterogeneity and backscatter on the dose distribution. Dose calculations were performed using Geant4 according to the original treatment parameters. The effect of the Axxent balloon applicator used in APBI which could not be modeled in the CT-based model, was modeled using a novel technique that utilizes CAD-based geometries. These techniques were validated experimentally. Results were calculated using two dose reporting methods, dose to water ($D_{w,m}$) and dose to medium ($D_{m,m}$), for the heterogeneous simulations. All results were compared against TG-43-based dose distributions and evaluated using dose ratio maps and DVH metrics. Changes in skin and PTV dose were highlighted.

Results

All simulated heterogeneous models showed a reduced dose to the DVH metrics that is dependent on the method of dose reporting and patient geometry. Based on a prescription dose of 34Gy, the average D_{90} to PTV was reduced by between ~ 4% and ~ 40%, depending on the scoring method, compared to the TG-43 result. Peak skin dose is also reduced by 10 – 15% due to the absence of backscatter not accounted for in TG-43. The balloon applicator also contributed to the reduced dose. Other ROIs showed a difference depending on the method of dose reporting.

Conclusions

TG-186-based calculations produce results that are different from TG-43 for the Axxent source. The differences depend strongly on the method of dose reporting. This study highlights the importance of backscatter to peak skin dose. Tissue heterogeneities, applicator and patient geometries demonstrate the need for a more robust dose calculation method for low energy brachytherapy sources.

Introduction

Low-energy photon brachytherapy is an established form of radiotherapy that is used in the treatment of prostate cancer(Nath *et al.*, 1995) and with potential for extensive use in breast cancer(Pignol *et al.*, 2006a). These forms of cancer treatment utilize millimeter size seeds that encapsulate a photon-emitting radioactive material adsorbed to the interior of the seed. Low energy HDR breast brachytherapy is nowadays possible with an electronic brachytherapy (eBx) source(Dickler, 2009) which delivers radiation using a miniaturized x-ray source.

The recently published AAPM Radiation Therapy Committee Task Group 186 (TG-186)(Beaulieu *et al.*, 2012) report has provided new guidelines for dose calculation and reporting in brachytherapy to address the shortcomings of the current TG-43U1(Rivard *et al.*, 2004b) dose calculation methodology. In contrast to the TG-43U1 methodology where, for dose calculation purposes, the patient is treated as a 15cm radius sphere of water with uniform unity density, TG-186 recommends the use of model-based dose calculation algorithms (MBDCA) alongside current TG-43U1 methods for dosimetry. While TG-186 has relatively minor consequences for dose calculation in high energy ^{192}Ir brachytherapy, these updated guidelines have a greater impact for low-energy brachytherapy where the dose calculations are known to depend strongly on the composition of the interacting tissues(Landry *et al.*, 2010b) as well as tissue heterogeneities(Afsharpour *et al.*, 2011a; Sutherland *et al.*, 2012).

Of particular relevance is the application of TG-186 to photon emitting sources found in Accelerated Partial Breast Irradiation (APBI) particularly low energy eBx sources such as the Zeiss Intrabeam (Carl Zeiss, Oberkochen, Germany) and the Axxent (Xoft, Fremont, CA). One of these systems, the Axxent, is similar to the MammoSite system (Hologic Inc., Bedford, MA) in which a balloon catheter is inserted into a breast lumpectomy cavity. The MammoSite system uses an ^{192}Ir source whereas the Axxent uses a 50 kV x-ray eBx source. The Axxent source is a miniature x-ray tube contained within a 5.1 mm flexible cooling sheath. Water is continuously circulated throughout the source's activation to prevent overheating. The source is non-radioactive, making it easier to store and transport. The dose rates at 1cm along the transverse axis in water are equivalent to a 370 GBq (10Ci) HDR ^{192}Ir source while the depth-dose characteristics are similar to ^{125}I and ^{103}Pd sources(Rivard *et al.*, 2006b). The Axxent source can be operated at a variety of voltages but is clinically mainly used at 50 kV. By comparison to ^{192}Ir , which emits photons of average energy 380 keV, the Axxent has a low energy source that emits photons as a continuous spectrum up to 50 keV with an average energy of 33 keV(Liu *et al.*, 2008). This allows the operation of the device with minimal shielding needed for medical staff during treatment. Low energy photons interact with tissue partially via the photoelectric effect which has an interaction probability that depends strongly on the average atomic number (Z) of the tissue ($\sim Z^3$). Knowledge of the composition/type of the breast tissue to be irradiated is therefore very important.

Tissues in the breast are composed of glandular and adipose tissues (Figure 1). The breast is structured with complex tree-like high density glandular tissue, composed of ducts and lobules, embedded in adipose confined on two sides by skin and ribs(Nelson *et al.*, 2008). TG-186 recommends tissue/material assignment based on contours approved by the radiation oncologist. However adipose and glandular tissue in the entire breast is not contoured. The proportion of glandular to adipose tissue varies in the population(Yaffe *et al.*, 2009) which

has been shown to be a significant factor in dose calculations for low energy sources like ^{103}Pd (Afsharpour *et al.*, 2010) or ^{125}I (Furstoss *et al.*, 2009). Moreover, the tissue composition of individual patients is not accurately known; the compositions listed in reports such as ICRU 46 (International Commission on Radiation Units and Measurements, 1992) and ICRP 89 (International Commission on Radiological Protection, 2002) are population averages based on samples. It has been shown that dose to specific tissues of interest in segmented breast models can show significant differences to breast models using composite breast compositions (Afsharpour *et al.*, 2010; Sutherland *et al.*, 2011).

In our study we present a retrospective TG-186 model-based dose calculation on patients who underwent APBI with the Axxent eBx source. We assessed the influence of using a realistic multi-tissue patient geometry (heterogeneous model) to determine the dose distribution. Two different tissue modeling schemes were explored. The importance of proper balloon applicator modeling was also studied. We compared dose distributions calculated using TG-43, two TG-186 models and two dose scoring methods.

Methods and Materials

Patient Cases

3D treatment planning CT images from 7 patients who underwent APBI were used to create the multi-tissue patient geometries simulated in this study. The CT image data was anonymized and de-identified prior to entry in this study. All patients had the Xofig balloon applicator inserted at the time of CT imaging and each patient was treated with the Axxent S700 source. The BrachyVision (Varian, Palo Alto, CA) treatment planning system (TPS) was used for determining the TG-43 dose calculations. The prescription dose regime for each patient was 10 fractions of 3.4 Gy for a total dose of 34 Gy. All treatment plans used a single applicator with multiple dwell positions and dwell times. Delineations of the planning treatment volume (PTV), skin and balloon wall were provided. The PTV margins were 0.8 cm to 1 cm for all 7 patients. The minimum PTV edge-to-skin distance varied from 0 cm to 1.7 cm and the breast size ranged from 340 cm³ to 2000 cm³. The CT data set provided the MC simulation under a variety of different backscatter conditions and tissue structures. The air kerma source strength (S_k), dwell times and positions were obtained from the DICOM file generated by the TPS.

Figure 1: A CT slice of an APBI patient highlighting the PTV (inside blue contours) and skin contour (red). The PTV is contoured around the balloon applicator while the source is inserted into the hollow air channel in the centre of the balloon during treatment. Adipose and glandular tissues are highlighted.

Geant4, patient geometry generator and dose analysis tool

The software package used for the simulations in this study was the Monte Carlo (MC) toolkit Geant4 v9.5p02. Geant4 is an all purpose MC simulation toolkit that provides a diverse set of software components that can be employed in a variety of settings, including the simulation of photon transport from low-energy sources (Agostinelli *et al.*, 2003b). This paper used the Lawrence Livermore National Laboratory low-energy electromagnetic model which simulates the low-energy photon interactions of the photoelectric effect, Compton scattering and Rayleigh scattering. The model uses the EPDL-evaluated (Cullen D, 1997) and EADL-evaluated (Perkins, 1997) libraries. All secondary electrons were made to deposit their energy locally because of their short range compared to typical voxel sizes; hence the dose was approximated by collision kerma. The photon energy transport cutoff was 1keV. In accordance with the TG-186 recommendations, both dose to medium in medium ($D_{m,m}$) and dose to water in medium ($D_{w,m}$) were reported along with dose to water in water ($D_{w,w}$) from TG-43U1. In this notation, the first index refers to the dose-scoring medium (m or w) and the second index indicates the photon transport medium (m or w). $D_{w,w}$, $D_{w,m}$ and $D_{m,m}$ were all scored using track-length scoring (Williamson, 1987) with mass energy-absorption coefficients lookup tables used. All calculations were performed using a networked cluster of computers using HTCondor (Douglas, 2005) to reduce calculation time.

CT DICOM images were used to generate Geant4-compatible patient geometries. The Hounsfield unit to density conversion was calibrated against CT quality assurance scans performed using the CatPhan phantom (The Phantom Laboratory, Salem NY). Certain inserts were excluded from the calibration to ensure a linear fit to enable better distinction of adipose and glandular tissue. The conversion of these images to Geant4-compatible geometries was performed using BrachyGUI (Poon *et al.*, 2008a), an in-house dose analysis tool. BrachyGUI utilizes the CT Hounsfield units and assigns a material and a density to each voxel in a format to create an *egsphant* file (Kawrakow, 2007) (Figure 2). The assignment of each material can be density-based (if the materials density range is known) or manually changed (if contour information is available). The voxel resolution of the DICOM images in this study, ranging

from 0.42mm x 0.42mm x 3mm to 0.97 x 0.97 x 3mm, was maintained through the conversion. BrachyGUI also functions as a dose analysis tool. It was used to compare dose metrics between the dose distributions from different patient models. Dose ratio maps were also used to visualize hot/cold dose regions when comparing distributions directly.

Source modeling

The Axxent source (hereafter referred to as the S700) was modeled in Geant4(Liu *et al.*, 2008) based on detailed descriptions and diagrams of the sources' tip and validated against MC simulations described in Rivard *et al.*(Rivard *et al.*, 2006b). The exact compositions and dimensions of the S700 source are proprietary. In this model, 50 keV electrons are set in motion at the cathode and transported to a tungsten anode. Photons were generated via bremsstrahlung splitting (N=100) and characteristic x-ray generation. Photons that reach the outer cooling water sheath of the source (diameter 5.1mm) were recorded into a phase space file and then terminated. 10^9 primary electrons were simulated to generate a phase space file with 7×10^7 photons. No electrons were recorded due to their short range. The phase space source was validated against TG-43 data from Rivard *et al.*(Rivard *et al.*, 2006b). to within tolerated uncertainties (<3%). This phase space source was used to simulate photon emission from the S700 at several dwell positions for each patient. It should be noted that S700 source used in experiments described later (see section *Tip/Air channel modeling*) has a slightly different tip design compared to the older MC model in this study and Rivard *et al.*(Rivard *et al.*, 2006b). The impact of the updated design has not been explored.

Absolute MC dosimetry

The phase space source was used to sample photons from a source model to simulate a relative dose distribution. For a dosimetry evaluation study, absolute dose is calculated. A conversion factor for Geant4 dose per particle values to absolute dose values was needed to properly compare TPS-based plans to Geant4-based plans. The conversion from dose per simulated photon to absolute dose was based on air kerma measurements performed on an Attix free-air chamber described in a separate study(Davis, 2009). A MC simulation, based on the Attix chamber experiment(Davis, 2009), was performed where a small scoring volume, modeled as the air chamber with a 1cm diameter aperture with no cover/filter, was placed at 1 meter from the source in an air phantom at STP. The contribution of external backscatter was negligible in the measured values and was not accounted for in the simulation. The MC relative air-kerma was calculated from the simulated air chamber and used in conjunction with the measured air kerma (uncorrected for air attenuation) to create an absolute dose conversion factor for Geant4. As a validation, the dose rate constant (DRC) was also calculated (0.69 cGy/hr/U) and compared against the measured value (0.709cGy/hr/U)(Xoft, 2009) with good agreement (~3%). The dose per particle to real dose conversion factor was applied to all simulation results based on the treatment plan's reference S_k . Due to the lack of correction for air attenuation and backscatter, care should be taken not to confuse these S_k , DRC and U in air values with real *in-vacuo* values used in other brachytherapy calibration standards. The absence of backscatter and air attenuation correction

factors reflect the current air kerma calibration method provided by Xofig. Future updates to the S700 air kerma calibration may include these corrections. It should be noted that absolute dose (Gy), instead of relative dose (arbitrary units), was calculated for all patient geometry simulations for the purposes of future clinical studies with the Axxent eBx device. However, as this is an intra-comparison Geant4 study, absolute dose is not essential to draw conclusions from this study's results.

TG-43 Validation

To validate the Geant4 TG-186 patient calculations, a Monte Carlo-based TG-43 (TG-43 MC) simulation was performed on all of the patient geometries. During the conversion from DICOM to egsphant in BrachyGUI, all voxels were assigned as water with unity density and all were simulated according to the original TPS reference S_k , dwell positions and dwell times with the S700 phase-space file, described in previous sections. All regions outside of the egsphant volume were set to water with unity density to simulate TG-43-equivalent backscatter. A comparison of the TG-43 MC results for each patient was made with the original treatment plan from the BrachyVision TPS. A visual comparison was made using BrachyGUI which allowed the use of dose ratio maps. The dose metric D_{90} , the minimum dose to 90% of the PTV volume, the percentage of the PTV receiving 100% 150% and 200% of the prescribed dose, V_{100} , V_{150} and V_{200} were calculated for each of the patients in both the TPS plan and the MC result and used to compare both calculation methods.

Water-Air model

As an intermediate to the heterogeneous model, a Water-Air model for each patient was generated and simulated. All tissue (density $> 0.26\text{g/cm}^3$) and applicator voxels were assigned as water with unity density while low density tissue (density $< 0.26\text{g/cm}^3$) such as lung and areas outside of the body were assigned as air (density $= 0.0012\text{g/cm}^3$). This simple model was similar to TG-43 but took into account the absence of backscatter from air outside the patient (which contributes to the overestimation of skin dose when using TG-43)(Raffi *et al.*, 2010) and low-density lung tissue inside the patient. This would be used to isolate the effect of tissue heterogeneity in regions where non-patient backscatter (or absence of) would be an important factor in dose differences when comparing to TG-43. The individual contribution of each of the backscatter components, lung backscatter and non-patient backscatter, was also calculated by selectively assigning each region to air or water.

Heterogeneous model

A fully segmented tissue model was the basis for the realistic multi-tissue patient geometry. The segmented model (referred to as the *heterogeneous model* hereafter) is a realistic patient geometry using CT-derived densities and proper tissue assignment and composition. This model is the recommended tissue model for TG-186 dose calculation(Beaulieu *et al.*, 2012). For simplicity, only 5 tissues were modeled, based on their clinical relevance: skin, adipose tissue, glandular tissue, lung and rib. Muscle tissue was not modeled. The assignment of air, lung, rib or skin to voxels was based on their density and/or anatomical location. Adipose and

glandular tissues were more difficult to distinguish using density assignment as there exists a degree of overlap between the two in terms of density (Afsharpour *et al.*, 2010). A threshold between the two was calculated, first, by averaging multiple density samples of regions of breast which were unambiguously adipose or glandular tissue. This established the approximate density range for both tissues. The final threshold was chosen as the minimum density at which the glandular duct structure most accurately reflected that on the CT image (minimum 0.94g/cm^3). Each patient had a different threshold, perhaps due to age-related density changes though the ages of the patients were unknown. Due to the nature of the threshold and the overlapping density ranges of adipose and glandular tissue, some adipose was modeled as gland. The composition for these tissues was taken from ICRU 46 (International Commission on Radiation Units and Measurements, 1992). (Table 1). The tissue segmentation was visually inspected for all patients (Figure 2).

