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Abstract

Low dose rate brachytherapy is a widely used modality for the treatment of prostate cancer. Most clinical treatment planning systems currently in use approximate all tissue to water, neglecting the existence of inhomogeneities, such as calcifications. The presence of prostatic calcifications may perturb the dose due to the higher photoelectric effect cross section in comparison to water. This study quantitatively evaluates the effect of prostatic calcifications on the dosimetric outcome of brachytherapy treatments by means of Monte Carlo simulations and its potential clinical consequences. Four pathological calcification samples were characterised with micro-particle induced x-ray emission (μ -PIXE) to determine their heavy elemental composition. Calcium, phosphorus and zinc were found to be the predominant heavy elements in the calcification composition. Four clinical patient brachytherapy treatments were modelled using Geant4 based Monte Carlo simulations, in terms of the distribution of brachytherapy seeds and calcifications in the prostate. Dose reductions were observed to be up to 30% locally to the calcification boundary, calcification size dependent. Single large calcifications and closely placed calculi caused local dose reductions of between 30–60%. Individual calculi smaller than 0.5 mm in diameter showed minimal dosimetric impact, however, the effects of small or diffuse calcifications within the prostatic tissue could not be determined using the methods employed in the study. The simulation study showed a varying reduction on common dosimetric parameters. D90 showed a reduction of 2–5%, regardless of calcification surface area and volume. The parameters V100, V150 and V200 were also reduced by as much as 3% and on average by 1%. These reductions were also found to relate to the surface area and volume of calcifications, which may have a significant dosimetric impact on brachytherapy treatment, however, such impacts depend strongly on specific factors in the patient's individual treatment. These factors include the number, size, composition and spatial distribution of calcifications in the prostate as well as the distribution of brachytherapy seeds.

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The Investigation of Prostatic Calcifications using μ -PIXE Analysis and their Dosimetric Effect in Low Dose Rate Brachytherapy Treatments using Geant4

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Low Dose Rate (LDR) brachytherapy is a widely used modality for the treatment of prostate cancer. Most clinical treatment planning systems (TPS) currently in use approximate all tissue to water, neglecting the existence of inhomogeneities, such as calcifications. The presence of prostatic calcifications may perturb the dose due to the higher photoelectric effect cross section in comparison to water. This study quantitatively evaluates the effect of prostatic calcifications on the dosimetric outcome of brachytherapy treatments by means of Monte Carlo simulations and its potential clinical consequences.

Four pathological calcification samples were characterised with micro-particle induced x-ray emission (μ -PIXE) to determine their heavy elemental composition. Calcium, phosphorus and zinc were found to be the predominant heavy elements in the calcification composition. Four clinical patient brachytherapy treatments were modelled using Geant4 based Monte Carlo simulations, in terms of the distribution of brachytherapy seeds and calcifications in the prostate. Dose reductions were observed to be up to 30% locally to the calcification boundary, calcification size dependent. Single large calcifications and closely placed calculi caused local dose reductions of between 30-60%. Individual calculi smaller than 0.5mm in diameter showed minimal dosimetric impact, however, the effects of small or diffuse calcifications within the prostatic tissue could not be determined using the methods employed in the study. The simulation study showed a varying reduction on common dosimetric parameters. D_{90} showed a reduction of 2-5%, regardless of calcification surface area and volume. The parameters V_{100} , V_{150} and V_{200} were also reduced by as much as 3% and on average by 1%. These reductions were also found to relate to the surface area and volume of calcifications, which may have a significant dosimetric impact on brachytherapy treatment, however, such impacts depend strongly on specific factors in the patient's individual treatment. These factors include the number, size, composition and spatial distribution of calcifications in the prostate as well as the distribution of brachytherapy seeds.

I. INTRODUCTION

Prostatic calculi are small firm objects formed from calcareous material deposited within the tissue of the prostate gland [1] and are more commonly found in older men [2],[3]. Calcifications may be identified using various imaging modalities, however they are most easily found during surgical removal of tissues in which they are contained [4]. Formation of these bodies has been found to occur in all regions within the prostate, with substantial variations in degree, frequency and distribution found amongst individuals [5]. Studies on whole mount sections of prostatectomy specimens found that calcifications were present in 88.6% of specimens in the prostate and ejaculatory system [5]. The development of prostatic calculi has found to be

more common in men with prostate cancer however no link between the two has been established [6]. Measurements of prostatic calculi samples by means of Fourier Transform Infrared (FTIR) microspectroscopic mapping and traditional FTIR and Raman microspectroscopy determined that prostatic calcifications composition is predominately carbonated hydroxyapatite [1]; however there was also a significant amount of calcium oxalate present in a number of the samples [1]. The Report of Task Group 186 identifies that there is limited data on the composition of prostatic calcifications although other studies have suggested that these may be similar to breast calcifications for which published data is available [7].

The presence of calcifications in the tumour target is of concern in Low Dose Rate Brachytherapy (LDR-BT). LDR-BT treatments have become frequently used for the treatment of organ confined or “localised” prostate cancer [8]. I-125 is a commonly used LDR isotope in brachytherapy treatments. It has a half-life of 60 days emitting x-rays with energies of 27.4, 31.4 and 35.5 keV [9]. Given the low energy output of I-125 radioactive seeds it is possible that calcifications may have a significant dosimetric impact. This is due to the dominance of photoelectric absorption in the keV ranges and the presence of the high Z elements of which they are composed [10]. The dosimetric effect of calcifications can be significant as they attenuate the photons emitted by the seed more efficiently than the surrounding prostatic tissue.