Figure 2: An eggsphant geometry file for Geant4 simulation with a fully-segmented breast geometry (right) converted from a HU-based CT image (left). The balloon applicator is also modeled here to highlight the air channel, saline-filled balloon and balloon tip (appearing as an artifact due to high absorption of barium).

The balloon applicator was modeled using 5 materials, air, saline solution, and 3 proprietary applicator materials. Air was present in the hollow applicator channel where the S700 source is inserted and repositioned at dwell points inside the applicator during the treatment. The applicator balloon is filled with a 0.9% weight per volume saline solution during APBI treatment. The applicator materials are the balloon wall, which is composed of barium-sulphate silicone compound, (acting as contrast medium for visibility on CT images), a balloon tip which compensates for the lack of attenuation by the air channel, prominent when dwell positions are far away from the tip of the applicator and a stiffener which maintains the rigidity and shape of the air channel (Figure 3).

Figure 3: A schematic diagram of the Axxent balloon applicator. The S700 source (purple) can be placed at multiple dwell positions inside the applicator to deliver the desired dose distribution, creating an air channel of variable length (blue). The source is replaced by a phase space file inside the applicator (green arrows) during MC simulation.

Table 1: The ICRU 46 tissue compositions for the 5 tissues modeled in the patients

Tissue	Element (% weight)										
	H	C	N	O	Na	Mg	P	S	Cl	K	Ca
Glandular	10.6	33.2	3	52.7	0.1	-	0.1	0.2	0.1	-	-
Adipose	11.4	59.8	0.7	27.8	0.1	-	-	0.1	0.1	-	-
Skin	10	20.4	4.2	64.5	0.2	-	0.1	0.2	0.3	0.1	-
Rib	6.4	26.3	3.9	43.6	0.1	0.1	6	0.3	0.1	0.1	13.1
Lung	10.3	10.5	3.1	74.9	0.2	-	0.2	0.3	0.3	0.2	-

Balloon Applicator modeling

Balloon wall

The balloon wall consists of a 0.3-0.5mm thick silicone shell with a relatively high concentration of barium sulphate (figure 3). The barium also attenuates the photon fluence emitted from the source during treatment to a greater degree than an equal thickness of water (Segala *et al.*, 2011). The decrease in dose due to balloon wall attenuation in treatments is not accounted for by TG-43 dosimetry but the manufacturer recommends an increase of 6% in source dwell times to offset the attenuation. Previous studies (Segala *et al.*, 2011) had shown that the degree of attenuation by the balloon was not uniform due to the variable thickness of balloon wall material that photons will traverse depending on its angle of incidence. This could not be corrected for by increasing the dwell times uniformly. The tip composition of the balloon applicator varied from patient to patient due to the type of applicator used and the degree to which it was inflated and deformed by the surrounding tissue. The balloon wall was difficult to model using the same CT to esophant geometry approach as used for the tissues since the thickness of the wall (~0.4mm) is much smaller than standard voxel sizes seen in the CT images of patients (up to 3mm). Thus voxelization

of the balloon wall leads to an over-estimation of the attenuation and consequently an under-estimation of the dose to the surrounding tissue.

Methods of modeling structures in voxelized patient geometries have been described in a previous study(Enger *et al.*, 2012). Geant4 allows the creation of parallel world geometries(Apostolakis, 2008) which can be used to overlap existing voxel geometries. Normally these geometries contain no mass and do not have any influence on the physical interactions of particles. A technique using Layered Mass Geometries (LMG) allows the analytic modeling of simple geometries, such as ^{125}I seeds, which can influence the transport of particles throughout the patient geometry. While LMG can be used to define simple objects, more complex geometries, such as a patient deformed balloon applicator, can not be recreated in the parallel world easily using combinations of simple geometries. Other sections of the applicator could be modeled by simple geometries and are referred to in the following section. A more complicated approach was needed for the balloon wall.

First, balloon wall contours for each patient, contained within the DICOM data, were imported into Meshlab (ISTI-CSI, Rome), an open source mesh-generating/processing tool. Meshlab links the balloon wall contour points to one another based on their nearest neighbour to construct a series of tetrahedral shapes that link together to create a convex hull mesh. A convex hull is the minimum geometrical volume that contains all of the contour points such that the vector between any two of the contour points does not lie outside of the volume. This convex hull was the outer surface of the balloon. As the balloon wall is a shell-type structure, a second geometry was needed to define the inner surface. A second convex hull geometry was made from the contour points and scaled down in size (using the balloon's center of mass as reference) so that each point of the surface was 0.4mm from its original position. This corresponds to the average thickness of the balloon wall over the entire applicator. Each of these geometries was saved separately as an inner and outer surface mesh files. The combination of both of these meshes was used to create the balloon wall.

CADMesh is a C++ library for loading CAD based geometries into Geant4(Poole *et al.*, 2012). The conversion of the mesh balloon wall geometry into a CADmesh-compatible assembly was performed using Tetnest(Poole *et al.*, 2012), a python-based script that imports surface meshes and creates the nested tetrahedral mesh. Figure 4 show how a uniformly thick (0.4mm) balloon wall model was created for the heterogeneous model simulations using Meshlab and Tetnest.

Figure 4: The conversion of the irregularly shaped balloon wall from a DICOM RT structure (Top left and right) to a complex array of tetrahedrals that create a convex hull geometry (Lower left) calculated using Meshlab and finally the CADmesh balloon wall (Lower right) created in Tetnest. The CADmesh wall geometry has been cut in the z-plane to display both surfaces. The green denotes the outer surface and the pink, the inner.

The balloon wall material was assigned to the geometry. The balloon wall geometry for each patient was created separately, based on the existing balloon applicator TPS contours. This procedure could be useful for many other applications with complex geometries. The technical aspects of this procedure and some benchmarks will be detailed in a future publication.

Tip/Air channel modeling

The air channel and tip of the balloon applicator were modeled using the LMG technique. Given the high concentration of high-Z material in the applicator tip, its irregular shape and small dimensions, voxelization of the applicator led to an over-estimation of its dimensions and an over-attenuation of dose in the region around the tip. Voxelization of the air channel results in an over/under estimation of the diameter of the air channel due to the large slice thickness (3mm) of the CT image depending on the angle and orientation of the applicator. Thus the tip and air channel were modeled using a combination of analytical geometries as much as possible. The dimensions of the air channel and the applicator tip were provided by Xofig. The resultant geometries were placed in the same parallel world as the CADmesh

balloon wall. The saline solution inside the balloon was the only section of the applicator that was voxelized. The composition of the tip varied depending on the size/type of the applicator used, which varied from patient to patient.

CADmesh Validation

Validation of the mesh/LMG technique was performed in Monte Carlo using a simple spherical geometry with a small finite wall thickness as a benchmark geometry. The geometry consists of a 0.4 mm thick wall that encloses a water sphere of radius 25mm. Like the balloon applicator, this wall geometry was constructed from two concentric spherical clouds of points which were changed into surface meshes in Meshlab and converted into a CADmesh compatible format by Tetnest, as described in the previous section. This wall geometry was placed in a 10cm × 10cm × 10cm voxelized water world (voxel size 1mm³). The geometry was simulated in Geant4 using a 50keV mono-energetic point source placed at the centre of the sphere. An identical geometry was simulated using analytical geometry modeling techniques in Geant4 and compared against the CADmesh dose calculations. 2 × 10⁹ histories were simulated for both cases and the maximum statistical uncertainty, at the outermost voxel was < 1%. Comparisons between the results were made using dose-ratio maps and all voxels agreed to within <0.5%.

Experimental validation

Validation of the mesh/LMG technique and the tip/air channel modeling was performed experimentally using EBT3 GAFchromic film using a simple in-house phantom. A water inflated Axxent balloon applicator was immersed in a PMMA box phantom approximately 6cm x 6cm x 6cm in dimensions with the remaining space inside the box filled with water. Pieces of EBT3 film were placed on three sides of the box and surrounded by PMMA backscatter (Figure 5). All film was irradiated to a minimum of 0.5Gy and a maximum of 8Gy. The EBT3 film was scanned using an EPSON PRO v750 scanner at 225dpi and processed using the triple channel method using Matlab(Hoof *et al.*, 2012).

A 1mm x 1mm x 0.6mm 120kVp CT scan of the phantom was used to create an egspgant geometry for allowing MC simulation of the experiment setup. An LMG balloon wall was created using contours of the applicator obtained from the CT scan. The LMG balloon wall was included as a parallel world geometry using the method described in section.2.8.1. Relative comparisons between the experimental and normalized MC results were evaluated using line profiles.

Inter-model comparison

DVH metrics were used to compare various dose-distributions quantitatively. The D₉₀ (minimum dose received by at least 90% of the volume of the PTV) was expressed as a percentage of the fractional dose of 3.4Gy. The volume metrics were expressed as a percentage of the total PTV volume. The volume metrics are important in terms of toxicity as V₁₅₀ and V₂₀₀ (volume receiving at least 150% or 200% of the prescribed dose) in interstitial brachytherapy have been correlated with increased occurrence of fat necrosis(Budrukkar *et al.*, 2012; Wazer *et al.*, 2001). Any differences between PTV metrics of different models were expressed as an absolute percentage and not a renormalized value. The doses to separate individual tissues in the PTV were not evaluated. The dose to skin was evaluated as the

highest minimum dose at any 0.2cc region of the skin ($D_{0.2cc}$). $D_{0.2cc}$ was expressed as a percentage of the prescription dose. In addition to dose metrics, dose ratio maps comparing each plan were calculated using BrachyGUI which calculated a ratio based on a direct voxel by voxel comparison between plans. Dose ratios are shown for $D_{m,m}$ and $D_{w,m}$ for the heterogeneous model vs. TG-43 MC for each patient. As dose to voxels outside the body are clinically irrelevant, dose to these voxels were not scored hence the dose in these sections is zero and should be ignored. A dose ratio map was also calculated for the heterogeneous model versus the Water-Air model. This dose ratio map isolated the dosimetric impact due to tissue heterogeneities alone.

Figure 5: Schematic diagram of experimental setup for the CADmesh validation

Results and Discussion

TG-43 Validation

When the TG-43 MC was validated against the BrachyVision TPS, the D_{90} agreed to within an average of 2.8% ($\sigma = 0.2\%$) (Table 2) for the 7 patients. Other dose metrics agreed to within 2-3%. The dose ratio of the two dose maps revealed that the largest discrepancies (10-20%) existed inside the balloon, close to the applicator channel and along the applicator proximal end (160° to 175°). It should be noted that disagreement between calculated and measured doses in these regions around the source has been reported previously (Rivard *et al.*, 2006b). These regions are not clinically significant due to their location. A reason for this disagreement could be due to the way the TPS interpolates the dose close to the center. The systematic discrepancy could be due to the difference in MC code used for the Rivard *et al.* validation dataset (version MCNP5) and that used in this study (Geant4). Small differences in the source model may also play a role as uncertainty in the position of the phase space origin and the thickness of the anode can have a large impact on the dose distribution.

Table 2: Average percentage difference between BrachyVision (TPS) and TG-43 MC calculation methods for dose metrics for the PTV for 7 patients. D_{90} and its standard deviation (σ) are expressed as a percentage of the prescription dose.

Model	Metric			
	D90 (%)	V100 (%)	V150 (%)	V200 (%)
TG-43 TPS (average)	101.2	90.9	46.3	21.3
TG-43 MC (average)	103.9	93	49.1	23.5
TPS – TG-43 MC	2.8	2.1	2.8	2.2
σ	0.2	0.4	0.2	0.3

Experimental validation

Line profiles for the top and bottom film pieces versus the Monte Carlo showed good agreement to within experimental/MC uncertainty (0.5 – 2.0%) (Figure 6a). The MC results were normalized to the max dose on each film piece for the TOP and BOTTOM region by the same scale. The difference between the top and bottom line profile can be explained due to the asymmetry of the phantom, as the source was not at equal distance from both film pieces. The TOP region (Fig 5) was also influenced by air bubbles within the applicator balloon which were accounted for in the MC model. Some disagreement was observed with the TIP region (figure 6b) where the MC model underestimates the peak dose around the central region (where the film was placed directly above the applicator tip) by between 6-20%. The TIP max dose was normalized to the MC by same normalization value as the TOP and BOTTOM pieces. The TIP disagreement between the MC and film model can be attributed to source position uncertainties which are enhanced by the air channel in the applicator. The uncertainties in the analytical geometry of the applicator tip were also a significant factor as were the uncertainties and variation in the balloon wall thickness particularly at the front. Despite this, the analytical/CADmesh applicator geometry is an improvement over voxelized models of the applicator which can overestimate the wall thickness by a factor of 4.

Figure 6: Line profiles of each of the film pieces from various areas of the phantoms versus the line profiles from equivalent regions on MC model. The TOP and BOTTOM regions are highlighted in (a) and the FRONT region in (b).

Water-Air model vs. TG-43 MC

The dose ratio map for the Water-Air model / TG-43 MC model can be seen in figure 7a. The ratio map demonstrates the regions where the absence of backscatter in the Water-Air model has the largest impact, most notably the skin. The DVH differences between both models (Figure 7b) show the effects of substituting an all-water geometry for a more geometrically

realistic water model taking the breast shape, the air and the presence of lungs into account. For 7 patients, an average D_{90} reduction of 3.8% ($\sigma = 2.4\%$) (Table 3) was calculated for the Water-Air model. Most of the reduction could be attributed to the absence of non-patient backscatter ($\sim 3.2\%$). The absence of backscatter in the lung accounted for the remainder ($\sim 0.6\%$) (Figure 7c) making it approximately 20% of the non-patient backscatter though the range of the contribution of the lung backscatter varied from 0% (for large breasts with PTV closer to the skin) to 37% (for small breasts or the PTV close to the ribs). The skin dose, $D_{0.2cc}$ was much lower for all patients with an approximate mean decrease of 9.4% from the TG-43 $D_{0.2cc}$ (Range -4.9% to -14.3%) in the Water-Air model signifying the large portion of dose contributed by erroneously modeled non-patient backscatter in TG-43. Lung backscatter constituted almost zero skin dose. Patient geometry, applicator positioning and dwell times play a large role in determining the dose reduction in the PTV, reflected in the relatively large range of $D_{0.2cc}$ reduction of between 0.7% to 7.2%. Larger breasts and deeper seated applicators lessen the impact of reduced backscatter from the outside air as is evident from the minimum PTV to skin distance measured in the Water-Air models which ranged from 0cm to 1.7cm for a PTV dose reduction of 7.2% and 0.7%, respectively. High skin dose is more probable in smaller breasts thus proper backscatter modeling is important. Skin dose has been shown to be critical to predicting cosmetic outcome of ^{192}Ir -based APBI(Vargo *et al.*, 2014a), though the dosimetry in this study was performed using TG-43. While there is an impact of backscatter on the skin dose for the low energy dosimetry, it is likely to be more important for higher energy dosimetry (^{192}Ir and ^{137}Cs) as a previous study has shown(Perez-Calatayud *et al.*, 2004) due to greater Compton scattering cross-section at higher energies.

Figure 7: (a) Dose ratio map for patient 7; Water-Air model / TG-43 MC. For the Water-Air model both lung and non-patient sections are modeled as air. Dose to air is zero in Water-Air. (b) A comparative DVH distribution for patient 7 taking into account the skin and PTV contours. (c) The contribution of lung and non-patient backscatter in TG-43.