The goal of this research was to quantify the effects of calcifications on the dosimetric parameters of low dose rate prostate brachytherapy treatments, which are used to evaluate clinical outcomes inpatient treatments. Previous studies showed that inaccurate modelling of LDR-BT in commercial treatment planning systems can significantly affect the dosimetric outcome of the treatment [11],[12],[13].

A study evaluating the impact of interseed attenuation for I-125 permanent seed implants found that variation in seed density causes reductions in the CTV D_{90} value of up to 3% [11]. For studies on the dosimetric impact of gold fiducial markers in patients receiving combined external beam and LDR seed treatments, large dose reductions (up to approximately 50%) were observed at the distal side of the fiducial markers, while a dose enhancement was observed at the proximal side [12]. As a result of these findings [11,12], it is understood that calcifications may result in comparable dose perturbations. The dosimetric effect of calcifications in LDR-BT, using Pd-103 and I-125 seeds has been quantified by means of Monte Carlo simulations [13]. Calcifications covering 1% to 5% of the prostatic volume were studied for two patients. For both cases, the value of D_{100} was reduced by as much as 25% for a 1% calcified prostate. When considering a prostate volume consisting of 5% calcification occupancy, D_{80} , D_{90} , and D_{100} were decreased by up to 32%, 37%, and 58%, respectively [13]. This demonstrates the need to study the dosimetric impact of calcifications in real patient LDR-BT treatments

Although calcification compositions such as hydroxypapatite [1] have been previously determined, this study investigates the presence and variance of heavy elemental components in pathological calcification samples through micro particle induced x-ray emission (μ -PIXE) measurements. The dosimetric effect of these components, both locally and

volumetrically, were determined by modelling clinical LDR-BT treatment plans, with and without the presence of calcifications, using a Geant4 Monte Carlo based application, *BrachyPlot*. I-125 seed and calcification data were extracted from clinical treatment plans, allowing the simulations to determine real clinical effects, not simply those from arbitrary seed and calcification positioning. The dose perturbations occurring around the calcification perimeters, as well as the effect of these local perturbations on clinical volumetric parameters, such as D_{90} , V_{100} , V_{150} and V_{200} , were studied.

II. MATERIALS AND METHODS

II.A Measurement of pathological calcification sample compositions

Four pathological calcification samples, obtained from patients undergoing prostatectomy, with age ranging from 68 to 79 years, were selected for μ -PIXE measurements using the Heavy Ion Microprobe (HIMP) at the Australian Nuclear and Science Technology Organisation (ANSTO) [14]. As seen in figure 1, each specimen varied significantly in shape and size.

Fig. 1. Pathological calcification samples of four different patients. A) Sample 1: 1.93 mm x 0.43 mm x 1.57 mm, B) Sample 2: 1.19 mm x 0.91 mm x 1.14 mm, C) Sample 3: 2.39 mm x 1.51 mm x 1.56 mm, D) Sample 4: 3.20 mm x 2.34 mm x 2.50 mm. These were measured using the largest dimension to fix the x axis and smallest orthogonal dimension to fix the y axis. Measurements were performed using callipers.

The HIMP uses a 10 MV Tandem accelerator to accelerate ions to the MeV energy range. In this analysis, a 3 MeV proton beam with typical spot size of between 5 and 10 μ m was used. At this spot size, beam currents between 0.4 and 0.5 nA can be achieved, which is sufficient for μ -PIXE analyses. A high-purity Germanium (Ge) detector was used with a 100 mm² active area to measure the characteristic X-rays

emerging from the calcification samples. The detector was located 100 mm from the sample to reduce pile up due to the high count rate. A 100 μm Mylar foil was used to reduce low energy X-rays count as well as prevent scattered protons from entering the detector. Samples were fixed to the sample holder by means of double sided carbon tape. This tape is very pure and does not contain trace elements higher than oxygen ($Z > 8$). The tape does not affect measurements and is effective in holding the samples providing good electric conductivity to allow target current measurement. Each sample was then scanned for approximately 20 minutes for extensive emission data to be obtained.

The average elemental concentrations in the samples were calculated using GeoPIXE [15], [16]. In $\mu\text{-PIXE}$, samples should be very flat, otherwise a shadowing effect can be observed in the elemental map. This is clearly visible in sample B of figure 2, which has separated in the middle. Therefore, only areas of the maps without shadowing were selected to calculate the concentration of high Z elements.

Fig. 2. $\mu\text{-PIXE}$ analysis on each of the four calcification samples (A): Sample 1 (B): Sample 2 (C): Sample 3 (D): Sample 4. The map for calcium content is shown in this particular case with moderate concentration in blue and high concentration in red. Green outlines show the selected regions.

II.B Geant4 LDR-BT dosimetric system *BrachyPlot*

The *BrachyPlot* application, developed at the Centre for Medical Radiation Physics, University of Wollongong, is a Monte Carlo simulation based on the GEANT4 Toolkit [17][18], and was designed to perform dosimetric studies addressed to clinical LDR-BT. The virtual treatment volume within *BrachyPlot* is modelled with a $20 \times 20 \times 20 \text{ cm}^3$ cubic water phantom, where Oncura model 6711 I-125 brachytherapy seeds can be placed in the desired arrangement, recreating a treatment plan. In terms of geometry and materials, the Oncura model 6711 I-125 brachytherapy seed was modelled in the simulation [19].

The radiation field consists of photons with I-125 emission energy spectrum, emitted from a random position located $1\mu\text{m}$ underneath the surface of the silver core, representing the I-125 implantation, with the emissions occurring in a random direction. The physical interactions included in the Geant4 application were modelled by means of the Livermore Low Energy Electromagnetic Package [20]. The threshold of production of secondary particles was fixed to a range of

$1\mu\text{m}$. The interactions modelled were the photoelectric effect, Compton scattering and Rayleigh scattering for photons, and Bremsstrahlung, ionisation and multiple scattering for electrons. Fluorescence emissions from atomic relaxation was also modelled. Auger electrons were neglected as their kinetic energy was less than or approximately equal to the energy cut, (1.5 keV) [21] corresponding to adopted a $1\mu\text{m}$ range cut in this study.

BrachyPlot does not use voxelised geometry within the Geant4 volume construction routines, however, the coordinates of all energy depositions within the sensitive water phantom were mapped to a three-dimensional scoring matrix. The sensitive volume, where the energy deposition was calculated, is a $7 \times 7 \times 7 \text{ cm}^3$ 3D mesh, centred within the water phantom, with $0.1 \times 0.1 \times 2 \text{ mm}^3$ voxels. This represents 15, 2mm thick imaging slices, with 5mm pitch, each providing a 2D dosimetric image with 700×700 pixels. Dose maps were calculated in axial plans that cover the prostate region. Dose deposition was only scored within the water phantom, not within any calcification volume or within I-125 brachytherapy seeds. Dose deposition was scored from both the energy liberated through interactions and from the non-transport of secondary particles created with energies below the transport threshold (equivalent to $1\mu\text{m}$ range).

II.B Validation of *BrachyPlot*

BrachyPlot was validated with respect to the dosimetric protocol prepared by the AAPM Task Group 43 (TG43-U1) [22]. A single Oncura 6711 seed was modelled at the centre of a $30 \times 30 \times 30 \text{ cm}^3$ liquid water phantom. 10 concentric scoring shells of thickness 0.05 mm were modelled around the seed, with radii from 5mm to 50 mm, in 5 mm increments. The secondary particle threshold and physical interactions were set to match that of *BrachyPlot*. Energy deposited within a scoring shell was stored in a two dimensional array for radial distance from the source and angle about the source axis, with the radial distance equal to the radii of the shell and the angle rounded to the nearest 5° , as demonstrated in figure 3. From the dose scoring array, the TG43 radial dose function values were calculated and compared to values published in the TG43-U1 report [22]. This allowed the verification of the suitability of the physics packages used in the *BrachyPlot* simulations for LDR-BT Monte Carlo modelling.

Fig. 3. Geant4 simulation validation scoring geometry

II.C Modelling real patient treatments in *BrachyPlot* using hydroxyapatite calcification compositions

BrachyPlot was used to calculate the dose in four patients deriving from real LDR sources distribution, with and without calcifications, with a maximum statistical uncertainty of 2%, obtained with $4 \cdot 10^{10}$ events per patient treatment. The 3D dose distribution calculated by means of *BrachyPlot* was used to calculate the clinical parameters D_{90} , V_{100} , V_{150} and V_{200} . These parameters indicate the effect of patient's individual calcifications over the entire prostate volume and are an indication of the dose coverage of the prostate for the LDR brachytherapy treatment. Geant4 version 9.4 was used for all simulations in the study. ROOT [23] was used as an analysis tool.

Four clinical LDR-BT treatment plans were studied in this research. The number of brachytherapy seeds used in the four patient plans varied as 88, 102, 82 and 83. The activities of the seeds were 0.508 U in all cases, except for patient 1, which was 0.4064 U.

The position of the seeds (using CT images) and the size and position of the calcifications (using ultrasound images) were retrieved for each patient, in order to model the treatment configuration in the *BrachyPlot* simulation. The CT data was comprised of approximately 12 to 16 images taken throughout the prostate region in 0.5 cm transverse plane (z-plane) slices. x and y coordinates for each seed were manually obtained by visually identifying the centroid of each seed on a DICOM image viewer (ImageJ) and imported into the *BrachyPlot* simulation, along with the corresponding z coordinate of the plane. The Ultrasound images were originally co-registered to the CT data for clinical planning and treatment.

Ultrasound imaging is essential for the location of the calcification formations due to its ability to identify regions of changing medium. The position and size of each contoured calcification were obtained directly from each patient slice. Like the CT image slices, each z-plane ultrasound slice is spaced by 0.5 cm. As with CT data, there are multiple ultrasound slices for each patient; however it was found that formations are usually only

found on three to five slices in most cases. Due to the complex nature of calcification formations, large single calcifications were modelled as spheres while clusters were approximated as a group of spheres. The diameter of each calcification was determined from the visible size of each on the ultrasound images.