Heterogeneous model vs. TG-43

Figures 8a and b shows the dose ratio maps of the heterogeneous model / TG-43 MC with the dose scored as $D_{w,m}$ (figure 8a) and $D_{m,m}$ (figure 8b). The figure also shows the dose ratios of the heterogeneous model / Water-Air model for $D_{w,m}$ (figure 8c) and $D_{m,m}$ (figure 8d). The slice of the simulated heterogeneous model's eggsphant geometry, from which the dose ratio maps were obtained, can be seen in figure 8e. In figure 8a, the $D_{w,m}$ scoring method gives a relatively uniform dose ratio distribution in the PTV in comparison to the $D_{m,m}$ (figure 8b). Higher density/Z regions at the ribs, where dose attenuation is larger than the surrounding tissues and water, creates a shadowing effect (figure 8a and 8c) where most of the dose is absorbed by the ribs but, as the dose for both methods is scored in water, a lower dose ratio is present for the heterogeneous model inside the ribs. Low density/Z regions, such as adipose tissue, have the reverse effect resulting in an increased dose ratio to regions further from the PTV. As with the Water-Air model in the previous section, there is also a missing backscatter component which reduces the skin and PTV dose. The average D_{90} to both the Water-Air and heterogeneous models decrease from the D_{90} calculated using TG-43 MC (Table 3) by about 3.8% and 5% respectively. This would seem to indicate that most of the dose reduction is due to the loss of backscatter while only 1.2% can be attributed to tissue heterogeneities which can be highlighted by the difference between the dose ratio maps in figure 8a and 8c. Similar reductions can be seen for the other dose metrics (Table 3). Figure 8b shows dose ratio maps when $D_{m,m}$ is used for dose reporting. Figure 8a and 8b demonstrate a large difference in the dose ratio distribution due to the difference in scoring method. The figure 8b ratio map demonstrates the dependence of $D_{m,m}$ on the tissue type with the dose ratio distribution closely resembling the tree-like pattern of glandular tissue in the eggsphant tissue model in figure 8e. The relative difference of the $D_{m,m}$ dose distribution to TG-43 MC is dependent on the tissue composition with glandular tissue and skin absorbing a higher $D_{m,m}$ dose than adipose tissue. By comparison to the $D_{w,m}$ result where tissue heterogeneity only reduced the D_{90} by 1.2%, if scored with $D_{m,m}$, the tissue heterogeneity reduces the D_{90} by, on average, 34.8%, a factor 9 more than the contribution of non-patient backscatter (3.8%). A comparison with figure 8d demonstrates the reduced impact of backscatter when scored with $D_{m,m}$. Only dose to rib and the lung region are higher in $D_{m,m}$. The ribs show a dose increase in all patients by approximately 300% compared to TG-43. An increase in rib dose absorption may not be significant when correlated against osseous toxicity. A previous study (Mandell *et al.*, 1985) had shown no correlation between the increased rib dose absorption of ^{125}I seeds implanted close to cortical bone throughout the body and incidence of bone fractures. ^{125}I is a low energy source with a mean photon energy similar to that of the S700 source.

(a) Dose ratio: Heterogenous Model $D_{w,m}$ / TG-43 MC

(b) Dose ratio: Heterogenous Model $D_{m,m}$ / TG-43 MC

(c) Dose ratio: Heterogenous Model $D_{w,m}$ / Water-Air

(d) Dose ratio: Heterogenous Model $D_{m,m}$ / Water-Air

(e) Heterogenous Model

Figure 8: XY plane dose ratio maps for the heterogeneous model / TG-43 MC scored with $D_{w,m}$ (a) and $D_{m,m}$ (b) and the heterogeneous model / Water-Air Model scored with $D_{w,m}$ (c) and $D_{m,m}$ (d). The contours in all figures are indicative of the ROIs. The dose to the balloon wall is ignored. (e) Slice from the heterogeneous model used for (a)-(d).

Note: lung/air dose is ignored in the Water-Air model and all ratios in air are overridden to zero.

Table 3: Dose metrics for each model / scoring method averaged for 7 patients.

D_{90} and $D_{0.2cc}$ are expressed as a percentage of the prescription dose, 34Gy. V_{100} , V_{150} , and V_{200} are expressed as a percentage of the PTV volume.

MODEL DVH metric	TG-43 – MC model ($D_{w,w}$) % - σ	Water + Air model ($D_{w,w}$) % - σ	Heterogeneous model ($D_{w,m}$) % - σ	Heterogeneous model ($D_{m,m}$) % - σ
PTV D_{90}	103.9 $\pm$ 2.5	100.1 $\pm$ 2.9	98.9 $\pm$ 3.1	65.3 $\pm$ 2.9
V_{100}	93.0 $\pm$ 2.0	90.0 $\pm$ 2.5	88.8 $\pm$ 3.3	45.9 $\pm$ 6.1
V_{150}	49.1 $\pm$ 3.6	46.5 $\pm$ 3.9	39.6 $\pm$ 4.7	13.9 $\pm$ 5.3
V_{200}	23.5 $\pm$ 3.8	22.1 $\pm$ 4.0	12.5 $\pm$ 5.3	3.4 $\pm$ 2.7
Skin $D_{0.2cc}$	92.9 $\pm$ 32.4	83.0 $\pm$ 33.5	81.4 $\pm$ 27.8	76.9 $\pm$ 25.8

In terms of inter-patient variability, the largest dose reductions occur in patients with smaller breasts (< 800cc) indicating that the difference between the heterogeneous model and TG-43 are sensitive to geometry as well as to tissue composition. It should be stated that a significant portion of the difference (particularly for $D_{w,m}$) between the TG-43 MC and the heterogeneous model is due to balloon wall attenuation which is partially accounted for in clinical practice by a recommended 6% increase in dwell times. This correction was not applied to the patients in this study. A simulation of the TG-43 MC geometry which included the CADmesh-modeled balloon wall for a single patient showed that the addition of the balloon wall reduced the D_{90} ($D_{w,w}$) by approximately 10%. For the heterogeneous model scored with $D_{w,m}$, this decrease is offset by the lower attenuation coefficient of adipose tissue which compensates the dose to regions around the balloon and increases it further from the applicator (seen in the high dose ratio in figure 8a and figure 8c).

Discussion and study limitations

We observed a greater degree of variability with an increased level of dose calculation model complexity. When compared to TG-43, the inclusion of the balloon applicator and tissue heterogeneities introduce a number of cold and hot spots which are scoring method dependent. The most significant changes occur near the organs at risk; the skin and ribs. Peak skin dose shows a general decrease over the 7 patients between 0.5% and 24% (Table 3) of the prescription dose depending on the patient geometry, method of scoring and model type. The reduced skin dose may have implications for dose escalation in APBI as skin dose is a planning constraint. As with the PTV, the choice of dose scoring method is important for determining rib dose with an increase or decrease from TG-43 MC observed with $D_{m,m}$ and $D_{w,m}$, respectively. The differences to the PTV dose observed with $D_{m,m}$ are difficult to evaluate clinically due to the different quantity that both dose scoring metrics represent and the limited experience in clinical evaluations performed using $D_{m,m}$ dosimetry. Within the PTV, the distribution of dose to the specific tissues (glandular/adipose) may be relevant to clinicians.

As reported before (Segala *et al.*, 2011), the balloon wall varies in thickness throughout the applicator. Given the relative low resolution of the CT data it is difficult to determine which sections are thicker/thinner. It would be difficult to incorporate these variations into the CADmesh technique for modeling the balloon wall without a higher resolution CT, and in this study a uniform balloon wall thickness was therefore modeled.

The study made use of population-averaged healthy tissue composition data rather than the patient's actual composition data. Variation in the tissue composition data ($\pm\sigma$) has already been shown to cause complex behavior in dose distributions irradiated with the Axxent system(Landry *et al.*, 2010b). Further study is needed to explore the suitability of averaged tissue composition with the Axxent system. Of particular interest is the impact of calcifications throughout the breast which has been shown(Sutherland *et al.*, 2011) to affect the photon fluence in ^{103}Pd treated breast geometries. No calcification distribution was incorporated into the patient phantoms in this study.

With regard to tissue segmentation, the degree of density overlap between glandular and adipose tissues created some assignment uncertainty. Mixed adipose and glandular voxels were not accounted for. The accuracy of the tissue segmentation is also dependent on the CT calibration curve and quality of the images. More precise individual breast compositions, identification of small calcifications and improved tissue segmentation may be possible with dual energy CT imaging(Ding *et al.*, 2013).

Conclusions

We analyzed the dosimetric impact of tissue heterogeneities and the applicator geometry retrospectively on APBI patients treated with the Xofig Axxent eBx source using MC simulation techniques. TG-43 and TG-186 tissue models were simulated and compared, and results for different dose reporting methods were explored. Simulated TG-186 models demonstrated a difference in predicted dose to all volumes of interest. TG-43 overestimates the doses to certain regions in the body, most notably the skin but underestimates in other regions such as the ribs. These changes are dependent on the dose reporting method. Reduced skin dose may permit dose-escalation and better predict cosmetic outcome. A novel technique for MC modeling of complex geometries based on mesh geometries was used for the first time in brachytherapy. More research is needed to determine the full extent of the role of tissue heterogeneities particularly in terms of clinical outcome. The significant differences between $D_{m,m}$ and $D_{w,m}$ raise questions about the choice of dose reporting metrics, PTV delineation and the role of TG-43U1.

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Chapter 4:

Measurement of absorbed dose to water around an electronic brachytherapy source. Comparison of two dosimetry systems: lithium formate EPR dosimeters and radiochromic EBT2 film

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Abstract

Purpose

Interest in HDR electronic brachytherapy operating at 50 kV is increasing. For quality assurance it is important to identify dosimetry systems that can measure the absorbed doses in absolute terms which is difficult in this energy region. In this work a comparison is made between two dosimetry systems, EPR lithium formate dosimeters and radiochromic EBT2 film.

Methods and Materials

Both types of dosimeters were irradiated simultaneously in a PMMA phantom using the Axxent EBS. Absorbed dose to water was determined at distances of 10 mm, 30 mm and 50 mm from the EBS. Results were traceable to different primary standards as regards absorbed dose to water (EPR) and air kerma (EBT2). Monte Carlo simulations were used in absolute terms as a third estimate of absorbed dose to water.

Results:

Agreement within the estimated expanded ($k=2$) uncertainties (5% (EPR), 7% (EBT2)) was found between the results at 30 mm and 50 mm from the x-ray source. The same result was obtained in 4 repetitions of irradiation, indicating high precision in the measurements with both systems. At 10 mm distance, agreement between EPR and Monte Carlo simulations was shown, while the geometry for the film measurement caused too large uncertainty in measured values which depend on the exact position (within sub-mm distances) of the EBS.

Conclusions:

This work has demonstrated good performance of the lithium formate EPR dosimetry system in accordance with earlier experiments at higher photon energies (^{192}Ir HDR brachytherapy). Results for the EBT2 film agreed with the results of Monte Carlo simulations of absorbed dose to water at 30 mm and 50 mm distance. It was also highlighted that there might be issues regarding the energy dependence and intrinsic efficiency of the EBT2 film that need to be considered for measurements using low energy sources.

Introduction

Interest in using high dose rate (HDR) electronic x-ray brachytherapy sources (EBS) for accelerated partial breast irradiation (APBI) or intraoperative radiation therapy (IORT) is increasing. Due to the low tube voltage (40-50 kV) the need for radiation shielding of treatment rooms is reduced. There are also studies showing how the use of EBS for APBI results in reduced doses to normal tissues compared to ^{192}Ir HDR. However, the issue is complicated by the sensitivity of calculated doses to patient tissue composition in this energy region (Mille *et al.*, 2010; White *et al.*, 2014a).

Experimental verification of dose distributions is an important feature of quality assurance in radiation therapy. It is difficult to perform dosimetric measurements around low energy (<50 keV) brachytherapy sources. Not only are dose gradients very steep, making accurate positioning and control over dose-averaging effects important, but the attenuation of photons in the keV energy region is also very sensitive to phantom material composition. It is furthermore not clear if calibrations to measure absorbed dose to water in absolute terms should be made using traceability to a primary water standard using a MV photon beam or to an air kerma standard in a kV radiation quality closer to that of the EBS. The highest accuracy in calibration coefficients in MV beams is achieved using traceability to a primary ^{60}Co water standard (Almond *et al.*, 1999; Andreo *et al.*, 2000). Calibrating absorbed dose in MV beams and measuring in kV beams, however, generally requires correcting the dosimetry system for effects of intrinsic efficiency. Intrinsic efficiency is defined as the signal per mean absorbed dose in the detector and should not be confused with the term energy dependence defined as the signal per absorbed dose to water. Various LiF thermoluminescent dosimeter (TLD) systems have shown a response per unit absorbed dose in the detector that is about 5%-10% higher in 20-50 kV beams than in MV beams (Carlsson Tedgren *et al.*, 2011; Davis *et al.*, 2003; Nunn *et al.*, 2008). On the contrary, the lithium formate electron paramagnetic resonance (EPR) dosimetry system used in this work shows an approximately 5% lower response in kV than in MV beams (Adolfsson *et al.*, 2010). The effect of variations of intrinsic efficiency with beam quality is often neglected and has not been investigated for many dosimetry systems including EBT2 radiochromic film in photon beams. This precludes calibration in a MV beam to assure accurate dosimetry.

Our lithium formate EPR dosimetry system has been used successfully for measurements of absorbed dose to water around ^{192}Ir HDR BT sources (Antonovic *et al.*, 2009). The aim of this work was to test this dosimetry system for measurements of absorbed dose to water around a low energy 50 kV Axxent EBS (Xoft Inc, San Jose, CA, USA) (Rivard *et al.*, 2006a) and to compare the results against an independent dosimetry system using radiochromic EBT2 film.

Materials and methods

This section is structured as follows: The theory underlying the derivation of absorbed dose to water from the measured dosimeter signal at various depths in a phantom is treated in 2.1. Measurement techniques and calibration methods to determine absorbed dose to water are described for the EPR dosimeters in 2.2 and for the EBT2 film in 2.3; the geometrical set-up for the measurements with the EBS is described in 2.4. Monte Carlo simulations to derive the energy-spectra of photons at different depths in the measurement phantom, a method to convert the results of MC calculations into absolute dose values including necessary correction factors are described in 2.5.

Theory

Derivation of absorbed dose to water from the measured signal

Determination of absorbed dose to water at beam quality Q , at the distance r from the EBS, is given by

$$\begin{aligned}
 D_{w,Q} = D_w(r) &= \frac{M_Q}{\left[\frac{M}{D_w}\right]_{Q_0}} \frac{\left[\frac{M}{D_w}\right]_{Q_0}}{\left[\frac{M}{D_w}\right]_Q} = \frac{M_Q}{\left[\frac{M}{D_w}\right]_{Q_0}} \frac{\left[\frac{M}{\bar{D}_{\det}}\right]_{Q_0}}{\left[\frac{M}{\bar{D}_{\det}}\right]_Q} \frac{\left[\frac{\bar{D}_{\det}}{D_w}\right]_{Q_0}}{\left[\frac{\bar{D}_{\det}}{D_w}\right]_Q} = \\
 &= \frac{M_Q}{\left[\frac{M}{D_w}\right]_{Q_0}} \frac{R_{Q_0}}{R_Q} \frac{\left[\frac{\bar{D}_{\det}}{D_w}\right]_{Q_0}}{\left[\frac{\bar{D}_{\det}}{D_w}\right]_Q} = \frac{M_Q}{\left[\frac{M}{D_w}\right]_{Q_0}} k_{Q,Q_0}
 \end{aligned} \tag{1}$$

Here M_Q is the detector signal at beam quality Q , $\left[M/D_w\right]_{Q_0}$ is the signal per unit absorbed dose to water at the calibration beam quality Q_0 , $R = M/\bar{D}_{\det}$ is the signal per mean absorbed dose in the detector and is generally a function of the beam quality as indicated by the indices Q and Q_0 . The quotient R_{Q_0}/R_Q corrects for different intrinsic efficiency of the detector material at calibration and at measurement. k_{Q,Q_0} is the beam quality correction factor.