Ultrasound image analysis showed that the calcification formations were typically situated in the periurethral region. The size and number of stones varied greatly in the four treatment plans under study. In two instances, calcification cluster groups consisting of multiple large (approximately 2mm diameter) stones were found. These were found centrally inside the prostate. Commonly smaller (less than 2 mm in diameter) stones are found to be isolated within the prostate. Each plan is unique however it appears that smaller stones are more common and their numbers vary significantly. In the study it was found that calcification numbers varied from 5 to 33, while diameters of individual stones varied from 0.2 to 3 mm. The variation of calcification formation in the four patient plans is summarised in Table 1.

Data set	Calcification Diameter range (mm)	No. of Calcifications	Percentage volume occupancy (%)
Patient 1	0.9 – 3.4	5	0.055
Patient 2	0.2 – 1.0	33	0.006
Patient 3	1.0 – 3.0	6	0.071
Patient 4	1.0 – 2.2	13	0.062

Table 1. Calcification variation across the four patient plans in regards to size, number and occupancy of the prostatic volume.

The calcifications were modelled as a hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) composition, as identified in [1], with the results displayed in section III.C. It should be noted that this composition differs to that recommended by TG-186 through the omission of carbon and nitrogen components as well a differing weight fractions. Alternatively the calcifications were modelled with the composition determined by means of μ -PIXE to determine the dosimetric effect of varying calcification composition; these results are displayed in section III.D. These compositions include high z trace elements which have not been considered in [1] or [7]. In all cases the calcifications were modelled with a density of 3.16 gcm^{-3} , which differs from the TG-186 recommended value of 3.06 gcm^{-3} .

All calcification bodies in the four patient LDR-BT treatments were modelled in *BrachyPlot*, however only those showing significant dosimetric effects were selected for complete analysis. The selection was based on calcification size, proximity to I-125 seeds and location in the prostate.

II.C.1 Study of local dosimetric effects

Four clinical patient LDR-BT plans were simulated in *BrachyPlot* with and without calcifications, and comparisons between the two cases were used to determine quantitatively the local dosimetric effect around calcifications of interest. In this section, the calcification composition was kept fixed to that of hydroxyapatite for all simulations. Across the four patient plans, fourteen individual calcifications were analysed in total, all of which varied in size, formation and location throughout the prostate. These unique stones were selected based on the factors as detailed in section II.C.

Two dimensional dose distributions were obtained in planes corresponding to slices containing calcifications. The relative percentage difference (RPD) with and without calcifications was calculated in the axial planes containing calcifications of interest. One dimensional dose distributions were obtained on each slice of interest horizontally through the location of the calcifications. Black vertical lines on the resultant plots indicate the boundary of the calcification. The dose is not calculated inside the calcification body and therefore no dose is measured between these lines for simulations containing calcifications. The displacement is indicated by the distance on either side of the boundary at which the dose calculated with and without calcifications fall within the statistical error affecting the simulation results. As individual dose values have an uncertainty of 2%, displacement was defined as the distance from the calcification boundary to the point at which both simulation plots are within a 4% uncertainty limit. The doses from two virtual voxels either side of each calculi containing both calcification and water were ignored as the volume of sensitive material (water) within the voxels was reduced.

II.C.2 Study of LDR-BT volumetric parameters

The impact of calcifications on the clinical dosimetric parameters for LDR brachytherapy treatments were studied for the same four patient plans. Parameters D_{90} , V_{100} , V_{150} and V_{200} were determined based on the simulation results obtained by means of *BrachyPlot*. The parameter D_{90} is the minimum dose received by 90% of the clinical target volume (CTV), while parameters V_{100} , V_{150} and V_{200} indicate the percentage of the CTV that receives at least 100%, 150% and 200% of the prescription dose respectively [24].

The total surface area and volume for all calcifications present in the patient plans were calculated and their impact on the clinical dosimetric parameters for LDR brachytherapy treatments studied. Since the exact Clinical Target Volume (CTV) could not be determined, and to eliminate discrepancies directly due to human

error during voluming, the 100% isodose (corresponding to a dose equal to 144 Gy or higher) surface was used to determine the CTV in simulations without calcifications. The same CTV was used in the simulations with the calcifications modelled. To determine the parameter D_{90} for simulations both with and without calcifications, the doses in all voxels within the CTV were extracted, and sorted from highest to lowest. The 90th percentile of the collection was specified as D_{90} . For each simulation, V_{100} , V_{150} and V_{200} were calculated by summing volume of the voxels that represented a treatment dose of 144 Gy, 216 Gy and 288 Gy respectively.

II.D Modelling real patient treatments in *BrachyPlot* using varied calcification compositions from μ -PIXE measurements.

In this section, the dosimetric impact of different calcification compositions are analysed. The composition of calcifications derived from μ -PIXE (see Table 2), are used to model the calcifications in the LDR-BT treatment plan of patient 3 in *BrachyPlot*. Patient 3 was chosen for this study as it displayed a number of calcifications with unique size and location in comparison to the other three plans. Using the four μ -PIXE derived calcification compositions, simulation data was obtained and analysed using the same process as the hydroxyapatite simulations. Since a single plan was used, each simulation contained exactly the same calcification and therefore four comparative simulations were obtained. As this plan contained less calcification bodies, analysis was only taken across five complimentary stones for each simulation.