Corrections were needed to convert the mean absorbed dose in the detector, $\bar{D}_{\det}$ (proportional to the measured signal) to the absorbed dose, $D_{\det}(r)$ in a small detector at points r , corresponding to the distances from the EBS at which the absorbed dose to water was measured. Details of the expressions used for determining the absorbed dose to water with the two detector systems and uncertainty estimations are given in the Appendix.

Relative intrinsic efficiency R_{Q_0}/R_Q

The intrinsic efficiency depends on the ionization densities and varies due to the linear energy transfer (LET) distribution of the secondary electrons. Intrinsic efficiency at brachytherapy beam qualities relative to ^{60}Co or MV photon beam has been thoroughly investigated for

lithium formate EPR dosimeters (Adolfsson *et al.*, 2010). No corresponding investigations have to our knowledge been performed for radiochromic film. A complicating factor for the film is its nonlinear dose response, i.e. M/D_w and thus $M/\bar{D}_{\text{det}}$ varies not only with the LET distributions along single electron tracks but also with the magnitude of the absorbed dose in the detector with ionization densities in sensitive targets formed by overlapping electron tracks.

Energy absorption properties relative to water

From knowledge of M/D_w , $M/\bar{D}_{\text{det}}$ could be determined provided $D_w/\bar{D}_{\text{det}}$ is known. Values of the latter quotient have until recently been unknown for radiochromic film due to lack of knowledge of the concentrations of high atomic number materials used to increase film sensitivity (Lindsay *et al.*, 2010). Sutherland and Rogers (Sutherland and Rogers, 2010) provided calculations of $D_w/\bar{D}_{\text{det}}$ using photon-electron transport Monte Carlo simulations and found the ratio to be close to the ratio of the mass energy absorption coefficients of the active film layer and water at photon energies < 50 keV. This indicates a state of charged particle equilibrium in the active layer at these energies. It is noted that at higher photon energies this does not hold and full photon-electron transport must be simulated to obtain the mean absorbed dose in the detector.

Since May 2009, the manufacturer of EBT2 film (ISP) has standardized the atomic composition of the active layer (Lindsay *et al.*, 2010). Film lot # A090310 was used in our experiment, atomic composition of the active layer is given in Table 1 (as provided by ISP, personal communication). Comparison of the ratios between the mass energy absorption coefficients for water and the active layer of three different batches of EBT2 film plus lithium formate are shown in Figure 1. Mass energy absorption coefficients were taken from NIST (Hubbell and Seltzer, 1995).

Figure 1. Mass energy absorption coefficients of water relative to lithium formate and the active layers of 3 different lots of EBT2 film; A090310 (used in this work) and 020609, 031109 investigated by Sutherland and Rogers (2010). Atomic compositions by Sutherland and Rogers were obtained from the manufacturer.

Figure 1 shows that the energy absorption of lithium formate relative to water vary considerably less with photon energy than the variations among the three EBT2 lots. Values of $\left[\overline{\mu_{\text{en}} / \rho}\right]_{\text{det}}^{\text{w}}$ (weighted over the energy fluences calculated for the Axxent source, see 2.5) for lithium formate were within 0.5% at the three measurement positions, while the corresponding values for lot A090310 were within 4%.

Results for A090310 used in this work coincide with lot 020609 as simulated by Sutherland and Rogers. It is noted that the standardized composition of the active layer results in a dosimeter with a larger energy dependence ($Z_{\text{eff}} = 9.18$) than lot 031109 ($Z_{\text{eff}} = 7.44$) at these low photon energies (Sutherland and Rogers, 2010).

Calibration methods

Calibration to measure absorbed dose to water with traceability to an absorbed dose to water primary standard presently requires the use of ^{60}Co or a MV photon beams. An alternative method with traceability to an air kerma standard was used for the film to avoid effects of the unknown intrinsic efficiency on the results of the dose measurements. Details of the calibrations of the EPR dosimeters and of the EBT2 film are given below.

Lithium formate EPR dosimeters

Measurement technique

The lithium formate dosimeters were cylindrical in shape with height 4.8 mm and diameter 4.5 mm. They consisted of 90% lithium formate and 10% paraffin (binding material). Signal evaluation was performed with a Bruker EleXsys E580 spectrometer, for details see earlier publications (Adolfsson *et al.*, 2010; Adolfsson *et al.*, 2012; Antonovic *et al.*, 2009; Gustafsson *et al.*, 2008).

Calibration process

Absorbed dose to water calibration was performed in a 6 MV photon beam using a Farmer type ion chamber. Due to the linear dose response of lithium formate, a two point calibration curve was used (Gustafsson *et al.*, 2008). The corrections necessary to convert absorbed dose to water in the calibration situation to absorbed dose to water at a specified distance from the EBS are described in the Appendix.

Two sets each of four dosimeters each were used for the calibration. One set was calibrated (in Linköping) before the EBS experiment (in Maastricht) and one set afterwards due to the time between experiment and read out of the EPR dosimeters. The results of the calibrations were the same and indicate the stability of the EPR dosimeters throughout the experiment and calibrations (Adolfsson *et al.*, 2014; Adolfsson *et al.*, 2012).

Radiochromic film

Measurement technique

The film was evaluated using a flatbed scanner Epson PRO V740 (Seiko Epson Corporation, Nagano, Japan). Image Acquisition was performed using FilmQA Pro (Version 1.0.4049.36336). All film pieces were scanned and the results were stored as TIFF images,

without any colour correction, at 225dpi in words of 48 bits (16 bits per colour channel) using the RGB transmission mode for the positive film. Absorbed dose to water was derived using the triple channel method (Micke *et al.*, 2011; van Hoof *et al.*, 2012). The film was kept in light-tight folders until use and while in use, exposure to light was kept to a minimum.

Calibration process

The absorbed dose to water film calibration was performed using a small animal micro-irradiator with tube voltage 50kV, 2.14 mm Al filtration and HVL = 1.54 mm Al (first layer). (PXi, North Branford, CT) (Granton *et al.*, 2012; van Hoof *et al.*, 2012). The Farmer chamber was used with traceability to a primary air kerma standard. To determine absorbed dose to water, the “in-air method” described by the AAPM task group 61 (Ma *et al.*, 2001) was used with slight modifications. The micro-irradiator was too small to use the recommended 10x10cm field and the recommended 100cm source to detector distance. Instead the field size was limited to a circular 2.5cm diameter field and the source to detector distance was 30.7cm (the distance to the isocentre) as described in Hoof *et al.*, 2012. The calibration curve consisted of 8 dose points from 0 to 15 Gy. A full description of the micro-irradiator and the film calibration process is available elsewhere (van Hoof *et al.*, 2012). The corrections necessary to convert absorbed dose to water in the calibration situation to absorbed dose to water at a specified distance from the EBS are described in the appendix.

Experimental set up for measurement in the EBS beam

A PMMA phantom previously used for EPR measurements around ^{192}Ir sources (Antonovic *et al.*, 2009) was used for the measurements, see Figure 2. The phantom is divided into square slabs of thickness 2.5 cm stacked on one another with a centrally drilled hole (5.1 mm in diameter). The EBS fitted tightly into the hole with some compression on the sides. It was inserted to the maximum depth of the hole at each time; the positioning (as indicated by markers on the source tip) was accurate to within < 1 mm. The center of the source and the center of the EPR chips were slightly out of plane by approximately 1mm. This was revealed in noting updated technical information about the source received after the experiment. (The updated information was taken into account when calculating the correction factors (see 2.5)). At each distance (10, 30 and 50 mm) from the EBS, four EPR dosimeters were positioned radially around the EBS (Figure 2b). Film pieces were positioned on top of the EPR dosimeters, a circular area on the part of the film that covered the underlying EPR dosimeter cross section was marked as the region of interest. The experiment was repeated four times at 30 and 50 mm (average irradiation time was 550 s for the four repetitions). One irradiation was made at 10 mm (irradiation time 88.5 s). Due to their limited lifespan, the irradiations were performed using two EBSs. A Markus M6 ion chamber (PTW, Freiburg, Germany) situated below the dosimeter slab was used to monitor the dose delivery. The dosimeters at 30 and 50 mm were simultaneously irradiated; irradiations of dosimeters at 10 mm were performed separately to avoid dose saturation of the film. The ramp-up dose of the EBS was determined to be less than 0.2% of the total administered dose.

Figure 2. Schematic figure of the PMMA phantom seen from the side (a) and from above (b). Dosimeters were positioned at 10, 30 and 50 mm from the EBS (A) and the film (B) on top of the EPR dosimeters between two PMMA slabs. The Markus chamber (C) was positioned below the film dosimeter plane. Not drawn to scale. Four dosimeters were simultaneously irradiated at each distance.

Monte Carlo simulations

Monte Carlo simulations were used in the derivation of corrections factors (see Appendix), to enable comparison of doses determined by EPR and film, and for calculations of the radial absorbed dose profile in the phantom. The latter dose distribution was translated into values of absorbed dose in terms of Gy using the Markus chamber (see 2.5.3).

The Geant4 MC program

The all-purpose MC simulation toolkit Geant4 v9.3 provides a diverse set of software components that can be employed in a variety of settings, including the simulation of photon transport from low energy sources (Agostinelli *et al.*, 2003c). In this work, the Lawrence Livermore National Laboratory low energy electromagnetic model which simulates the low energy photon interactions of the photoelectric effect, Compton scattering and Rayleigh scattering was used. The electron atomic binding effects on Compton cross sections at low energies were taken into account. The model uses the EPDL (Cullen *et al.*, 1997), and EADL (Perkins *et al.*, 1997) evaluated cross section libraries. All secondary electrons were made to deposit their energy locally due to their short range compared to typical voxel sizes; hence absorbed dose to water is approximated by water collision kerma. The cutoff energy for photons was 250 eV.

The geometry

A mathematical model of the PMMA phantom, EPR dosimeters and films used in the experiment was built with Geant4. The atomic compositions of the materials used are shown in table 1. The EBS source (Axxent S700) was carefully modelled in Geant4 (Agostinelli *et al.*, 2003) and validated by comparing measured and simulated TG-43 parameters in Rivard *et al.* (2006). Using this model, 50 keV electrons were set in motion at the cathode and transported to a tungsten anode. Photons were generated via bremsstrahlung splitting (number of secondary photons equal to 100) and characteristic x-ray generation. Photons that reach the outer cooling water sheath of the source (diameter 5.1mm) were recorded into a phase space

file and then terminated. 10^9 primary electrons were simulated to generate a phase space file with 7×10^7 photons. No electrons were recorded due to their short range. The phase space source was validated against TG-43 data from Rivard et al, (2006) to within tolerated uncertainties ($<3\%$). This phase space source was used to simulate photon emission from the S700 in this work and has been used previously (White *et al.*, 2014b).

Three separate simulations for each distance were run utilizing track-length scoring and two billion photon histories for each simulation. The values of photon energy fluence differential with respect to energy obtained in the simulations were used with mass-energy absorption coefficients for water to derive values of absorbed dose to water under conditions of charged particle equilibrium.

Table 1. Atomic composition of materials used in the MC simulations.

Material	Atomic composition (percentage by weight)								
	H	C	O	Li	N	Ar	Br	Na	Cl
Lithium formate	4.32	17.16	68.59	9.92	-	-	-	-	-
Paraffin	14.98	85.02	-	-	-	-	-	-	-
EBT2 sensitive layer lot # A090310	9.55	58.2	28.3	0.92	0.23	-	1.31	0.38	1.15
Air	-	0.012	23.18	-	75.53	1.28	-	-	-
PMMA	8.05	59.98	31.97	-	-	-	-	-	-

Converting Monte Carlo results to absolute dose values

Monte Carlo simulations were used for a third estimate of D_w in terms of Gy. Relative MC doses in terms of fGy/particle were coupled to absorbed dose to water (in Gy) at 30 mm from the EBS, determined by an independent film irradiation (unpublished results). At this irradiation, the film was positioned 30 mm from the EBS in a separate PMMA phantom with the Markus chamber perpendicularly to the beam axis. MC simulations were used to determine the relationship between the readings of the Markus chamber in the two geometries, allowing transfer of the absorbed dose to water determined in the independent film irradiation to the absorbed dose to water at 30 mm in the present experiment.

Results

Table 2 shows absorbed dose to water as determined by the three different systems and Table 3 shows the quotients between the results of each system. In both film and EPR dosimetry systems, the absorbed dose was determined as the average of four detectors distributed around the source to minimize positional uncertainties (see Figure 2). At 10 mm distance, the geometry for the film measurement caused large uncertainty in the measured values depending on the exact position (within sub-mm distances) of the EBS, therefore, the film measurement at 10 mm was left out. The EPR measurements at 10 mm were considerably less influenced by the EBS position, within 3% for an uncertainty in the EBS position of ± 1 mm relative to the symmetry axis of the EPR dosimeters, the corresponding value for the film was 22%.

Table 2. Results of absorbed dose to water determined by EPR dosimeters, EBT2 film and Monte Carlo simulations. The expanded (k=2) relative uncertainties were 5% (EPR) and 7% (film) except at 10mm where the measurement uncertainty was 6% for EPR. Uncertainty in the MC simulated doses is estimated to 7%. See Table A1 in appendix for details.

Repetition	EPR			Film			MC		
	10 mm	D _w (Gy) 30 mm	50 mm	10 mm	D _w (Gy) 30 mm	50 mm	10 mm	D _w (Gy) 30 mm	50 mm
1	9.4	10.7	2.6	-	10.1	2.6	9.4	10.3	2.4
2		10.5	2.5		10.0	2.6		10.2	2.4
3		10.8	2.6		10.3	2.7		10.5	2.5
4		9.6	2.3		9.1	2.4		9.3	2.2

Table 3. The quotient of results displayed in Table 2.

Repetition	D _w (EPR)/D _w (MC)			D _w (film)/D _w (MC)			D _w (EPR)/D _w (film)		
	10 mm	30 mm	50 mm	10 mm	30 mm	50 mm	10 mm	30 mm	50 mm
1	1.01	1.04	1.08	-	0.98	1.08	-	1.05	0.99
2		1.03	1.05		0.98	1.09		1.05	0.96
3		1.03	1.07		0.97	1.09		1.05	0.98
4		1.03	1.05		0.98	1.08		1.05	0.97

Agreement within the estimated expanded (k=2) uncertainties (see Appendix) was found between the results obtained with the two dosimetry systems at 30 mm and 50 mm. This implies that the use of the two different calibration methodologies worked satisfactorily. The agreement between the results with the two dosimetry systems at repeated irradiations is noticeably good indicating that the type A statistical uncertainties are small for both systems. At 10 mm distance the EPR agreed with the MC calculated value within the estimated uncertainty.

Discussion

Monte Carlo calculations of absorbed dose to water

The inclusion of film measurements from a separate experiment to convert the MC calculations to absorbed dose to water in absolute values (Gy) may have introduced a bias of the MC results as indicated by the good agreement between the MC calculated and film dose values at 30mm (the depth of normalization (2.5.3)). The agreement between the results obtained by the EPR dosimeters and the EBT2 films in this study (Tables 2-3) supports the validity of the adopted approach. Uncertainties in the MC calculated values are dominated by the uncertainty in the value for absorbed dose to water that was determined using film dosimetry.

Energy dependence and intrinsic efficiency of EBT2 film dosimeters

Using the results of Sutherland and Rogers 2010, it was possible to calculate the absorbed dose in the active film layer allowing analysis of the energy dependence of M/D_w published using the new standardized film in terms of $M/\bar{D}_{det}$. Brown *et al.* (Brown *et al.*, 2012) investigated the energy response of monochromatic x-rays (25, 30 and 35 keV) with a 4 MV clinical photon beam as reference. Their results indicate variations in relative intrinsic efficiencies of $R_{25keV}/R_{35keV} = 0.95$ and $R_{25keV}/R_{4MV} = 0.63$. For a 50 kV x-ray beam (25.5 keV effective energy) relative to a 6 MV photon beam (effective energy 1.4 MeV) results by Butson *et al.* (Butson *et al.*, 2010) indicate a relative intrinsic efficiency of $R_{50kV}/R_{1.4MeV} = 0.57$, consistent with the result $R_{25keV}/R_{4MV} = 0.63$ of Brown *et al.* Arjomandy *et al.* (Arjomandy *et al.*, 2012) measured depth doses in water at 75 kV. Dose response calibration was performed at 75 kV. Compared to measurements with an ion chamber, the film showed an over-response of 8-9% at a depth of 10 cm compared to the normalization depth of 2 cm. The effective energy was noted to increase from 32.1 keV to 38.4 keV. Only 3% of this increase can be assigned to an increase in the energy absorption of the film relative to water indicating an increase in relative intrinsic efficiency consistent with the results of Brown *et al.* An increase in effective energy of only 1 keV, from 34 keV to 35 keV in our EBS measurements at 50 mm compared to 30 mm is not likely to have a noticeable effect on the results. It may be of some interest here to note that Kirby *et al.* (Kirby *et al.*, 2010) noted an under-response of 0.6 for the EBT2 film in the Bragg-peak of protons and suggested a model of explanation similar to those used in explaining the relative intrinsic efficiency of low energy photons relative to MV photon beams for TLDs and EPR dosimeters.

Conclusions

This work is a contribution to developing reliable experimental methods suitable for dosimetry around low energy brachytherapy sources, in particular high dose rate EBS. The EPR dosimeters were found to yield results in agreement with Monte Carlo simulations at three distances (10, 30 and 50 mm) from the source in the phantom. The EBT2 films agreed with Monte Carlo and EPR at 30 mm and 50 mm. At 10 mm, the uncertainty in the exact positioning of the EBS was too large to get a reliable estimate using EBT2 films. This work has shown the complexity of measurements around this type of source and the importance of detailed knowledge of the properties of the dosimetry system used. It was also shown that lithium formate EPR dosimetry is a good candidate for the purpose and it was deduced that there might be issues regarding energy dependence and intrinsic efficiency of the EBT2 film that need to be considered in future measurements.

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Appendix

Determination of absorbed dose to water with EPR dosimeters

Determination of absorbed dose to water using EPR dosimeters in the PMMA phantom at a distance r from the source follows Eq (A1).

$$D_{w, \text{phan}, 50\text{kV}}(r) = M_{50\text{kV}}(r) \left[\frac{D_w}{M} \left[\bar{s}_{\text{col}} \right]_{\text{w}}^{\text{PMMA}} \bar{f}_{\text{B}} \right]_{6\text{MV}} \frac{R_{Q_0}}{R_Q} \left[\frac{\bar{\mu}_{\text{en}}}{\rho} \right]_{\text{det}}^{\text{w}} f_{\text{vol}} \frac{\bar{D}_{\text{det}, \text{MC}}}{\bar{D}_{\text{lithium formate}}} \quad (\text{A1})$$

where M denotes the EPR signal, $\left[\bar{s}_{\text{col}} \right]_{\text{w}}^{\text{PMMA}}$ is the mass collision stopping power ratio between PMMA and water and converts absorbed dose to water to absorbed dose to PMMA; $\bar{f}_{\text{B}} = \bar{D}_{\text{det}} / D_{\text{PMMA}}$ is the Burlin cavity theory coefficient and converts absorbed dose to PMMA to the mean absorbed dose in the detector. Detailed information and numerical values of these factors are found in Antonovic *et al.* (Antonovic *et al.*, 2009). R_{Q_0} / R_Q is the correction for intrinsic efficiency (Adolfsson *et al.*, 2010) and was set to 1.06.

The values of $\left[\bar{\mu}_{\text{en}} / \rho \right]_{\text{det}}^{\text{w}}$ were determined to be 1.249, 1.246 and 1.243 at 10 mm, 30 mm and 50 mm respectively by weighting over the photon energy fluence spectrum at the three measurement positions in the phantom. Mass energy absorption coefficients were taken from NIST (Hubbell and Seltzer, 1995). The volume averaging correction factor, f_{vol} , was calculated with MC as the quotient of the absorbed dose to a 1 mm³ “point detector” situated at the centre of the EPR dosimeter and the absorbed dose to the full size detector. The values of f_{vol} at 10, 30 and 50 mm were 1.020, 1.023, and 1.030 respectively. The last factor in Eq A1 is needed to account for the fact that the signal is proportional to the dose registered in the lithium formate grains and not to that registered in the surrounding paraffin. This factor was calculated using MC simulations as described in detail by Adolfsson *et al.* (Adolfsson *et al.*, 2010).

Determination of absorbed dose to water with EBT2 film

Determination of absorbed dose to water using the EBT2 film in the PMMA phantom at the distance r from the source followed Eq (A2)

$$D_{w, \text{phan}, 50\text{kV}}(r) = \frac{M_{\text{phan}(r)} \left[\frac{M}{D_w} \right]_{\text{cal}, 50\text{kV}}}{\left[\frac{M}{D_w} \right]_{\text{cal}, 50\text{kV}} \left[\frac{M}{D_w} \right]_{\text{phan}, r}} f_{\text{pos}} f_{\text{vol}} = \frac{M_{\text{phan}(r)} \left[\frac{\bar{\mu}_{\text{en}}}{\rho} \right]_{\text{w}, \text{cal}, 50\text{kV}}^{\text{det}}}{\left[\frac{M}{D_w} \right]_{\text{cal}, 50\text{kV}} \left[\frac{\bar{\mu}_{\text{en}}}{\rho} \right]_{\text{w}, \text{phan}, r}^{\text{det}}} \frac{R_{Q_0}}{R_Q} f_{\text{pos}} f_{\text{vol}} \quad (\text{A2})$$

The film was calibrated to measure air kerma free-in-air using the TG61 protocol (Ma *et al.*, 2001). Absorbed dose to water was calculated by multiplying air kerma with the ratio of the weighted mean of the mass energy absorption coefficients for water and air yielding water kerma, i.e., absorbed dose to water under charged particle equilibrium. The quotient $[\bar{\mu}_{\text{en}} / \rho]_{\text{w,cal,50kV}}^{\text{det}} / [\bar{\mu}_{\text{en}} / \rho]_{\text{w,phan,r}}^{\text{det}}$ was set to unity. A correction for film position in the phantom f_{pos} was derived by MC calculation of the absorbed dose to water in the volume occupied by the film in the experiment and the same volume positioned at the centre of the EPR dosimeters (in the absence of the EPR dosimeter). Numerical values at 30 and 50 mm were 1.020 and 1.030 respectively. A volume averaging factor f_{vol} for the film was applied, derived similarly to the volume averaging for the EPR dosimeters. The quotient of the absorbed dose to a “film point” (1 mm³) and the absorbed dose to the full size film area was calculated. Numerical values at 30 and 50 mm were 0.991 and 0.976 respectively.

In the last equality of Eq A2 it is assumed that the signal from the film is proportional to the mean absorbed dose to the detector. The factor R_{Q_0} / R_Q takes into account any deviation from this assumption caused by different LET distributions of the secondary electrons at calibration and in the measurement in the PMMA phantom. Here, R_{Q_0} / R_Q was assumed to be unity.

Uncertainty in the experimentally determined absorbed dose

The total combined relative standard uncertainties in absorbed dose $u(D_{\text{w,phan,50kV}}(r)) / D_{\text{w,phan,50kV}}(r)$, derived from Eqs (A1) and (A2) were estimated by quadratically adding the relative standard uncertainties of its parameters (JCGM 2008)). Derivation of the uncertainties for the EPR dosimeters was described in detail in (Antonovic *et al.*, 2009; Adolfsen *et al.*, 2010). The estimated uncertainties are presented in Table A1.

Estimates of the relative standard uncertainties related to the film calibration (points 2 and 3 in Table A1) were taken from the AAPM protocol (Ma *et al.*, 2001). The mass-energy absorption correction factor (point 4 in Table A1) was set to unity. However, for a film with the composition of the active layer in Table 1 (the film used in this work), corrections of 0.975 and 0.966 at 30 mm and 50 mm, respectively, should be applied. This correction was not introduced in calculating $D_{\text{w,phan,50kV}}(r)$ since it cannot be ascertained that the atomic composition is exactly that aimed at by the manufacturer. Instead, we used the information in Figure 1 to estimate uncertainties caused by neglecting the correction. Assuming maximum possible deviations of 2.5% (30mm) and 3.4% (50mm) from unity for this factor, standard uncertainties were obtained by dividing with $\sqrt{3}$ (assuming a triangular probability distribution).

The uncertainty in MC calculated doses depend on the statistical uncertainty in the MC simulations, the uncertainty in the film dose at the normalization depth (30mm) and a correction to account for the different positions of the Markus chamber in the experiment

used for normalization (perpendicular to the beam axis) and in the experiment itself (see Figure 2). The combined relative standard uncertainty was estimated to be 3.5%.

Table A1. Components contributing to the combined relative standard uncertainty for EPR dosimeters and EBT2 film.

Source of uncertainty EPR	Distance (mm)			Source of uncertainty EBT2	Distance (mm)	
	10	30	50		30	50
1. $u(M_{50kV})/M_{50kV}$	0.4%	0.4%	0.4%	1. $u(M)/M$	0.5%	0.5%
2. $u(D_w/M)/D_w/M$	1.7%	1.7%	1.7%	2. $u(M/K_{air})/M/K_{air}$	2.1%	2.1%
3. $u(\bar{S}_{col}^{PMMA}_w)/(\bar{S}_{col}^{PMMA}_w)$	0.5%	0.5%	0.5%	3. $u\left(\left[\frac{\bar{\mu}_{en}}{\rho}\right]_w^{air}\right)/\left[\frac{\bar{\mu}_{en}}{\rho}\right]_w^{air}$	1.5%	1.5%
4. $u(\bar{f}_B)/\bar{f}_B$	0.5%	0.5%	0.5%	4. $u\left(\frac{\left[\frac{\bar{\mu}_{en}}{\rho}\right]_w^{det}}{\left[\frac{\bar{\mu}_{en}}{\rho}\right]_w^{phan}}\right)/\frac{\left[\frac{\bar{\mu}_{en}}{\rho}\right]_w^{det}}{\left[\frac{\bar{\mu}_{en}}{\rho}\right]_w^{phan}}$	1.5%	2.0%
5. $u(R_{Q_0}/R_Q)/(R_{Q_0}/R_Q)$	1.0%	1.0%	1.0%	5. $u(R_{Q_0}/R_Q)/(R_{Q_0}/R_Q)$	-	-
6. $u\left(\left[\frac{\bar{\mu}_{en}}{\rho}\right]_{det}^w\right)/\left[\frac{\bar{\mu}_{en}}{\rho}\right]_{det}^w$	0.5%	0.5%	0.5%	6. $u(f_{pos})/f_{pos}$	1.0%	1.0%
7. $u(f_{pos})/f_{pos}$	1.5%	0.5%	0.5%	7. $u(f_{vol})/f_{vol}$	1.0%	1.0%
8. $u(f_{vol})/f_{vol}$	1.0%	1.0%	1.0%			
9. $u\left(\frac{\bar{D}_{det,MC}}{\bar{D}_{lithium\ formate}}\right)/\frac{\bar{D}_{det,MC}}{\bar{D}_{lithium\ formate}}$	0.5%	0.5%	0.5%			
Combined 1-9				Combined 1-7		
$u(D_{w,phan,50kV}(r))/D_{w,phan,50kV}(r)$	3%	2.5%	2.5%	$u(D_{w,phan,50kV}(r))/D_{w,phan,50kV}(r)$	3.3 %	3.6%

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Chapter 5:

A comparison of the relative biological effectiveness of low energy electronic brachytherapy sources in breast tissue: A Monte Carlo study.

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Abstract

Purpose

Electronic brachytherapy sources use low energy photons to treat the tumor bed during or after breast-conserving surgery. The relative biological effectiveness of two electronic brachytherapy sources was explored to determine if spectral differences due to source design influenced radiation quality and if radiation quality decreased with distance in the breast.

Method and Materials

The RBE was calculated through the number of DNA double strand breaks (RBE_{DSB}) using the Monte Carlo Damage Simulator (MCDS) in combination with other Monte Carlo electron/photon spectrum calculations. 50kVp photons from the Intrabeam (Carl Zeiss Surgical) and Axxent (Xoft) through 40-mm spherical applicators were simulated to account for applicator and tissue attenuation in a variety of breast tissue compositions. 40kVp Axxent photons were also simulated. Secondary electrons (known to be responsible for most DNA damage) spectra at different distance were inputted into MCDS to calculate the RBE_{DSB} . All RBE_{DSB} used a cobalt-60 reference. RBE_{DSB} data was combined with corresponding average photon spectrum energy for the Axxent and applied to model-based average photon energy distributions to produce an RBE_{DSB} map of an accelerated partial breast irradiation (APBI) patient.

Results and Discussion

Both Axxent and Intrabeam 50kVp spectra were shown to have a comparable RBE_{DSB} of between 1.4 and 1.6 at all distances in spite of progressive beam hardening. The Axxent 40kVp also demonstrated a similar RBE_{DSB} at distances. Most RBE_{DSB} variability was dependent on the tissue type as was seen in rib ($RBE_{DSB} \approx 1.4$), gland (≈ 1.55), adipose (≈ 1.59), skin (≈ 1.52) and lung (≈ 1.50). RBE_{DSB} variability between both sources was within 2%. A correlation was shown between RBE_{DSB} and average photon energy and used to produce an RBE_{DSB} map of a dose distribution in an APBI patient dataset.

Conclusion

Radiation quality is very similar between electronic brachytherapy sources studied. No significant reductions in RBE_{DSB} were observed with increasing distance from the source.

Introduction

Electronic Brachytherapy (eBt) is a form of radiotherapy that utilizes low energy photon emission to treat cancer. Low energy brachytherapy has advantages in terms of limiting dose to organs at risk while maximizing the dose to clinically relevant regions due to the higher attenuation/absorption of low energy photons in matter. One notable advantage is the higher linear energy transfer (LET) of secondary electrons generated by low energy photons (Reniers and Verhaegen, 2006). Low energy electrons transfer their kinetic energy to the surrounding matter with a higher ionization density than electrons generated by high energy photons. The higher LET induces a greater level of damage in tissue and, as such, has a greater relative biological impact than a higher energy photon source. The relative biological effectiveness (RBE) is a ratio of the doses for two different radiation sources that yield the same biological impact, such as the surviving cell fraction. RBE is a complex quantity determined by biological endpoint, dose-rate, total dose, fractionation scheme and also the radiation quality/LET (Nikjoo and Lindborg, 2010). Higher RBE is indicative of greater biological damage, where the dose deposited by a source causes a larger amount of clinically useful tumour damage and/or greater organ complications. Currently, the International Commission on Radiation Protection assigns a radiation weighting factor of unity for all photon emitting sources (ICRP, 2007), equating the biological effectiveness of high and low energy photon sources.