III. RESULTS AND DISCUSSION

III.A Pathological sample compositions

Results from the Heavy ion microprobe found the following components were present in most of the samples: phosphorus (P), sulphur (S), chlorine (Cl), potassium (K), calcium (Ca), iron (Fe), zinc (Zn), and strontium (Sr). Bromine (Br) was also detected but in such low concentrations (order of parts per million) that the contribution of this element was considered insignificant.

The specific concentrations of the elements contained in each sample are provided in Table 2.

Element	Sample 1 (%)	Sample 2 (%)	Sample 3 (%)	Sample 4 (%)
Phosphorus	23.08 ± 4.62	24.89 ± 4.98	1.05 ± 0.21	14.96 ± 2.99
Sulphur	0.29 ± 0.06	0.34 ± 0.07	2.68 ± 0.54	3.17 ± 0.64
Chlorine	0.44 ±	0.24 ±	0.70 ±	0.11 ±

	0.09	0.05	0.14	0.02
Potassium	0.06 ± 0.01	0.84 ± 0.17	0.26 ± 0.05	0.60 ± 0.12
Calcium	39.55 ± 7.91	35.56 ± 7.11	27.07 ± 5.41	30.08 ± 6.02
Iron	0.007 ± 0.001	N/A	0.012 ± 0.002	0.06 ± 0.01
Zinc	7.74 ± 1.55	3.04 ± 0.07	0.46 ± 0.09	4.99 ± 1.0
Strontium	0.035 ± 0.007	0.026 ± 0.005	N/A	0.032 ± 0.006
Undetectable Components	~28.78	~35.07	~67.77	~46.02

Table 2. Elemental concentration percentages measured in each calcification sample using μ -PIXE measurements.

The results showed that most of the samples have a similar formation. Although variations occur in each case, the samples display a similar pattern with higher concentrations of calcium, phosphorus and zinc. Figure 4 shows the concentration maps for these three elements in the case of sample 1. The only major discrepancy amongst the samples was a low phosphorus concentration measured in sample 3. As the overall percentage of high z elements is low in this sample, it is likely that this stone may contain a high concentration of lighter elements not detected by μ -PIXE. There are a number of possible discrepancies in the measurement of elemental concentrations which may account for relative variations in the sample results. As the calcification body is not a flat surface, characteristic x-rays generated from within a cavity or on the posterior side of the calcification will be attenuated and therefore a loss of data will occur.

Fig. 4. Phosphorus (P), Calcium (Ca) and Zinc (Zn) elemental maps for the calcification stone obtained from sample 1. The axis on the right represents the percentage of detected x-ray emissions from the specific element over the entire sample.

The variations in sample concentrations may be due to the synthesis process. If synthesis occurs in a different manner in each patient, it might explain why relative variations are observed, however this problem goes beyond the scope of this paper. It is difficult to obtain a total understanding of the concentrations found in a wide variety of patients when four samples only were

analysed, however these measurements are important as it is the first time μ -PIXE has been used to study the composition of prostatic calcifications. Future examination of other samples would be useful to increase statistics and gain a more comprehensive understanding of the composition of calcifications.

As μ -PIXE is not capable of detecting lighter elements such as hydrogen, carbon and oxygen which are fundamental components of known calcifications compositions [1], a complete composition analysis is not possible using this technique alone. Particle induced gamma emission (PIGE) techniques can determine low Z components however this was not available at the facility and therefore could not be utilised for this study. As lighter elements could not be detected by μ -PIXE as described, it has been assumed that the missing undetectable concentration percentages can be approximated by oxygen for calcification modelling in simulation studies. This is consistent with the previously mentioned literature showing hydroxyapatite and calcium oxalate being major components comprising calcifications.

III.B BrachyPlot validation

Figure 5 shows the radial dose function obtained by means of a Geant4 simulation by TG43 published values. The Geant4 simulation agrees with TG43 within 5% for distances within 50 mm from the source. This agreement of radial dose function with depth indicates the energy spectrum emitted from the seed, as well as the physical interaction models used in the simulation are adequate for the study.

Fig. 5. Radial dose function for the Oncura 6711 seed, as generated using Geant4 and published in the TG43 reference data.

III.C Hydroxyapatite calcification composition simulation results

III.C.1 Calcification local dosimetric effect

As seen in figure 6, the calcification is located in close proximity to an LDR brachytherapy seed and indicates a reduction predominately to the posterior side of the boundary with respect to the I-125 seed, as shown in

figure 7. The reduction on the left side of the boundary starts at approximately 26% and takes a distance of 2.2 mm from the calcification boundary to be statistically insignificant. The dose on the right hand side (in front of the I-125 seed), however, shows that the initial dose at the boundary reduction is approximately 7% which becomes statistically insignificant at a distance of 0.4 mm from the calcification boundary.

Fig. 6. Comparative dose effect in the 2 cm z-plane due to calcification presence in patient 1 (1 pixel = $0.1 \times 0.1 \text{ mm}^2$).

Fig. 7. Dose along the x-axis passing through the centre of the 2 mm diameter stone shown in Fig. 6.