One endpoint for determining RBE is the number of radiation-induced DNA strand breaks (Semenenko and Stewart, 2004). DNA damage can be expressed in terms of double strand breaks (DSB) and single strand breaks (SSB) to the DNA. SSB tend to correlate poorly with biological effectiveness while DSB and clusters of DSB have been postulated to lead to greater DNA damage (Goodhead, 1994) (Nikjoo and Lindborg, 2010). The RBE for SSB or DSB induction can be calculated by:

$$\text{RBE} = \frac{(\text{Strand break yield})_{\text{Reference}}}{(\text{Strand break yield})} \quad (1)$$

Where ‘strand break yield’ refers to DSB or SSB yields.

A previous study had estimated the RBE of a 50kV eBt source (Axxent S700, Xoft Inc, CA) in a variety of tissues, reporting an enhanced RBE_{DSB} compared to reference Co-60 photons (Reniers *et al.*, 2008). The RBE_{DSB} was estimated to be about 1.5 in breast tissue and about 1.1 – 1.2 in bone. However, this study used only non-clinical simplified phantom geometries with uniform tissues and ignored the effects of the Axxent balloon applicator, clinical breast tissue mixtures (adipose and gland mixtures) and the variation of RBE with distance from the source.

In the present study the RBE_{DSB} for the 50 kVp Axxent S700 (Xoft, San Jose CA) and the Intrabeam (Carl Zeiss Surgical, Oberkochen, Germany) were calculated using MC simulations. MC-based photon spectral data for the Axxent and Intrabeam sources was used from model x-ray tube simulations (Watson and Seuntjens, 2014; Liu *et al.*, 2008). The differences in radiation quality between 40kVp and 50kVp modes of the Axxent were also explored, taking into account applicators and tissues of different thickness and composition.

The 40 kVp mode provides steeper dose distributions and may lead to even higher RBE values (Mestres *et al.*, 2008), but this is currently clinically unexplored. The difference in radiation quality was also investigated between both eBt sources both operated at 50 kVp, but with a different design leading to differences in emitted photon spectra. ~

Methods and Materials

Electronic Brachytherapy Sources

Intrabeam

The Intrabeam source is a low energy drift-tube eBt source, approximately 3 mm in diameter and 10cm in length (Elliott *et al.*, 2011). The Intrabeam source can be used in single fraction partial breast irradiation as an alternative to external beam breast irradiation for carefully selected patients (Kraus-Tiefenbacher *et al.*, 2005) (Deneve *et al.*, 2012) (Eaton *et al.*, 2012). (Elliott *et al.*, 2011; Sanders *et al.*, 2007). IORT presents many advantages over external beam radiotherapy and has been the subject of an extensive 10 year randomized control trial, TARGIT (Vaidya *et al.*, 2001). The Intrabeam source utilizes a 50keV beam of electrons directed through the drift tube to a thin gold transmission target, located at the tip, to generate a bremsstrahlung x-ray spectrum (Figure 1). The electron accelerator section of the Intrabeam source is located in part of the Intrabeam exterior to the patient. The Intrabeam source can be used with various sizes of spherical solid applicators made of polyetherimide (PEI), with diameters ranging from 1.5 – 50mm. Photon spectra for specific applicators were not available. To determine the spectral attenuation due to applicator/tissue attenuation, a calculated photon spectrum from the Intrabeam source, obtained from an EGSnrc-based MC model of the source, was used in this study as the initial spectrum (Watson and Seuntjens, 2014). The calculated half value layers of the bare probe and various spherical applicators were in close agreement with measured data from literature. The Intrabeam produces a continuous bremsstrahlung spectrum with a low average energy (13.7keV) that is dominated at low energies by gold K-edge characteristic x-rays. These are rapidly attenuated by the surrounding applicator (Watson and Seuntjens, 2014) In this study, only the 40mm PEI spherical applicator was modeled with uniform composition and density.

Axxent source

The Axxent eBt source is a miniature x-ray tube approximately 2.3mm in diameter and 1.5cm in length. Electrons generated in the tip are accelerated through a 50kV potential (Liu *et al.*, 2008) after which they strike a tungsten transmission anode target (Figure 1). The anode also contains yttrium for added material strength and the source contains silver for conductivity. Characteristic x-ray peaks are generated at the tungsten L-edge, yttrium and silver K-edges between 9.7keV and 22.3keV with a continuous bremsstrahlung photon spectrum up to 50keV with an average energy of 25.3keV. The 40kVp Axxent spectrum also comprises these characteristic photons and has a slightly lower average energy (22.2keV). The target material (gold vs. tungsten) is the main difference between the two eBt sources studied (Intrabeam vs.

Axxent). Much of the low energy photon spectrum is attenuated by a water-cooling sheath around the anode. The MC-calculated Axxent spectrum used in this study has been validated against measured data (Liu *et al.*, 2008).

The Axxent applicator consists of a saline-inflated silicone balloon with a hollow air channel to accommodate the Axxent source at varying dwell positions. The applicator size ranges in diameter from 30mm to 60mm though the actual size depends on the amount of saline injected. The balloon applicator surface is composed of an outer sheath (thickness ~ 0.3 - 0.5 mm) of silicone and barium sulphate, a CT contrast material that enhances imaging contrast between the balloon applicator surface and the surrounding planning target volume (PTV) (Segala *et al.*, 2011). Barium is a high-Z element that strongly attenuates photons with energies at and above the binding energy of its K-edge (37.4keV). The lack of attenuation in the air channel for forward-emitted photons is compensated for by a high-Z silicone tip (Figure 1).

The Axxent applicator was modeled as a 40mm diameter sphere with a 0.4mm thick barium-impregnated silicone wall. The applicator diameter of the Axxent and the Intrabeam were identical.

Figure 1: A schematic drawing (top) of the Axxent balloon applicator with the S700 source. The balloon wall varies in thickness between 0.3mm and 0.6mm. The Intrabeam applicator (bottom) consists of a simpler plastic applicator around the needle-like source (drawings not to scale).

Electronic brachytherapy photon spectra

Figure 2: The calculated photon spectra from the surface of the Axxent (50kVp and 40kVp) and Intrabeam eBt sources. Simulated anode x-ray production (characteristic photons and bremsstrahlung) for both sources was calculated (Watson and Seuntjens, 2014; Liu *et al.*, 2008)) prior to the simulations described in this paper. Characteristic x-ray peaks are prominent in all spectra and lower the average photon energy. Note that these photons are rapidly attenuated by the source applicator.

Monte Carlo codes Geant4, EGSnrc and MCDS

Three MC tools were used in this study to determine the RBE for both sources and geometries. Geant4 (Agostinelli *et al.*, 2003) was used to determine photon attenuation around the applicators in the tissues. EGSnrc (Kawrakow, 2000) was used to calculate the secondary electron spectrum that each attenuated photon spectrum generated around the sources and Monte Carlo Damage Simulator (MCDS) (Stewart *et al.*, 2011) was used to calculate the degree of DNA damage for the inputted electron spectrum. All MC programs were used sequentially for each source/kVp (Figure 3). Simulations were performed in simple spherical geometries (Figure 4) and complex CT-based patient geometries (Figure 5) in Geant4. Geant4 was used for the initial photon simulations due to prior experience with CT-based patient geometries with low energy sources. EGSnrc was used for the electron production segment of the workflow. EGSnrc is considered a benchmark for electron simulation problems (Poon and Verhaegen, 2005; Maigne *et al.*, 2011). While the electron spectra could have been calculated using Geant4 in this work, EGSnrc was used for this task for consistency with previous work (Reniers *et al.*, 2008).

Photons from three photon emission spectra (Figure 2) were sampled and scored at different distances from the surface of their respective applicators. The photon/electron spectra were scored in water, adipose, glandular, lung, rib or skin geometries (table 1). Tissue assignment in the CT-based geometries used tissue segmentation algorithm (Afsharpour, 2011) to reflect

the complex distribution of tissues in the breast. The RBE_{DSB} was calculated for CT-based geometries using a calculated RBE_{DSB} /Average photon energy relationship (see 2.5).

Figure 3: A flowchart demonstrating the workflow from the initial spectra to RBE_{DSB} mapping.

Geant4

The software package used for the photon simulations in this study was the MC toolkit Geant4 v9.5p02. Geant4 is an all-purpose MC simulation toolkit that provides a diverse set of software components that can be employed in a variety of settings, including the simulation of photon transport from low-energy sources (Agostinelli *et al.*, 2003). These simulations used the Lawrence Livermore National Laboratory low-energy electromagnetic model for Geant4 (*G4LowEnergy*) which simulates the low-energy photon interactions of the photoelectric effect, Compton scattering and Rayleigh scattering. The model uses the EPDL-evaluated (Cullen D, 1997) and EADL-evaluated (Perkins, 1997) libraries. The photon energy transport cutoff was 1 keV. Geant4 was used to model the applicator for both sources embedded in a shell of variable thickness (Figure 4) and composed of a component of breast tissue (table 1). Photon transport was simulated using Geant4 and scored in a vacuum shell geometry. Electron production was ignored at this stage as the primary electrons would be calculated separately using another MC code as described in the previous section. All Geant4 simulations were run for 40M histories to give a <0.1% statistical uncertainty for low attenuating tissues close to the applicator, and 1-2% for highly attenuating rib at 40mm from the surface of the applicator.

EGSnrc

For the spherical simulation geometry that generated photon spectra in Geant4, its subsequent primary electron spectrum was calculated using EGSnrc (Kawrakow, 2000), a general purpose C++-based Monte Carlo code.

Each electron spectrum was determined using a technique described in a previous study (Reniers *et al.*, 2008). Here, the electron spectrum was scored by simulating interactions from the photon spectrum attenuated through the applicator/tissue material in the previous section. Primary electrons, produced from the photo-electric effect, bound Compton scattering and the Auger relaxation process, were scored between two concentric spheres close to the photon source (simulated as a point source). Compton and photo-electrons were generated down to a cutoff energy of 0.1keV while Auger electrons were produced down to a cutoff of 1keV, (sub-1keV Auger electrons are irretrievably discarded by EGSnrc). Only primary electrons were produced and scored while secondary electrons were ignored. It should be noted that the cutoff for Auger electrons was insufficient to accurately model the electron spectra for low energy photon spectra in EGSnrc, requiring a manual correction for sub-keV Augers. Calculating the proportion of Auger electrons in the electron spectrum is important due to their relatively high LET.. 100 million histories were simulated to reduce the statistical uncertainty to less than 0.1%.

The primary tissue components which produce Auger electron transitions are the elements C, N and O, which yield electrons at around 280eV, 373eV and 502eV, respectively. As EGSnrc does not calculate Auger electrons of these energies, it was necessary to estimate the Auger contribution to the total electron spectra. The number of Auger electrons generated was estimated by the total number of photo-electrons scaled according to the photoelectric cross-section of C, N or O (Berger *et al.*, 2005), the fluorescent yield (≈ 0 for low-Z elements) and the mass-fraction of the element in the tissue/material. Auger electrons are also generated by vacancies created by K-shell electron interaction in Compton photon scattering. The cross-section for the K-shell electron in Compton scattering is dependent on the energy of the incident photon (Stutz, 2014). Estimates for the number of K-shell vacancies (and subsequent Auger electrons) were obtained using cross-section data (Stutz, 2014).

Monte Carlo Damage Simulator

The Monte Carlo Damage Simulator (MCDS) (Semenenko and Stewart, 2004) is a simple and fast MC-based program to simulate the formation of DNA damage by different types of radiation. MCDS presents a faster alternative to microdosimetry MC simulations for detailed DNA models (Nikjoo *et al.*, 2002) which are time-consuming. The number of DSB are calculated based on the incident primary electron spectrum on the edge of a single cell model with a fixed nucleus diameter (5 μ m). Damage due to secondary electrons due to slowing-down of primary electrons is accounted for in MCDS. For this study the number of DSB per cell per giga-base-pair was the metric to determine the damage to a cell by a source. DSB are calculated based on the number of lesions within a predetermined number of base-pairs, where two SSB within 8 to 80 base pairs of each other could be considered a DSB (Semenenko and Stewart, 2004). The classification of breaks by complexity has been explored in other studies (Nikjoo *et al.*, 1997) and has been incorporated into MCDS. MCDS also accounts for oxygenation of the cell and the chemical repair that occurs under hypoxic

condition (Stewart *et al.*, 2011) Hypoxia in cells tends to increase radio-resistance (Georgakilas *et al.*, 2013) and DSB yield under oxygenated and hypoxic conditions has been studied (Carlson *et al.*, 2006) (Whitaker and McMillan, 1992). In this study, two breaks on opposing DNA strands with a separation of less than 10 base pairs (MCDS default) is considered a DSB. In comparison to the classic DNA track structure MC simulations, MCDS agrees to within 1% for 225kVp, Co-60 and 29kVp photon sources (Hsiao and Stewart, 2008). DSB yields predicted by MCDS agree to within 7% for <2keV characteristic x-rays in V79 cells described in experimental studies. (Botchway *et al.*, 1997; de Lara *et al.*, 2001).

Variations in photon and electron spectra with depth

To calculate the RBE_{DSB} variation with depth for both eBt sources the change in photon spectra with distance from the applicator was first calculated using Geant4 by simulating the transport of the photons through a series of tissue geometries of different thicknesses.. With Geant4, a series of concentric shells were used to model all materials (Table 1) individually in the simulated geometry (Figure 4). The outermost shell was composed of a tissue found in/near the breast. Embedded in the tissue shell was a thin scoring shell (<0.1mm). The innermost shell was a 40mm diameter applicator model. The total thickness of tissue was large (150mm) such that it could be considered infinite for the purposes of simulating backscatter. The tissues (Table 1), derived from ICRU-46 (International Commission on Radiation Units and Measurements, 1992), reflected the density and composition of bulk tissue in the breast. A water-based model was also used to model TG-43 conditions.

Table 1: The ICRU 46 tissue compositions for the 5 tissues modeled

Tissue	Element (% weight)											Density (g/cm ³)
	H	C	N	O	Na	Mg	P	S	Cl	K	Ca	
Glandular	10.6	33.2	3	52.7	0.1	-	0.1	0.2	0.1	-	-	1.02
Adipose	11.4	59.8	0.7	27.8	0.1	-	-	0.1	0.1	-	-	0.95
Skin	10	20.4	4.2	64.5	0.2	-	0.1	0.2	0.3	0.1	-	1.09
Rib	6.4	26.3	3.9	43.6	0.1	0.1	6	0.3	0.1	0.1	13.1	1.41
Lung	10.3	10.5	3.1	74.9	0.2	-	0.2	0.3	0.3	0.2	-	0.26

Figure 4: A schematic setup to determine the attenuated photon spectra for the eBt sources using Geant4. The Axxent and Intrabeam applicators are modeled as a 40mm sphere of saline/PEI (orange) and a 0.4mm balloon wall (green) in the case of the Axxent. Both eBt sources are modelled as isotropic point sources (red dot). The tissue depth (grey) and subsequent spectral scoring shell (dark red) varied from 0 to 40mm. Full backscatter conditions were included outside the scoring shell and backscattered photons were scored. The setup to determine the electron spectrum using EGSnrc is not shown.

The distance of the scoring shell from the surface of the applicator varied from 0mm to 40mm. The varied distance allows the calculation of RBE_{DSB} at the edges of the PTV (0-10mm) (Keisch *et al.*, 2007) and inside normal tissue around the PTV (10-40mm). Photons from the source were generated isotropically from the centre of the applicator. The small anisotropy and source dimensions (Rivard *et al.*, 2006), were not included in this study as this was expected to have only a minor influence on the RBE calculations. As mentioned in previous sections, photons that were transported across the tissue, either un-attenuated or scattered were scored in the spectra scoring shell. Missing photon backscatter from the vacuum region beyond the medium sphere was accounted for. Each photon spectrum was imported into EGSnrc to determine the primary electron spectra with the low energy C, N and O Auger portion of the spectrum for each tissue determined manually using the XCOM data (Berger *et al.*, 2005).

Calculation of RBE_{DSB}

The DSB yield was calculated in MCDS for both eBt sources. The biological cells containing the DNA were assumed to be fully oxygen-saturated ($pO_2=100\%$) due to the removal of the

primary (possibly hypoxic) tumour in IORT and APBI patients prior to irradiation. Therefore, primarily normal oxygenated tissue is investigated in this study. DSB yield was simulated in 2.5×10^5 cells to give a statistical uncertainty of 0.2%. The reference DSB yield was calculated for a Co-60 electron spectrum. Derived from transporting 1.25MeV photons in water in EGSnrc. RBE_{DSB} was then calculated with Eq1.

RBE in a realistic APBI patient geometry

An RBE_{DSB} map was produced accounting for breast tissue heterogeneities, photon and electron spectral changes due to the balloon applicator and tissue attenuation. This map was calculated for a realistic patient geometry derived from a DICOM CT image of an APBI patient treated using the Axxent. In a prior study (White *et al.*, 2014) a CT image was converted into a material/density mapped voxelized phantom (Figure 5) using a tissue contouring method (Afsharpour *et al.*, 2011) and the dose distribution was calculated using Geant4. A similar method could be used to calculate the photon spectra in all the phantom tissue voxels allowing for the modeling of tissue-specific RBE_{DSB} distributions similar to proton LET-based maps (Grassberger *et al.*, 2011). The calculation of a RBE_{DSB} map presents some challenges. Fast MC DNA damage calculation algorithms are not a feature of Geant4 or EGSnrc, making direct RBE calculations difficult. Calculating the full photon and electron spectrum for each voxel in a patient geometry is also cumbersome due to the sheer number of voxels present in patient images and the time to calculate the RBE_{DSB} . Calculating the RBE_{DSB} in a water-based TG-43 geometry may produce a generic radiation quality model which could be used to determine the change in RBE_{DSB} with distance from the source, however x-ray spectra may harden significantly due to changes in tissue composition with low energy photons attenuated to a great degree in high density/atomic number regions such as the ribs. Knowledge of the tissue composition is important for determining the Auger transitions with the carbon, oxygen and nitrogen-rich soft tissues contributing the lowest energy (and highest LET) electrons to a spectrum (Auger electrons with 280eV, 373eV and 502eV, respectively), compared to a phosphorus and calcium-rich (2keV and 4keV) tissue such as bone. Thus, tissue heterogeneities and patient geometry might reduce the accuracy of a simple water-based RBE model.

Computational limitations, the volume of spectral data and the large number of voxels in a patient geometry meant that a simpler method of RBE_{DSB} determination needed to be developed..

Figure 5: A material/density geometry (right) for a Geant4 simulation with a fully-segmented breast geometry converted from a CT image (left). The balloon applicator is also modeled here to highlight the air channel, saline-filled balloon and balloon tip (appearing as streaking artifacts (left) due to high photon absorption of barium).

In this work, for different breast tissues, simple relationships were derived between the mean photon energy and the RBE_{DSB} as a function of distance from an Axxent applicator balloon. These were then applied to mean photon energies calculated for all voxels in the APBI case. Assignment of RBE_{DSB} values was based on the material index (table 1). The tissue segmentation assumed no mixed composition voxels. Visualization of the average energy/RBE map was performed using an in-house brachytherapy dose analysis tool, BrachyGUI (Poon *et al.*, 2008).

Results and Discussion

Axxent vs. Intra-beam : comparison of RBE

The DSB yield for the reference radiation quality Co-60 was calculated as $8.50 \text{ Gbp}^{-1}\text{Gy}^{-1}$ under normoxic conditions, which is in agreement with those calculated using other Monte Carlo methods (Kirkby *et al.*, 2013) and with experiments, when taking uncertainties into account (de Lara *et al.*, 2001). The RBE_{DSB} for the Axxent and Intra-beam 50kVp spectra were compared at different distances from the surface of their applicators for a variety of tissues. The RBE_{DSB} for different tissues was considerably different, ranging between 1.4 and 1.6 at all distances from both sources. The full RBE_{DSB} and damage yields are shown in Figure 6. The difference between the two sources is small and depends slightly on the tissue type: $<1.3\%$ for adipose, gland, and lung tissue and $<0.5\%$ for rib.

The RBE_{DSB} for both sources did not decrease substantially with distance (Figure 6), in spite of spectral hardening, particularly through rib, where only a small decrease in RBE_{DSB} was calculated between 0mm and 20mm ($<1\%$). The absence of a spectral hardening effect on RBE_{DSB} and the similarity between both sources would seem to suggest that photons from the lower range of the spectrum (10-30keV), which are attenuated more readily than those at higher energies, do not somehow contribute to RBE_{DSB} significantly or are compensated for by the processes triggered by higher energy photons. Auger electrons generated from the photo-electric and Compton processes are the most influential aspect of the electron spectrum for both sources, contributing approximately 40-50% of the DSB. When the Auger electrons are excluded, the average RBE_{DSB} for both sources decreases to approximately 1.3. As previously shown, Compton and Auger electrons below 8keV significantly increase the damage to DNA (Reniers *et al.*, 2008). Although a harder photon spectrum would be expected to result in a lower DSB yield, this is not the case as though spectral hardening yields a reduction of photo-electrons and therefore a reduction in photo-electric-generated Auger electrons; (the photoelectric cross-section is higher at lower photon energies), it results in a relative increase in both low-keV Compton electrons and sub-keV Compton-generated Auger electrons which offsets the decrease in DNA damage caused by the harder photon spectrum. It was calculated using the K-shell cross-section (Stutz, 2014) for the photon input

spectrum for each source that the portion of Auger electrons from Compton to total number of Auger interactions

$$\left(\frac{\text{Auger}_{\text{Compton}}}{\text{Auger}_{\text{photoelectric+Compton}}} \right)$$

ranged from 12% to 32% (average 21%) for the Axxent and 8% to 30% (average 17%) for the Intrabeam eBt sources depending on the tissue's C, N, and O composition. This portion increases with increasing distance.

With respect to previous studies (Reniers *et al.*, 2008, Kellerer, 2002; Brenner and Amols, 1989; Bernal *et al.*, 2011; Kuhne *et al.*, 2005), where the RBE (in terms of physical damage, induction of chromosome aberrations and DSBs in water) for low energy sources (Mammography (29kVp) and characteristic x-rays (<5kV)) was calculated to be on the order of 1.15 to 1.3, the values reported in this study are elevated (~1.4-1.6) and comparable to another Axxent RBE study (Reniers *et al.*, 2008). Literature values for DSB probabilities (comparable to those calculated using MCDS) more closely match the RBE_{DSB} in this study when the Auger component is excluded (1.3).

Detailed, CPU intensive track length Monte Carlo (MC) simulators have modelled DNA strand breakages for photons (Friedland *et al.*, 1999), showing RBE_{DSB} on the order of 1.4 to 1.64 for K-edge electrons while RBE for cell deactivation for low energy photons has been quantified experimentally, using V79 cells irradiated with characteristic x-ray (de Lara *et al.*, 2001; Liu *et al.*, 2013) and with the former (de Lara *et al.*, 2001) compared retrospectively with DNA damage simulators with good agreement (Stewart *et al.*, 2011). The more recent of the two studies (Liu *et al.*, 2013) utilized the Intrabeam source to determine clonogenic deactivation in 4 cell types demonstrating an average RBE of 1.3 (Confidence Interval 1.25 – 1.36). Mammography sources have also been studied and were initially hypothesized to have higher RBE (~ 2) compared to high energy sources (Brenner and Amols, 1989). Radiation quality has been calculated using other methods. Detailed lineal energy distributions of mammography sources have been calculated using Monte Carlo techniques and shown to produce ionization clusters approximately 35% higher than 300kVp photon sources (similar to Ir-192) (Verhaegen and Reniers, 2004)

Axxent Vs. Intrabeam 50kVp

Figure 6: The calculated DSB yield and RBE for the Axxent (Ax) and Intrabeam (IB) 50kVp eBt sources

Figure 7: Electron spectra for mammary gland in an Axxent 20mm radius applicator setup at 0mm (black) and 40mm (pink), normalized against the total fluence. The spectra have distinct regions where Compton and photo-electrons are generated. A decrease in Auger (~20%) and photo-electrons and an increase in Compton electrons is observed in the 40mm spectra due to spectral hardening. The N auger peak is relatively small due to the low concentration of nitrogen in gland tissue.

40kVp vs. 50kV: Axxent

A comparison of the RBE_{DSB} for the 40kVp and 50kVp spectra of the Axxent source was made for a variety of tissues at depths from 0 to 20mm. The DSB yield and RBE_{DSB} for both sources can be seen in Figure 8. For both operating voltages similar RBE_{DSB} were obtained with a small increase in RBE_{DSB} for most tissues (average 0.9%) for the 40kVp spectrum. The small increase in RBE_{DSB} for the 40kVp Axxent and Intrabeam spectra described in the previous section, demonstrates the relative RBE_{DSB} insensitivity in the 40-50 kVp range to spectral changes. As in the previous section, the reasons for the insensitivity could be due to the offsetting of the effects of spectral hardening by increased Compton electron production. Due to this Compton offsetting, a 'plateau' effect may exist for 30-50kVp Bremsstrahlung spectra where the RBE_{DSB} experiences only small changes. For the tissue with the greatest degree of spectral hardening, rib, the differences in RBE_{DSB} between 40 and 50 kVp sources is also negligible, perhaps due to the reduced sub-1keV Auger production caused by the reduced portion of H,C,N and O elements and a lower fraction of Compton electrons, in favour of the increased fraction of 4keV Auger electrons from the calcium-rich rib tissue. As the RBE_{DSB} is the smallest for rib (approximately 1.4) this would seem to indicate that the RBE_{DSB} is more dependent on tissue composition (through the proportion of low energy C, N and O Auger electrons) than on spectral hardening.

Figure 8: The DSB yield and RBE_{DSB} for 40kVp and 50kVp Axxent eBt spectrum in tissue.

RBE mapping of APBI patient

A plot of RBE_{DSB} vs. average photon energy is shown in Figure 9 for the two dominating tissue types in breast; gland and adipose. Similar relationships were calculated for other tissues with good correlation between average energy and RBE_{DSB} . Combination of the 40 and 50 kVp results demonstrates a link between the average energy of a photon spectrum in these tissues and its RBE. This relationship was fit to a quadratic equation for each tissue, allowing a conversion factor for average photon energy to RBE. Figure 9 contains more points at greater distances (0 – 40mm), allowing for a more detailed RBE vs. average energy relationship than seen in figure 6 and 8 (0 -20mm).

Figure 9: The RBE_{DSB} vs. average photon energy plot for gland tissue ($R^2 = 0.99$) and adipose ($R^2 = 0.99$) for the Axxent eBt source

The mean photon energy map in an example breast case is shown in Figure 10. A RBE_{DSB} map for the same case is shown using the RBE_{DSB} /Average photon energy conversion equations from Figure 9. This figure shows the RBE_{DSB} distribution in various tissues, as segmented in Figure 5. As had been observed in previous sections, the ribs show the lowest RBE_{DSB} (approximately 1.4). The effect of spectral hardening on RBE_{DSB} can be seen in adipose and gland tissues with a slight (<2%) decrease from the centre of the balloon applicator. Skin demonstrated an RBE_{DSB} between adipose and gland throughout, with only a slight decrease (<2%) at the most distal regions. This kind of RBE_{DSB} map may help to assess biological damage throughout breast tissue (or in any other applications of low energy brachytherapy sources).

In addition to the small changes in beam quality, other factors will likely play a more important role in RBE, such as the large fall-off in dose-rate at greater distances from the source. Consequentially the lack of a reduction in RBE_{DSB} at large distances from the source may mean a greater degree of DNA damage in healthy tissue, however this is offset when taking into account the biological weighted dose (dose $\times$ RBE). The absence of any major impact of spectral hardening (Figure 9) on RBE_{DSB} disagrees with the assertion of a number of studies (Brenner *et al.*, 1999; Liu *et al.*, 2013) that spectral hardening of the Intrabeam eBt source could cause a decrease in cell deactivation (and hence RBE) with distance from a source.

Figure 10: A single transverse slice in the source plane demonstrating an average photon energy map (top) and average RBE_{DSB} map (center) of an APBI patient treated with the Axxent 50kVp source. A histogram of the RBE_{DSB} over the PTV volume for multiple patients (Bottom) shows the variation between adipose and gland. Peak amplitudes differ due to variations in the ratio of adipose/gland (Yaffe *et al.*, 2009) and indicate a percentage of the PTV volume. RBE_{DSB} in the balloon applicator and surrounding air were ignored.

Limitations

Some assumptions about the composition of breast tissue and the composition and dimensions of the cell, inherent to the use of MCDS, are made. In this study, it is assumed that the ICRU tissue compositions in bulk tissue hold for the microscopic cellular level. However there are compositional differences between the cell components between cells which may result in a difference in electron spectra generated by cellular material and extra-cellular material particularly for short-range Auger electrons. The manual calculation of Auger electrons also holds some degree of uncertainty and serves only as an approximation of the actual Auger yield. The accuracy of the manual calculation is estimated to be about 20% by comparing Auger yields above 1 keV for a uniform NaCl phantom with EGSnrc versus manual calculations; results not shown. The RBE impact of the Auger electrons is also uncertain. While Auger electrons have an influence on the RBE, the range of Auger electrons is small ($<0.1\mu\text{m}$) compared to an estimated human cell size (10-100 μm diameter range) so Auger electrons generated throughout the cell and DNA structure may have a greater impact on RBE than Auger electrons generated outside the cell (Thomson *et al.*, 2013). Indeed, the cellular and DNA composition may be more important for determining the Auger yield from a photon spectrum than the average tissue composition. However as both the Intrabeam and Axxent eBt sources have comparable photo-electron spectra, it is unlikely that any inaccuracies in Auger electrons will result in differences in RBE between the two. It should be noted that the percentage variation of RBE with distance is within the maximum accuracy of MCDS (1%) compared to track-length DNA simulations (Hsiao and Stewart, 2008). The differences between each source and mode (Figure 6 & 8) relate to experimental results may be masked within the clinical uncertainty of referenced measured data ($\sim 7\%$) used to validate MCDS (Hsiao and Stewart, 2008).

Conclusion

The Axxent and Intrabeam eBt sources have small differences in their emitted photon spectra, resulting in insignificant differences ($<1\%$) in RBE_{DSB} in all tissues investigated when calculated using MCDS. The contribution of low energy Auger electrons is important and therefore also proper modeling of the processes giving rise to them. The differences in RBE_{DSB} are small for different kVp in the Axxent eBt source ($<1\%$) indicating that a lower kVp does not confer any significant advantage to RBE. Other factors such as dose-rate and cell repair time may be more important factors.