Figures 8 and 9 show the results obtained for a calcification cluster in patient 3, close to the position of a LDR treatment seed. This calcification, presents a dose reduction of approximately 22% on the posterior side of the calcification boundary. This dose reduction becomes statistically insignificant at a distance of 3.6 mm from the calcification. It was once again found that there is a small reduction on the anterior side of the calcification (closest to the I-125 seed). This was slightly greater than 4% and became insignificant at 1 mm from the boundary. The major difference in this case is the high dose reduction in the central region, between the two calcifications composing the cluster. In this 0.5 mm region the average reduction observed was 50%.

Fig. 8. Comparative dose effect in the 2 cm z-plane due to calcification presence in patient 3 (1 pixel = $0.1 \times 0.1 \text{ mm}^2$).

Fig. 9. Dose along the x-axis passing through the centre of the calcification cluster (both 3mm in diameter) shown in Fig. 8.

Figures 10 and 11 provide an example of dosimetric effect due to a large 2.4 mm diameter calcification found in patient 4, detected on the 1.5 cm axial prostate plane. As can be observed in figure 11, this calcification creates a gradual reduction either side of its boundary. On the left hand side of the plot, initial boundary reductions start at approximately 24% and become insignificant at 2 mm from the calcification boundary. The initial reduction to the right side of the plot is slightly lower at 17% and only takes 0.6 mm to become statistically irrelevant.

Fig. 10. Comparative dose effect in the 1.5 cm z-plane due to calcification presence in patient 4 (1 pixel = $0.1 \times 0.1 \text{ mm}^2$).

Fig. 11. Dose along the x-axis passing through the centre of the 2.4 mm diameter stone shown in Fig. 10.

In patient 2, a number of small calcifications with a diameter of less than 0.5 mm were detected, as shown in figure 12. Upon quantitative analysis, it was determined that these small individual calcifications provided very little dosimetric perturbation. Limitations in the identification of small calcifications using ultrasound, including the size and number of calcifications of diameter below 0.5 mm, restrict the inclusion of the effects of small and diffuse calcifications within the prostatic tissue in the study, therefore these effects should not be ignored.

Fig. 12. Comparative dose effect in the 1 cm z-plane due to calcification presence in patient 2 (1 pixel = 0.1 x 0.1mm²).

From the analysis of all identified calcifications, the results found substantial local dose reductions at the boundary of calcifications when their diameter is larger than approximately 0.5 mm. The amount of dose reduction depends strongly on the brachytherapy seeds location and on the size of the calcification. Calcification formations with diameter between 1 and 2 mm show dose reductions on the boundary between 7 and 30%. Calcifications larger than 2 mm in diameter show dose reductions in a similar range, however, reductions of 20-30% are observed more often. The most significant dose reductions are those found between two large stones in a cluster formation (figures 8 and 9). These reductions were found to be between 33-62%. Dose reductions were observed up to distances ranging between 0.5 mm

and 4 mm from the calcification boundary in all cases, however these values are strongly dependent on calcification size and proximity to brachytherapy seeds. A significant dose reduction (greater than 7%) at the boundary of calcifications with diameter bigger than 0.5 mm is always observed independently of their relative position with respect to the brachytherapy seeds. Another significant finding of these simulations is the shadow effect caused by calcification and seed alignment (i.e. Fig. 6 and 7). In this configuration, dose reductions between 10-30% are observed behind the calcification as in other cases, however the distance from the calcification boundary where the dose reduction becomes negligible is increased by at least 1 mm.

III.C.2 Impact of calcifications on LDR-BT volumetric parameters

Table 3 shows the LDR-BT clinical parameters determined by means of the *BrachyPlot* simulations, modelling the treatments of four real patients. The composition of the calcification is hydroxyapatite.

Patient simulation	Calculi Surface area (cm ²)	Calculi Volume (cm ³)	D ₉₀	V ₁₀₀	V ₁₅₀	V ₂₀₀
1	0.66 cm ²	0.029 cm ³	-2.83 ±0.47	-1.21 ±0.21	-1.26 ±0.33	-0.51 ±0.38
2	0.26 cm ²	0.003 cm ³	-2.39 ±1.72	-0.46 ±0.42	-0.42 ±0.21	-0.12 ±0.41
3	0.90 cm ²	0.038 cm ³	-2.36 ±0.25	-1.02 ±0.14	-2.50 ±0.10	-1.02 ±1.20
4	1.07 cm ²	0.033 cm ³	-2.27 ±1.13	-1.13 ±0.16	-1.00 ±0.32	-0.51 ±0.30

Table 3. The reduction percentages caused to the clinical parameters by hydroxyapatite calcification inclusion in the prostatic volume. The errors are obtained from the combination of the standard deviation of 20 simulations, of 2 billion histories each.

The results showed a reduction of approximately 2% to 3% for D₉₀, independently from the total calcification area and volume. Reductions were also found in V₁₀₀, V₁₅₀ and V₂₀₀ although these were much lower with reductions no greater than 2.5% in all cases. V₂₀₀ was quite low for all patients and this is likely to be determined by the distance of calcifications from the brachytherapy seeds. It was observed that the parameters V₁₀₀, V₁₅₀ and V₂₀₀ of Patient 2 had reductions two times smaller than the other three patient cases. This appeared to be determined by the small total surface area and volume of this patient's calcifications. Patient 3 is characterised by a higher

reduction in V_{150} and V_{200} and this should be due to the presence of a large calcification in very close proximity with a brachytherapy seed. From the analysis of the dosimetric parameters, the dose reductions calculated in all patients were not clinically significant as they are smaller than a few percent. It is important to note that calcification have a very significant local dosimetric effect which is not evaluated in the determination of the dosimetric parameters.