RBE_{DSB} maps were used to visualize the changes in beam quality in a realistic patient geometry. The RBE_{DSB} map highlights the dependence of RBE_{DSB} on tissue composition. The RBE_{DSB} map may be used, combined with a dose map, to allow biological weighted dose mapping. It may also be allowed to assess differences in biological damage in patients with large differences in gland/adipose tissue mixtures.

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Chapter 6: Discussion

The challenges associated with accurate dose calculation, dosimetry and RBE modeling of low energy brachytherapy have been explored in this thesis. Aspects of the TG-186 recommendations were incorporated in dose calculations and how they compare to TG-43U1 were calculated and measured quantitatively. These included tissue heterogeneities, composition variability and applicator attenuation effects. While some radio-nuclides sources were analyzed in this thesis, the main focus of the thesis was mostly on electronic brachytherapy sources.

Chapters 2 and 3 have shown the influence of tissue composition variations, applicator dose perturbation and patient geometry considerations for the Axxent electronic brachytherapy source (EBS) compared to conventional water-based geometries. In chapter 3, potentially significant differences between TG-43 and TG-186 DVH metrics were calculated, particularly for the skin where patient-dependent peak dose decreases were observed. In chapter 2, the dose uncertainty due to atomic trace composition was calculated. It was found that tissue uncertainties may reduce the D_{90} in permanent implanted prostate brachytherapy with I125 and Pd103 seeds by up to 15% when comparing simulated tissue with and without trace elements present. Both studies show the importance of tissue composition and accurately modeled patient geometries in low energy brachytherapy.

Several dosimetry methods for low energy HDR brachytherapy were explored in chapter 4: novel EPR alanine dosimeters, EBT2 radiochromic films and Monte Carlo simulations. The challenges associated with brachytherapy dosimetry, the steep dose gradients and finite source size, were highlighted as were the energy dependence and intrinsic efficiency of EBT2 film. While, ideally, detectors should exhibit no volume-averaging, self-attenuation, angular anisotropy or energy dependence, in practice these can only be minimized by the right selection of dosimeter on a source-by-source basis (Tanderup *et al.*, 2013). Regardless of the suitability of EPR alanine or film dosimetry to HDR low energy brachytherapy, they may be unsuited to monitor time-resolved treatment delivery in patients or non-static phantoms due to position uncertainty or their inability to measure the instantaneous dose-rate. MOSFET, plastic scintillation or radioluminesce dosimeters have been proposed as candidates for high and low energy brachytherapy dose verification (Andersen *et al.*, 2009; Cherpak *et al.*, 2012; Kertzscher *et al.*, 2011).

The RBE of two low energy electronic brachytherapy sources was explored in chapter 5, demonstrating the similarities in radiation quality between two sources with different spectral outputs. DNA damage simulations utilizing the spectral simulations of the Axxent electronic brachytherapy sources were combined with APBI patient CT datasets from chapter 3 to produce RBE_{DSB} maps of whole breast to observe how spectral hardening affects radiation quality through a realistic patient geometry. The study challenges the notion that softer photon spectra always lead to higher beam qualities and provides a hypothesis for a 'plateau' in radiation response for bremsstrahlung sources for certain energy ranges and introduces the concept of RBE-weighted dose maps.

TG-186 has provided a framework for improvements to high and low energy brachytherapy, most notably recommending the use of model-based dose calculation algorithms. The chapters in this thesis aim to provide insight into the improvements possible in low energy brachytherapy using Monte Carlo-based calculation methods. The work described may also be used as a stepping stone to resolve numerous topics mentioned in TG-186. In chapter 3,

describing APBI dose calculation, both $D_{m,m}$ and $D_{w,m}$ are reported for the PTV and skin OAR. Due to the fundamental quantitative differences between $D_{m,m}$ and $D_{w,m}$, it is unknown which dose reporting method best correlates to clinical outcome (Ma and Li, 2011b) (Tedgren and Carlsson, 2013). Indeed clinical studies which report $D_{m,m}$ in brachytherapy are virtually non-existent. This provides an argument for the use of $D_{w,m}$, in that all clinical experience has been using TG-43 ($D_{w,w}$), making $D_{w,m}$ results consistent with reporting in previous studies (Beaulieu *et al.*, 2012). Given the lack of experience with $D_{m,m}$ -based clinical studies, chapter 3 offers a useful methodology of correlating both $D_{w,m}$ and $D_{m,m}$ dose distributions with clinical outcome, whether it be survival or toxicity outcome, in prospective and retrospective studies.

The influence of backscatter on superficial OARs, in this case the skin, is also highlighted in chapter 3. As TG-43-based dose calculations consistently over-predict the dose to skin, MBCDA models which calculate backscatter correct could potentially permit dose escalation in patients with a lower calculated skin dose though it is unknown whether TG-43U1 skin dose tolerances, based on empirical clinical practice, are applicable. A previous study (Shi *et al.*, 2010) into model-based dose calculation for APBI patients with the Axxent EBS predicted similar decreases (17%) in maximum dose to the skin, however no attempt was made to correlate this to skin toxicity. Indeed limited skin toxicity data after APBI using EBS has been published. The only study for skin toxicity involving the Axxent source merely recommended an optimal method of balloon catheter insertion prior to irradiation in order to minimize theoretical skin dose (Hepel *et al.*, 2010a) rather than correlate skin toxicity with dose in patients cohorts. As this study calculates skin dose based on current treatment planning system parameters (TG-43U1), it fails to account for non-patient backscatter considerations. Some skin-toxicity data is available for similar treatment modalities. One study has shown that dose to skin volume, in excess of 100% of prescription dose, has been correlated proportionally to severity and frequency of occurrence of skin toxicity for MammoSite-treated patients (Vargo *et al.*, 2014b). As MammoSite uses the higher energy Ir-192 source, dose distributions are not subject to tissue heterogeneities to the same degree as EBS.

Individual variability to tissue composition is a topic discussed in chapter 2. As had been shown in a previous study (Landry *et al.*, 2010b) which demonstrated the sensitivity of dose calculations of low energy sources to population bulk tissue composition uncertainties/deviations in MBDCa, chapter 2 shows that the trace element composition also influences the dose distribution in a non-negligible way. A fully comprehensive H,C,N,O and trace composition of human tissues relevant to low energy sources is lacking. While certain studies provide population distributions of bulk tissue composition (White, 1986) and precise trace element composition (Carvalho *et al.*, 2007b), combined studies could not be found. The differences in H, C, N and O concentration between cancerous and healthy tissue samples are also challenging as no bulk tissue composition data is known to exist for cancerous tissue. The increased trace element concentration for cancerous prostate tissue is not accounted for in the ICRU 46 report (International Commission on Radiation Units and Measurements, 1992), which only accounts for average healthy tissue composition. As seen in chapter 2, the impact of trace elements should not be understated and in the absence of more complete tissue composition data, trace elements, population/individual variability and the relative differences between healthy and cancerous tissue present a non-negligible

uncertainty that should be included in model-based dose calculations. There may also be unknown elements to trace element composition in humans such as environmental factors specific to geographical regions/diet/genetics(Freeland-Graves *et al.*, 2014). The eventual magnitude of this uncertainty merits future investigation.

Shortcomings and limitations in radiochromic film-based dosimetry were shown in chapter 5 while lithium formate EPR dosimeters were shown to be a more precise method of dose determination. The shortcomings for the EBT2 film may be due to the orientation and angle of irradiation with respect to the source. Dose gradients across the film did not allow for accurate dosimetry for points close to the source. While the need for accurate dosimetry in brachytherapy has been previously highlighted, the difficulties with these dosimeters may have a minimal impact on in-vivo dosimetry in APBI brachytherapy. Though film measurements at 10mm presented with large uncertainties, in clinical situations, the inflatable Axxent balloon applicator surrounds the source, increasing source-to-tissue distance and reducing the steep dose gradient across the PTV, making EBS dosimetry close to the source (<15mm) of lesser clinical importance.

EBT2 film also presents issues with regard to energy dependence, calibration and film heterogeneities that also exist for EBT3 film. A study of I-125 dosimetry using EBT3 film calibrated for low energy has shown demonstrated similar energy dependence when compared to film calibrated to 6MV photon(Morrison *et al.*, 2014). As with chapter 5, the EBT3 film was calibrated for low energy sources using an orthovoltage external beam source and in addition to (separately) using 6MV, 200kVp and the I-125 brachytherapy source itself. Film calibrated using higher energy sources produced a poorer fit (and hence dose accuracy) for the low energy source while the 75kVp source generated the most accurate fit due to larger dose uncertainties inherent to brachytherapy.

The issues encountered with EBT2 film in chapter 5 may also be due to the relative position of the source with respect to the film plane during irradiation and the position during post-irradiation scanning. In external beam radiotherapy film dosimetry, the film plane is typically perpendicular to the plane of the beam and sufficiently faraway from the active layer such that any regions of film off the central beam axis have a minimal angle of incidence (figure 1). As brachytherapy sources may be closer to the plane of the film, the angle of incidence increases. Post-irradiation scanning involves measurement of optical density of the film using light which, like EBRT, passes through the film plane perpendicularly. As the active layer of the film is not an infinitely thin detector, the mean distance radiation must transverse increases with decreasing source distance. This may be exasperated with larger film pieces at closer distances and inhibit film usage for aspects of brachytherapy such as anisotropy, $F(r)$, measurements required to determine TG-43 parameters..

Figure 1: A schematic diagram representing photons passing through the film active layer (thickness t) from sources at different distances d . Photons traverses a length of x through film which increases with increasing angle θ .

It may be this factor that is responsible for the poor agreement seen in chapter 5 and further work is needed to determine if film orientation with respect to the source reduces accuracy. While the International Commission on Radiological Protection (ICRP, 2007) recommends assigning a radiation quality factor of unity for all photon emitting sources, previous studies (Reniers *et al.*, 2008) have shown that RBE_{DSB} for low energy brachytherapy sources is not unity. Work in Chapter 5 has shown similar values for RBE_{DSB} (an indicator of radiation quality) for both EBS sources investigated and are in agreement with reported values in other studies (Liu *et al.*, 2013; Marthinsen *et al.*, 2010). As RBE is a complex quantity influenced by dose-rate, total dose and fractionation, the results reported in chapter 5 represent only one of the factors that determines biological effectiveness. While both the Axxent and Intrabeam sources are used in the partial breast irradiation, the typical fractionation scheme and total dose for both sources are different (Herskind *et al.*, 2005). The Intrabeam is used for single fraction IORT (Vaidya *et al.*, 2001) while the Axxent may be used for single fraction IORT or for multi-fraction APBI (Dickler *et al.*, 2009). Aspects of fractionation and dose delivery time have been explored in other studies (Herskind *et al.*, 2005) and are beyond the scope of this thesis.

This thesis introduces RBE_{DSB} maps for brachytherapy treatments. These provide a useful visual aspect to determining radiation quality throughout a realistic patient geometry, but it is not known how this element of RBE could be implemented clinically. Spectral hardening was not shown to significantly decrease RBE_{DSB} throughout the breast geometry which is influenced more by tissue composition than by spectral changes. LET mapping in hadron therapy shows promise in identifying regions where particle slow-down, particularly around the Bragg peak, results in increased RBE locally, opening up the possibility of LET-weighted dose distributions (Grassberger *et al.*, 2011). Ideally this would enable tighter dose-constraints for organs at risk. The degree to which RBE_{DSB} mapping can be incorporated in future treatment planning systems is not yet known. While recommendations for the future of tissue and applicator heterogeneities, dose reporting and dosimetry in brachytherapy have been proposed (Beaulieu *et al.*, 2012), no such recommendation have been given with respect to radiological modeling and RBE.

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Chapter 7:

Valorization addendum

Innovation

This thesis served to address the complexities inherent to dose calculation, dosimetry and radiobiological effectiveness with respect to electronic brachytherapy sources, in particular the Xofig Axxent.

Model-based dose calculation algorithm

The AAPM TG-56, which provides a code of practice for brachytherapy quality assurance, recommends a dose delivery accuracy of 5-10% to a target volume. The recommendations also state that dose distributions calculated using treatment planning software should be accurate to within $\pm 2\%$. While certain dosimetry protocols (TG-43) assume that the patient can be assumed to be a water-sphere for dose calculation purposes, the complex patient composition and geometry present a challenge for low energy photon sources which are sensitive to composition variations and backscattering. The quantifying of these heterogeneities in chapter 2 and 3 can be used to improve dose delivery accuracy.

The combination of techniques for breast tissue segmentation and CAD-mesh applicator model allows more accurate assignment of heterogeneous tissues to patient geometries as well as modeling of sub-voxel size applicator features. A deformed inflatable balloon applicator would be difficult to model in Monte Carlo platforms using CSG.

Relative biological effectiveness

The low variability of radiobiological effectiveness in low energy brachytherapy for tissues calculated in chapter 5 demonstrate a lack of influence of beam hardening on radiation quality. This may reduce the complexity of low energy brachytherapy sources in terms of radiobiological considerations.

The similarity in RBE for electronic brachytherapy sources for different operating voltages (40kVp and 50kVp) seems to indicate that lower peak voltages does not confer a higher biological effectiveness.

EPR Dosimetry

The difficulties associated with in-vivo dosimetry around brachytherapy sources are well-established. Measurement of absorbed dose for low energy photons present extra challenges due to the material heterogeneities that enhance the dose differences between tissues more than at higher energies.

The results in chapter 4 show the viability of EPR Lithium-formate dosimetry at low energies due to the favourable dose response at distances close to the source. Lithium formate dosimeters are materially-equivalent to water and are sufficiently small, making them suitable for brachytherapy dosimetry.

Clinical Relevance

The techniques for dose calculations and breast tissue segmentation described in chapter 3 can significantly improve dose calculation accuracy and may serve as a foundation for a Monte Carlo-based treatment planning system in the future. The lower-than-expected organ-at-risk dose in certain patients may permit dose escalation in certain patients that would be difficult to predict in TG-43-based planning systems.

Results describing the influence of trace elements on dose distributions for low energy sources can be incorporated into more accurately quantifying dose uncertainty. More accurate elemental tissue composition data may be obtained in the future and allow a further refinement of this uncertainty.

Chapter 5 describes predicts the iso-effectiveness between electronic brachytherapy, in terms of radiobiological effectiveness. While source-based RBE is not yet a criterion for photon radiotherapy (RBE assumed to be 1 for all sources), the various RBE described in tissue may be useful for incorporation into future treatment planning systems.

The clinical benefits of small brachytherapy dosimeters, described in chapter XX, are apparent given the difficulties in accurate dosimetry in low energy brachytherapy. Accurate pre-treatment planning and post-treatment evaluation using CT planning may not be possible, particularly in intra-operative radiotherapy using electronic brachytherapy sources. EPR-based dosimeters potentially offer greater re-usability and accuracy at shorter distances compared to EBT-based film.

Societal relevance

Brachytherapy is a radiotherapy treatment modality, widely used due to advantages it offers in treatment and cosmetic outcome. Brachytherapy treatment planning has not kept up with radiotherapy in terms of dose calculation and has only recently started to move away from water-based models.

The scientific findings discussed in this thesis can be used to improve dose calculation accuracy by properly accounting for applicator and tissue heterogeneities present, in particular, in breast patients. Improved accuracy may be useful for determining the possibility of dose escalation which can increase the dose to clinical relevant regions while maintaining an acceptable dose to organs at risk. The findings also serve to improve/refine dosimetric uncertainty in low energy brachytherapy in general.

Commercial Relevance

EPR dosimetry may become a standard quality assurance evaluator in low energy brachytherapy. The Monte Carlo techniques used may also be incorporated into a future Treatment planning system.

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