III.D Varied Calcification Composition Simulation Results

III.D.1 Local dosimetric effect

The effect of varied calcification composition, based on μ -PIXE results, was assessed for a number of stones in the plan of patient 3. In this section, greater statistics were generated to give less uncertainty between the varied composition simulations. The convergence was determined at the point at which the calcification and no calcification data were within statistical error. For moderate isolated stones (approximately 1.5 - 2mm in diameter), it was found that variations in the calcification composition reduced the dose delivered locally to the calcification boundary between approximately 10 to 20%. The local dose was affected up to approximately 2mm from the calcification boundary with convergence distances between compositions only varying by less than half a millimetre. Figure 13 shows the dose along the x-axis through a 1.7 mm diameter stone for the different calcification compositions used.

Fig. 13. Dose along the x-axis passing through the centre of a 1.7mm diameter stone in patient 3 (for 4 different calcification compositions).

Composition	Left boundary reduction (%)	convergence distance: Left (mm)	Right boundary reduction (%)	Convergence distance: right (mm)
1	-13.9 $\pm$ 2.5	1.5	-18.7 $\pm$ 2.5	1.4

2	-16.3 $\pm$ 2.5	1.3	-13.0 $\pm$ 2.5	1.3
3	-9.3 $\pm$ 2.5	1.2	-15.3 $\pm$ 2.5	1.4
4	-11.5 $\pm$ 2.5	1.3	-16.1 $\pm$ 2.5	1.2

Table 4. Initial dose reductions and convergence distance on the left and right boundary of the 1.7mm diameter).

In the case of the calcification cluster (seen in figure 8), varying the calcification composition produced reductions in the dose locally to the boundary on the anterior and posterior side in regards to the nearby brachytherapy seed. On the anterior side of the calcification boundary, dose reductions were between 3 - 6%, with the dosimetric effect becoming negligible within 2mm for all compositions. On the posterior side of the calcification boundary reductions were between 22 - 26% and the dosimetric effect became negligible between 3.5 - 4.5 mm. In the region between the two calcifications, dose reductions achieved values between 50 - 60%. As previously determined, the study showed that the boundary dose reductions depend strongly on calcification size and proximity to LDR seeds. It was found that there was a very limited dependency of the dose reductions in respect to the different calcification compositions studied in this section. Table 5 shows the range of reductions measured using the varied calcification compositions in patient 3.

Diameter of calcifications analysed (mm)	Left boundary reduction range (%)	convergence distance range: Left (mm)	Right boundary reduction range (%)	Convergence distance range: right (mm)
2 x 3 mm (Cluster)	22.4 - 25.8	3.5 - 4.5	2.9 - 4.5	1.5 - 1.8
2mm	17.3 - 21.9	1.3 - 2.2	11.2 - 18.7	1.3 - 1.5
1.8mm	7.6 - 14.2	0.8 - 1.7	15.1 - 26.2	0.5 - 1.5

Table 5. Dose reduction and convergence ranges for varied calcification size and compositions.

The dose reductions are of the same magnitude of those found with the fixed hydroxyapatite composition, however slightly larger in most cases. This is determined by the greater presence of high Z elements in the calcification compositions measured by μ -PIXE. With respect to composition 1, 2 and 4, composition 3 was characterised by smaller dose reductions in a number of cases, determined by the higher concentration of oxygen ($Z=8$) and therefore by a reduced probability of photoelectric absorption. The results obtained with

composition 3 were closer on average to the results of the fixed hydroxyapatite composition used on the same patient plan. When changing the composition of calcifications, it was found that all simulations varied by less than 11%.

III.D.2 Effect of calcification composition on LDR-BT clinical dosimetric parameters

The dosimetric effect on the parameters for LDR brachytherapy treatment were analysed for the four μ -PIXE simulations in the same manner as the fixed hydroxyapatite composition simulations.

The impact of composition in the fixed plan of patient 3 gave reductions to D_{90} , V_{100} , V_{150} and V_{200} as shown in Table 6. The surface area and total volume of the calcifications are 0.90 cm^2 and 0.04 cm^3 , respectively.

Patient 3 composition	D_{90}	V_{100}	V_{150}	V_{200}
μ -PIXE sample 1	-4.13 ± 0.15	-0.72 ± 0.09	-5.24 ± 0.09	-2.41 ± 0.79
μ -PIXE sample 2	-3.65 ± 0.16	-0.46 ± 0.11	-5.46 ± 0.08	+2.56 ± 0.58
μ -PIXE sample 3	-3.62 ± 0.13	-0.41 ± 0.08	-5.39 ± 0.08	-2.61 ± 0.70
μ -PIXE sample 4	-2.86 ± 0.13	0.76 ± 0.09	-3.08 ± 0.08	-1.62 ± 0.80

Table 6. Reduction percentages caused to the clinical parameters by the inclusion of varied calcification compositions in the prostatic volume for patient 3. The errors are obtained from the combination of the standard deviation of 50 simulations, of 2 billion histories each.

The results of these simulations show that the reductions caused to D_{90} (between 2.8-4.2%) are higher in comparison to those found with the fixed hydroxyapatite composition for patient 3. For V_{100} reductions were found to be similar to the hydroxyapatite composition while V_{150} and V_{200} were approximately 2 times greater. From the findings there appears to be no significant trend that shows that varying composition (based on μ -PIXE measurements) has a distinct effect in each of the four cases. Based on the obtained results it is difficult to assess the impact of varied composition. It does however appear that the addition of heavy elements included in the calcification structure has increased the reductions to some of the dosimetric parameters in comparison to those presented in section III.C.

IV. CONCLUSION

Brachytherapy is a widely used radiotherapy treatment in Australia and in the world to cure prostatic cancer.

Commercial treatment planning systems (TPS) currently used in radiotherapy approximate all materials to water without considering the existence of prostatic calcifications. This research consisted in the evaluation of the dosimetric effect of prostatic calcifications in real clinical brachytherapy treatments. The morphology of four pathological calcification samples was studied. The size of a stone can vary from submillimeter size to 3 mm in diameter, the number of stones in a single patient varied between two to over 80. The shape of the calcifications can be either spherical or present irregularities. More pathological calcifications should be examined in future studies to increase the statistics.

One section of the study consisted in measuring the elemental concentrations in four pathological calcification samples by means of μ -PIXE analysis, at ANSTO. This study showed that the higher contributing heavy elements in the calcification composition are calcium, phosphorous, zinc. Oxygen was not detected however this is assumed to be one of the most abundant elements as the concentration ratios suggest a hydroxyapatite composition. From the measurements, the calcification compositions were found to vary significantly among different patients.

A Geant4 simulation was developed to study the dosimetric effect of calcifications in four real clinical treatments. The position of the brachytherapy seeds and of the calcifications was retrieved by Computed Tomography and ultrasound images. The calcifications were modelled in the simulations as spheres with dimensions as determined from patients' treatment imaging. This study showed that the presence of calcifications reduce the dose locally. The dose reduction depends on the size and proximity of the stones to the brachytherapy seeds. The average of dose reduction at the boundary was approximately 20% and reaching a maximum, extreme value of 60% at the calcification boundary. On average it was found that larger stones produce a higher local dose reduction. On average dose reductions were observed up to a few millimetres from the calcification boundary, however severity was dependent strongly on relative location of the stone with respect to the brachytherapy seeds. Although stones with diameters of less than 0.5 mm provided limited results in this work, the dosimetric perturbations caused by these small calcifications should not be discounted. Future studies will be useful in determining the dosimetric impact of these extremely small calcifications. This will involve performing simulations with calcification input based on the variation of Hounsfield units within the patient CT, as opposed to the identification of calcifications on ultrasound. This method will not only assist in the inclusion of diffuse calcifications within the prostatic tissue into the simulation, but will provide model based

determinations of the effects of calcifications on brachytherapy dosimetry, in line with the TG-186 recommendations [7]. Dosimetric parameters used in prostate brachytherapy treatments, D_{90} , V_{100} , V_{150} and V_{200} , were calculated for the four treatment plans, using a fixed hydroxyapatite composition as well as a fixed patient plan using four compositions determined by μ -PIXE.

It was found that D_{90} was reduced in all cases between 2-4.2% regardless of calcification total surface area, volume and composition. Reductions of this magnitude are equivalent to those caused by interseed attenuation effects as studied by Carrier et al. [11]. In contrast, the studies of Chibani et al. [13] found the parameter D_{90} was reduced by as much as 37% when considering a 5% calcified prostate volume. The simulation techniques of Chibani et al. [13] vary greatly to those presented in this study. The code developed by Chibani et al. [13] randomly distributes calcification voxels over the entire prostate volume and therefore does not form a singular calcified body. It is also found that calcification occupancy of 5% is two times greater than those adopted in this study based on clinical patient data. Discrepancies between the two studies may be due to the specification of the CTV used for the determination of the dosimetric parameters. Given the different configuration of the study, it is difficult to draw any conclusion from the comparison with the work of Chibani et al. [13].

The parameters V_{100} , V_{150} and V_{200} were affected by calcification surface area and volume; however the effect in most cases is no more than 5.5%.

The reductions caused to the clinical dosimetric parameters in this study are not considered clinically significant; however the observed local dose reductions, not considered in these parameters, may affect the clinical outcome of LDR prostate cancer treatments. Therefore this work shows that the use of dosimetric parameters may not be sufficient to characterise the effect of calcifications. More research in this direction will be of great benefit to the studies of the dosimetric effects of prostatic calcifications on clinical LDR brachytherapy treatments. There are some limitations to this work, in which the impact of diffuse calcifications has not been considered. In the instances where calcifications too small for detection in the imaging modalities are present in the prostatic tissue, the effects of these on the dose depositions are not accounted for. Future adaptation of TG 186 planning systems may assist in improving the dosimetric calculations for low dose rate prostate brachytherapy in the presence of prostatic calcifications.

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